Postauthorization Safety Program—Validation of the Clinical Practice Research Datalink for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder

Prepared for:

Astellas Pharma Global Development, Inc.

1 Astellas Way
Northbrook, IL 60062

Final Report

Study #178-CL-116:

A long-term observational study in the CPRD
to prospectively evaluate the incidence and the validity of new cardiovascular and malignant events (excluding non-melanoma skin cancer) in patients using pharmacological treatments for overactive bladder

Version 1.0, Final, August 21, 2015

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PASS INFORMATION

Title	Postauthorization Safety Program—Validation of the Clinical Practice Research Datalink for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder
Version identifier of the final study report	1.0
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Active substance	Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium
Medicinal product	Emselex, Toviaz, Kentera, Vesicare, Detrol, Detrusitol, Sanctura
Product reference	EU/1/12/809/001-018
Procedure number	EMEA/H/C/002388
Marketing authorization holder(s)	Astellas
Joint PASS	No
Research question and objectives	▪ Characterize users of medications to treat overactive bladder (OAB) (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium). ▪ Describe the patterns of use of OAB drugs, including duration of treatments, drug switching, and use of medications as add-on therapy. ▪ Assess and confirm the processes and algorithms used to assess the cardiovascular and cancer endpoints of interest. ▪ Describe the availability of potential confounders in the Clinical Practice Research Datalink (CPRD). ▪ Estimate the incidence rates of cardiovascular endpoints in new users of OAB drugs by individual OAB drug and overall. ▪ Estimate the incidence rate ratio of cardiovascular endpoints in users of each of the OAB drugs compared with tolterodine, a frequently used OAB drug. ▪ Estimate the incidence of sex-specific, multiple-cancer, composite endpoints (one for men and one for women), during the first year after start of treatment and during subsequent years, among new users of antimuscarinic drugs used in the treatment of OAB.
Country(-ies) of study	United Kingdom

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APPROVAL PAGE (1 OF 3)

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Study #178-CL-116
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The following people have reviewed this document and given their approval:

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APPROVAL PAGE (2 OF 3)

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APPROVAL PAGE (3 OF 3)

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Astellas Europe

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 ABSTRACT

Title: A long-term observational study in the CPRD to prospectively evaluate the incidence and the validity of new cardiovascular and malignant events (excluding non-melanoma skin cancer) in patients using pharmacological treatments for overactive bladder

Keywords: cancer, cardiovascular safety, CPRD, pharmacoepidemiology, OAB drugs

Rationale and Background

Mirabegron is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and urinary frequency. The United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) requested a postapproval evaluation of cardiovascular safety. The FDA also required the evaluation of cancer risks. This study is part of a program to prepare for a postmarketing safety assessment of cardiovascular and cancer risks associated with mirabegron use and to validate algorithms that can be implemented in future cohorts that include mirabegron users.

Research Question and Objectives

- Characterize users of OAB drugs (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) with respect to selected covariates.
- Describe the patterns of use of OAB drugs, including duration of treatments, drug switching, and use of medications as add-on therapy.
- Assess and confirm the processes and algorithms used to assess the cardiovascular and cancer endpoints of interest.
- Describe the availability of data for potential confounders.
- Estimate the incidence rates of cardiovascular endpoints in new users of antimuscarinic drugs by individual OAB drug and overall.
- Estimate the incidence rate ratio (IRR) of cardiovascular endpoints in users of each of the OAB drugs compared with tolterodine, a frequently used OAB drug.
- Estimate the incidence of two sex-specific, multiple-cancer endpoints (one for men and one for women) during the first year after start of treatment and during subsequent years among new users of antimuscarinic drugs used in the treatment of OAB.

Study Design

This was a cohort study conducted with data from the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) for patients newly exposed to specified medications to treat OAB: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium.

Setting

This study used information collected in the CPRD to identify the study cohorts. Study outcomes were ascertained from general practice records in the CPRD and via linkage to external data sources—Hospital Episode Statistics (HES) hospitalization data, the Office for National Statistics (ONS) mortality data, and data on cancer diagnoses from the National Cancer Data Repository (NCDR)—for a subset of specific general practices that permit such linkage. The study period was January 1, 2004, through December 31, 2012.

Subjects and Study Size, Including Dropouts

Patients in the study had at least 12 months of continuous enrollment in the database, followed by an index prescription for oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine, provided that the agent was not prescribed during the previous 12 months; patients were aged 18 years or older at the time of the index prescription.

Patients were excluded if they had a diagnosis of cancer other than non-melanoma skin cancer or had a diagnosis of human immunodeficiency virus (HIV) infection.

The study included all eligible patients and their eligible follow-up time during the study period.

Variables and Data Sources

Data sources were the CPRD GOLD database, HES, ONS, NCDR, and questionnaires completed by general practitioners (GPs) contributing to the CPRD.

Person-time was classified based on individual OAB drug prescriptions.

The cardiovascular endpoints of interest were acute myocardial infarction (AMI), stroke, cardiovascular mortality (including coronary heart disease death and cerebrovascular disease death), and all-cause mortality. The composite endpoint of major adverse cardiovascular events (MACE)—nonfatal AMI, nonfatal stroke, or cardiovascular mortality—was also examined.

The cancers included in the composite endpoints were the 10 cancers with the highest incidence rates in the general population, excluding non-melanoma skin cancer:

- Males: prostate, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, and pancreas
- Females: breast, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, corpus uteri, and pancreas

A broad range of characteristics, including demographics, that define elevated cancer risk, relevant diagnoses related to OAB, health care utilization, and use of other medications were evaluated. Key confounders, body mass index (BMI), smoking history, and menopausal status were evaluated also through the GP questionnaires.

Results

Study Cohort and Drug Utilization Study

The study cohort included 119,912 new users of OAB drugs, with a mean duration of follow-up of 3.3 years (range 1 day to 9 years). Of the index therapy episodes (one per cohort member), 33% were for oxybutynin, 31% for tolterodine, 27% for solifenacin, 4.6% for trospium, 1.9% for fesoterodine, 0.1% for darifenacin, and 2.8% for multiple drugs. The mean (SD) duration of index therapy episodes was 5.5 (10.9) months for oxybutynin, the shortest among all medications, and the longest was 8.9 (14.4) months for darifenacin. Of the study patients, 73% were exposed to a single drug during follow-up (i.e., were exposed only to the drug on which they entered the cohort). There were 245,800 therapy episodes (28% oxybutynin, 27% solifenacin, 26% tolterodine, and 10% polytherapy).

Females composed 70% of the study cohort. The mean age at cohort entry was 62.4 years, 64.5 for males and 61.5 for females; 16% of the patients were between 18 and 44 years of age; and almost 50% were aged 65 years or older. At cohort entry, 50% of the patients had a recorded history of OAB; 81% had diagnostic codes for hypertension or received antihypertensive treatment; 11% had diabetes; and in CPRD GOLD, 47% were never smokers, 35% former smokers, and 16% current smokers. Information on smoking was missing in CPRD GOLD for 1.2% of the study cohort.

Of the 119,912 patients in the study cohort, 65,691 (55%) were eligible for linkage to HES and to ONS mortality data, 51,541 (43%) were not eligible for linkage to any data source, and all but one of the remaining patients were eligible for linkage to HES only. The study cohort eligible for linkage to HES, ONS mortality, and NCDR data was 57,577 individuals (48%).

Validation of Cancer Endpoints

Cancer diagnoses were validated in a subcohort of 50,840 new users of OAB drugs without a history of cancer that were drawn from the study cohort. This is called the validation cohort. Provisional cancer cases in this validation cohort were identified by electronic search for diagnostic codes in GP medical records. Patient profiles with OAB drug exposures masked were reviewed and discussed by clinical reviewers. Confirmed cases had evidence of cancer treatment, more than one occurrence of the same cancer diagnosis code, or a subsequent "cancer care review" code. Patients in practices linked to NCDR and HES data could become confirmed cases by using the linked data. NCDR data covered the period from January 1, 1985, through December 31, 2010 only.

The electronic search identified 1,486 provisional cancer cases in GP records, 825 from linked and 661 from non-linked practices. Clinical review of GP records confirmed 792 (96%) cases in linked practices and 616 (93%) in non-linked practices. In linked practices, 1,051 cases were confirmed using all available data sources, of which 279 (27%) were not identifiable through GP records and were obtained by linkage to NCDR and HES data (54 from cancer registry, 107 from HES, and 118 from both), while 185 confirmed cases (18%) were identifiable only through GP records. Of 720 confirmed cases identified in linked practices during years with NCDR data (2004-2010), 492 (68%) were in GP records, 608 (84%) in NCDR data, and 581 (81%) in HES; 22 (3.1%) were in GP records only, 54 (7.5%) in NCDR data only, and 56 (7.8%) in HES only; 215 (30%) were in two sources, and 373 (52%) were in all three sources. Of these 720 cases, 32% were not in GP records, with lower values for cases missing from GP records for cancers treated by GPs (breast, 9.7%; prostate, 21%) and higher values for others (lung, 53%; pancreatic, 52%; renal, 64%).

Study of Cancer Incidence in Users of Antimuscarinics to Treat Overactive Bladder

Among all 119,912 new users of study drugs, 4,117 new users with incident study cancers ascertained from GP records, HES, or NCDR were identified during 399,365 person-years of follow-up: 534 bladder (325 male, 209 female), 886 female breast, 545 colorectal (233 male, 312 female), 495 lung (214 male, 281 female), 182 melanoma (49 male, 133 female), 144 non-Hodgkin lymphoma (63 male, 81 female), 138 pancreas (48 male, 90 female), 932 prostate, 125 renal (53 male, 72 female), and 136 uterine.

In males, 1,917 study cancers occurred in 113,294 person-years, and the incidence rate (95% confidence intervals [CIs]) for the male-specific composite cancer endpoint was 16.92 per 1,000 person-years (16.17-17.70). (All incidence rates and CIs in this report are estimated per 1,000 person-years unless otherwise stated.) In females, 2,200 study cancers occurred in 286,071 person-years, and the incidence rate (95% CI) for the female-specific composite endpoint was 7.69 (7.37-8.02).

To estimate incidence rates for exposure to the various study OAB drugs, rates were standardized to the age and sex distribution of the entire follow-up time of the study cohort. The standardized incidence rate (SIR) (95% CI) for the sex-specific composite cancer endpoint among males ever exposed to study OAB drugs ranged from 15.33 (14.32-16.40) for tolterodine to 19.82 (8.33-39.42) for darifenacin. In females, the SIR (95% CI) for the sex-specific composite cancer endpoint among those ever exposed to study OAB drugs ranged from 6.70 for darifenacin (3.04-12.74) to 7.97 (7.46-8.51) for oxybutynin. In an analysis of all study cancers, the SIRs (95% CIs) for ever-exposure to study OAB drugs were similar across study drugs, ranging from 9.78 (7.82-12.07) for fesoterodine to 10.88 (10.38-11.41) for oxybutynin.

In males, the SIR (95% CI) for the sex-specific composite cancer endpoint related to single exposure to a study OAB drug ranged from 14.22 (11.03-18.05) for trospium to 19.75 (1.51-73.99) for darifenacin. In females, the SIR (95% CI) for the sex-specific composite cancer endpoint related to single exposure to a study OAB drug ranged from 5.84 (0.15-32.52) for darifenacin to 8.36 (4.76-13.53) for fesoterodine. In an analysis of all study cancers, the SIRs (95% CIs) for single exposure to a study OAB drug were similar across study drugs, ranging from 9.81 (1.68-29.51) for darifenacin to 11.18 (7.63-15.79) for fesoterodine.

The rates of bladder cancer and prostate cancer decreased over time since cohort entry. The bladder cancer incidence rate (95% CI) was greater in earlier periods: 2.52 (2.23-2.84) for less than 1 year since cohort entry, 1.16 (0.95-1.42) for 1 to less than 2 years since cohort entry, and 1.0 or less for 2 or more years since cohort entry. The prostate cancer incidence rate (95% CI) was 14.17 (12.89-15.54) for less than 1 year since cohort entry, 6.81 (5.81-7.93) for 1 to less than 2 years since cohort entry, and decreased more gradually with longer time since cohort entry. The incidence rate (95% CI) for these two cancers was higher less than 6 months after OAB drug start: bladder 3.42 (2.96-3.94) and prostate 19.34 (17.30-21.55). In contrast, risk of other cancers did not show this effect of time since cohort entry.

Validation of Cardiovascular Endpoints

Validation efforts in this study were based on various sources of information, including registries, hospital discharge diagnoses, and clinical review of electronic primary care records (for 5,593 cardiovascular endpoints), complemented by information provided on questionnaires sent to GPs, who checked medical records. These questionnaires had a response rate of 80%, which yielded 1,904 assessable questionnaires and allowed estimation of positive predictive values (PPVs) and negative predictive values (NPVs) with good precision.

The validation of electronic algorithms to identify AMI supports the usefulness of the algorithms used. PPVs were above 90% for definite, probable, and possible cases when definition 1 (documented code for AMI but no code for any other symptoms associated with AMI) was used, suggesting that cases identified by these algorithms are to be included as cases in the study. However, for possible AMI cases using definition 2 (at least one code for a symptom possibly related to AMI, without a documented code for AMI), the PPV was only 2.5% (95% CI, 1.6%-3.8%), suggesting that cases identified by this definition should not be considered cases unless using further validation processes.

For stroke, the electronic algorithm used for stroke ascertainment resulted in lower PPVs, none higher than 80%. During clinical review of patient profiles of unconfirmed cases, the following Read codes, none of them diagnostic codes, were found to be frequent: 662M.00, Stroke monitoring; 662o.00, Haemorrhagic stroke monitoring; 8HTQ.00, Referral to stroke clinic; and 9N0p.00, Seen in stroke clinic. We updated the electronic stroke definitions excluding these codes, and the PPVs rose to 92% (95% CI, 85%-96%) for definite stroke, 79% (95% CI, 69%-87%) for probable stroke, and 84% (95% CI, 70%-93%) for possible stroke. The updated algorithm did not identify 48 cases of stroke confirmed by the GPs through questionnaires out of the total 246 stroke cases confirmed by GPs (20%).

The NPV for non-case alive (individuals who did not develop AMI or stroke and were alive at the end of follow-up) was 99% (95% CI, 95%-100%) and for non-case dead (individuals who did not develop AMI or stroke and died during the study period) was 84% (95% CI, 77%-90%). This means that among non-case deaths, 16% were cases with an AMI or stroke.

Validation of Covariates

Information on smoking in the CPRD GOLD database was missing for only 3 patients (0.17% of 1,731 questionnaires with information on smoking). Based on CPRD GOLD data, on the closest day before the endpoint date, 287 patients (17%) were current smokers, 701 (41%) were former smokers, and 732 (42%) were never smokers. In comparing CPRD GOLD data with information from GP questionnaires, 84% of patients identified as current smokers in CPRD GOLD data were also current smokers according to GP questionnaires, 77% identified as former smokers in CPRD GOLD data were also former smokers according to GP questionnaires, and 97% identified as never smokers in CPRD GOLD data were also never smokers according to the GP questionnaires.

Information on obesity (defined as BMI ≥ 30 kg/m^2) was missing for 27% of the 1,713 patients with questionnaire information on obesity when using only information from CPRD GOLD up to the endpoint date. For 74% of patients with missing data on BMI in the CPRD GOLD database, obesity information was provided on the returned GP questionnaire. Of the

patients classified as obese according to CPRD GOLD data, 82% were confirmed through the GP questionnaire; of the patients who were not obese (BMI < 30) according to CPRD GOLD data, this status was confirmed by the GP questionnaire for 92% of the patients.

Pre/postmenopausal status was not correctly identified using CPRD GOLD data (evaluation conducted only on female patients). Of patients with recorded codes for menopause in CPRD GOLD data prior to the endpoint date, 83% were confirmed by their GPs as having gone through menopause prior to the endpoint date, but 3.6% were reported to be premenopausal. Of patients without recorded codes for menopause in CPRD GOLD data before the endpoint date (assumed to be premenopausal based on electronic data), 12% were confirmed as premenopausal, but 77% were reported as having gone through menopause by their GPs.

A history of AMI according to CPRD GOLD data was confirmed by the GP questionnaire in 70% of the cases, and no history of AMI was confirmed in 96%. History of stroke according to CPRD GOLD data was confirmed by the GP questionnaire in 44% of the cases, and no history of stroke was confirmed in 88%.

Study of Cardiovascular Disease Incidence in Users of Antimuscarinics to Treat Overactive Bladder

All 119,912 patients were included in the cardiovascular analysis. Of these patients, 1,983 had an AMI, 2,184 had a stroke, and 2,097 died of cardiovascular causes (1,126 coronary heart disease deaths and 1,007 cerebrovascular disease deaths; please note that both causes could be listed in a patient's death certificate). A total of 4,728 patients experienced an event considered in the MACE definition. Of the 119,912 patients who used one of the OAB drugs studied, 9,487 died of any cause.

For AMI, the SIR (95% CI) was 4.90 (4.53-5.29) cases per 1,000 person-years for any current use of any OAB drug and 6.07 (5.28-6.94) for recent use. For stroke, the SIR (95% CI) was 6.00 (5.60-6.43) for current use of any OAB drug and 6.42 (5.61-7.32) for recent use.

When analyzing mortality, the SIR (95% CI) for current use of any OAB drug was 19.87 (19.13-20.63) for overall mortality, 4.53 (4.18-4.90) for cardiovascular mortality, 2.63 (2.36-2.91) for coronary heart disease death, and 1.99 (1.76-2.24) for cerebrovascular disease death. The SIR of MACE was 12.19 (11.61-12.80) for current use of any OAB drug and 15.59 (14.31-16.96) for recent use.

Of the three most used OAB drugs—oxybutynin, tolterodine, and solifenacin—the incidence of each of the cardiovascular endpoints (AMI, stroke, cardiovascular mortality, coronary

heart disease death, cerebrovascular mortality, overall mortality, and MACE) was lower for solifenacin and greater for oxybutynin. As an example, the incidence of the composite endpoint MACE was lower for current use of solifenacin (SIR, 9.82; 95% CI, 8.88-10.84) and greater for oxybutynin (SIR, 14.32; 95% CI, 13.10-15.62) and for tolterodine (SIR, 12.63; 95% CI, 11.63-13.69).

The point estimates for the IRRs for AMI, stroke, cardiovascular mortality, MACE, and overall mortality for current exposure to oxybutynin were consistently greater than 1 in the various analyses performed using different adjustments (standardization, multivariate Cox proportional hazard models, and Mantel-Haenszel propensity score–stratified analysis) and comparators (tolterodine, any other OAB drug, and no use of OAB drugs). In contrast, point estimates for IRRs for AMI, stroke, cardiovascular mortality, MACE, and overall mortality for current exposure to solifenacin were all lower than 1.

The propensity score–adjusted IRR (95% CI) for MACE for current use of oxybutynin was 1.14 (1.01-1.30) compared with current use of tolterodine and 1.25 (1.12-1.39) compared with current use of any other study drug. The propensity score–adjusted IRR (95% CI) for overall mortality for current use of oxybutynin was 1.26 (1.14-1.38) compared with current use of tolterodine and 1.38 (1.27-1.50) compared with current use of any other study drug.

The propensity score–adjusted IRR (95% CI) for overall mortality for current use of trospium was 1.12 (0.94-1.33) compared with current use of tolterodine and 1.16 (1.00-1.35) compared with current use of any other study drug.

The propensity score–adjusted IRR (95% CI) for MACE for current use of solifenacin was 0.65 (0.56-0.76) compared with current use of tolterodine and 0.70 (0.61-0.80) compared with current use of any other study drug. The propensity score–adjusted IRR (95% CI) for overall mortality for current use of solifenacin was 0.68 (0.60-0.77) compared with current use of tolterodine and 0.67 (0.60-0.74) compared with current use of any other study drug. The propensity score–adjusted IRR (95% CI) for cerebrovascular death for current use of solifenacin was 0.45 (0.28-0.73) compared with current use of tolterodine and 0.46 (0.31-0.66) compared with current use of any other study drug.

Discussion

In this cohort of 119,912 patients with prescriptions for OAB drugs, the majority of patients were female (70%), approximately 50% were aged 65 years or older, and most patients (73%) used a single OAB drug during follow-up. The observed exposure patterns were well suited to detecting acute adverse events for individual OAB drugs.

Information on smoking in the CPRD GOLD database was fairly complete and accurate. Information on obesity was available for three-fourths of the patients and was fairly accurate. For menopause, history of AMI, and history of stroke, the definition used to identify those covariates in CPRD GOLD data did not have a high PPV.

Most cancers in GP records were confirmed by clinical profile review. A substantial number of additional cancers were identified in linked practices by linkage to other data sources (NCDR and HES), and this provided some estimate of the number of cancer cases of various types that may be missed in non-linked practices. The SIRs of cancer for the individual OAB drugs did not differ considerably. Cancer incidence rates were generally similar among the study OAB drugs whether analyzed as ever-exposed or as single-drug–exposed. Protopathic bias and detection bias are plausible explanations for higher incidence rates of bladder and prostate cancers during the initial period of follow-up after starting OAB drug treatment than in subsequent periods. These findings complicate investigation of any potential causal relation between exposure to OAB drugs and prostate or bladder cancer.

The validation of electronic algorithms to identify AMI supported the usefulness of the algorithms used. PPVs were above 90% for definite, probable, and possible cases when definition 1 was used. Possible AMI identified with only codes for chest pain are unlikely to be confirmed cases of AMI. For stroke, the original electronic algorithm used resulted in lower PPVs, none of them higher that 80%. We updated the electronic stroke definitions, excluding codes for referral to stroke clinics and stroke monitoring but not for incident stroke, and the PPVs rose to 92% for definite stroke. However, the updated definition did not identify 20% of stroke cases confirmed by the GPs.

In contrast to the study of cancer incidence in users of antimuscarinics to treat OAB, SIRs of cardiovascular endpoints for the individual OAB drugs differed. In the different analyses performed, the point estimates of the IRRs for AMI, stroke, cardiovascular mortality, MACE, and overall mortality for current exposure to oxybutynin were consistently greater than 1. In contrast, point estimates of the IRRs for AMI, stroke, cardiovascular mortality, MACE, and overall mortality for current exposure to solifenacin were lower than 1.

The results suggest the possibility of forming an aggregated exposure classification ("other OAB drugs") for the comparative study of cancer incidence in relation to use of the new OAB drug mirabegron. For the comparative study of cardiovascular safety endpoints of mirabegron, a comparator should be chosen taking into account the results from this and other validation studies.

Marketing authorization holder and research funding source: Astellas Pharma Global Development, Inc.

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2 LIST OF ABBREVIATIONS

AMI	acute myocardial infarction
BMI	body mass index
BRCA	breast cancer gene
BRCA1	breast cancer 1, early onset gene
BRCA2	breast cancer 2, early onset gene
CHD	coronary heart disease
CI	confidence interval
CONF	case(s) confirmed in the cancer case validation process
CONF-1	type 1 confirmed cases in the cancer case validation process
CONF-2	type 2 confirmed cases in the cancer case validation process
CONF-3	type 3 confirmed cases in the cancer case validation process
CONF-4	type 4 confirmed cases in the cancer case validation process
CPRD	Clinical Practice Research Datalink, United Kingdom
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration, United States
GOLD	online database of the CPRD
GP	general practitioner
GPP	*Guidelines for Good Pharmacoepidemiology Practices*
GPRD	General Practice Research Database; forerunner of the CPRD (UK)
GVP	Good Pharmacovigilance Practices
HES	Hospital Episode Statistics, United Kingdom
HIV	human immunodeficiency virus
ICD	International Classification of Diseases
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
ID	identification number
IMD	index of multiple deprivation
IRR	incidence rate ratios
[redacted]	[redacted]
MACE	major adverse cardiovascular events
MHRA	Medicines and Health Care Products Regulatory Agency
NCDR	National Cancer Data Repository, United Kingdom
NHL	non-Hodgkin lymphoma
NPV	negative predictive value
OAB	overactive bladder
ONS	Office for National Statistics, United Kingdom

OXMIS	Oxford Medical Information Systems (coding system)
PASS	postauthorization safety study
PPV	positive predictive value
PROV-1	type 1 provisional cases in the cancer case validation process
RTI-HS	RTI Health Solutions, a business unit of RTI International
SAP	statistical analysis plan
SCR-1	screening method 1 in the cancer case validation process
SCR-2	screening method 2 in the cancer case validation process
SCR-3	screening method 3 in the cancer case validation process
SD	standard deviation
SEER	Surveillance, Epidemiology and End Results Program (US)
SIR	standardized incidence rate
THIN	The Health Improvement Network, United Kingdom
UK	United Kingdom
US	United States
VAL-1	validation method 1 in the cancer case validation process

3 INVESTIGATORS

RTI Health Solutions (RTI-HS) is responsible for conducting the study in the Clinical Practice Research Datalink (CPRD) database. The core research team is listed below. Other RTI-HS contributors are listed in Section 4.

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5 MILESTONES

Task/Milestone	Anticipated Timing	Actual Timing
Submission of study protocol to the FDA	March 31, 2013	March 25, 2013, version 3.0
[redacted]	August 2013	August 5, 2013
[redacted]	August 2013	August 30, 2013
EU PAS registration protocol version 3.0, date March 25, 2013	January 2014	January 13, 2014
Amended protocol submission to the FDA	April 16, 2014	April 23, 2014, version 3.1
Final statistical analysis plan	December 2013	December 16, 2013
Start of data collection[b]	March 2014	March 31, 2014
End of data collection[c]	May-June 2014	June 11, 2015
Statistical analysis plan submission to the FDA	February 2015	27 February 2015, version dated 21 January 2015
Submission of preliminary validation study report to the FDA (regulatory milestone)	March 2015	March 31, 2015
Submission of study report to the FDA (regulatory milestone)	August 2015	August 2015

CPRD = Clinical Practice Data Link; EU PAS = European Union Postauthorization Study; FDA = Food and Drug Administration.

[a] RTI Health Solutions is a business unit of RTI International, a not-for-profit research organization.

[b] Start of data extraction from the CPRD to RTI Health Solutions.

[c] Analytic data set for primary objective finalized by RTI Health Solutions.

6 RATIONALE AND BACKGROUND

Mirabegron is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and urinary frequency.

Astellas obtained marketing authorization for mirabegron in the United States (US) on June 28, 2012,[1] and in the European Union (EU) on December 20, 2012.[2] The US Food and Drug Administration (FDA)[1] and the European Medicines Agency (EMA) included a postapproval requirement to evaluate cardiovascular safety. The FDA also required a postapproval commitment to evaluate cancer risk.[1]

To prepare for a postmarketing safety assessment of cardiovascular and cancer risk associated with mirabegron use, this study has been designed to describe drug-use patterns among users of antimuscarinic drugs commonly used in the treatment of OAB, to calculate background rates of cardiovascular and cancer outcomes in this population, and to validate outcome-specific case-identification algorithms based on the clinical data recorded by general practitioners (GPs). Upon validation, these algorithms can be implemented in future cohorts that include mirabegron users to allow for an efficient and timely evaluation of cardiovascular and cancer risks associated with mirabegron as part of the required postauthorization study to be conducted in the US and the EU.

The present report provides the results of the validation study conducted in the Clinical Practice Data Link (CPRD)* population in the United Kingdom (UK).

The body of this report is organized into the following sections. Findings of the literature review are summarized in the next section, 6.1. The research objectives are presented in Section 7. Amendments and updates to the protocol are summarized in Section 8. Section 9 contains details of the research methods, and Section 10 contains the results. A summary of key results, limitations of the study, interpretive comments, and generalizability is found in Section 11, and overall conclusions are found in Section 13. The report also contains the following information in annexes: key findings of validation studies that have been conducted in the CPRD (Annex 2), incidence rates for cancer endpoints in the United States (Annex 3), Read codes that were used to identify cases of overactive bladder, characteristics of patients and notes on the identification of these characteristics in the CPRD (Annex 4), a list of the patient characteristics captured in the study with the description or categories used (Annex 5), diagrams depicting the proportions of cancer cases identified by each specific data source (Annex 6), graphical presentations of incidence

* The name of the database was General Practice Research Database (GPRD) at the time of many of the studies in the literature review; we use CPRD here for consistency.

rates of cancer by time since entry into the study cohort (Annex 7), and tables of the analysis results (Annex 8).

6.1 Literature Review

6.1.1 Drug Utilization

Some studies on drug utilization have been identified, and key findings are summarized below as they are of relevance to the design of the postapproval safety program.

One study explored the utilization of drugs to treat OAB in the CPRD in the UK.[3] In the period 1987-2004, the authors found 68,910 patients with codes for symptoms of OAB and without benign prostatic hypertrophy, diabetes, renal problems, or concomitant urinary tract infection, who were followed for a mean of 4.2 years. A total of 3,009 of these patients were on treatment at the time the symptoms were recorded, and 16,435 started OAB drugs after the symptoms were recorded. The 16,435 patients who started OAB drugs after having symptoms recorded had a mean age of 55.7 years, and 58% were female. Overall, 74% of the patients with pharmacologic treatment received a single OAB drug during follow-up, 21% received two different drugs, and the rest received more than two drugs. The most commonly used initial drug was oxybutynin (62%), followed by tolterodine (28%). Patients receiving tolterodine as the initial treatment during follow-up were the least likely to switch treatments. Tolterodine was the most common drug for patients' first switch (53%), followed by oxybutynin (22%). Oxybutynin was the only OAB drug available at the beginning of the study period.

In another drug utilization study that also used electronic medical records from the general population in the UK for years 1991-2007, the 29,369 adult female users of OAB drugs that composed the study cohort had a mean age of 63.9 years. This study was conducted in The Health Improvement Network (THIN) database, which partially overlaps with the CPRD in terms of contributing practices. In this study, the most commonly prescribed drug was also oxybutynin, with 51% of therapy episodes, followed by tolterodine, with 34%.[4] The mean time from recorded OAB symptoms to first drug treatment was 28.7 months, and the mean (SD) number of treatment episodes per patient was 1.65 (1.31). A total of 11% of the study patients had more than three treatment episodes during follow-up. Overall drug discontinuation at 6 months was 59%, although it varied by drug—53% for solifenacin and 89% for terodiline (an old OAB drug that has been withdrawn because of cardiotoxicity). At 12 months, overall drug discontinuation was 77%, lowest for extended-release tolterodine (76%) and highest for terodiline (99%). Switching happened in 16% of the treatment episodes. Of the identified episodes, 5% had prescriptions for more than one anticholinergic drug issued the same day.

In a more recent drug utilization study from the THIN population from years 2007-2008, 36% of the 6,143 therapy episodes in 4,833 patients aged 40 years or older were for tolterodine and 32% were for oxybutynin.[5] Mean duration of therapy episodes was 4 to 6 months for all antimuscarinics except flavoxate, which had the fewest users. Although extended-release forms have been reported to have higher adherence than immediate-release forms,[6,7] in this study, therapy episodes with the two forms of tolterodine had practically the same mean length, 5 months. Therapy episodes for the extended-release form of oxybutynin had a mean duration of 4.8 months, while those for the immediate-release form had a mean duration of 3.9 months. Adherence to all OAB drugs declined steeply in the first few months of treatment and less so later.[5]

In a study using reimbursed prescriptions from the county of Funen in Denmark for years 1999-2006, 66% of the individuals prescribed OAB drugs were women (mean age, 68.0 years) and 34% were men (mean age, 69.0 years).[8] All drugs had discontinuation rates over 50% at 6 months and over 75% at 12 months, with the exception of trospium chloride, which had a discontinuation rate of 64% at 12 months. Another study from approximately the same region looked into discontinuation of treatment in relation to surgery for urinary incontinence in years 1997-2010. The authors noted that, among women who were on pharmacologic treatment for urinary incontinence (mean age 60.9 years) prior to surgery, 27% continued with pharmacologic treatment 61 to 365 days after surgery.[9]

6.1.2 Cardiovascular Morbidity in Patients With Overactive Bladder

Persons with OAB may have increased cardiovascular comorbidity. Because the autonomic nervous system participates in the regulation of heart rate, blood pressure, and the continence-voiding process, dysfunction of the autonomic nervous system may result in both cardiovascular comorbidity and OAB.[10] Obesity and diabetes have been associated with OAB and stress urinary incontinence.[11] In a study performed in the HealthCore Integrated Research Database and GE Healthcare database in the US for years 2000-2006, baseline cardiovascular comorbidity was higher in patients with an OAB diagnosis or treated with OAB antimuscarinic medications (39%) than in age- and sex-matched patients without either OAB codes or OAB antimuscarinic treatment (21%).[12] Cardiovascular comorbidities or risk factors with a higher prevalence in the OAB group included, among others, hypertension, diabetes, ischemic heart disease, and cardiac conduction disorders. In addition, the prevalence of use of non-OAB drugs with antimuscarinic effect was also higher in the OAB group: 33% versus 17% for patients without OAB codes or OAB antimuscarinic treatment. Prevalence of cardiovascular comorbidity was similar in patients with OAB treated with OAB antimuscarinic medications (39%) and in age- and sex-matched patients

with OAB with no such treatment (38%); use of non-OAB drugs with antimuscarinic effect was higher in treated patients (37% vs. 29% for untreated patients).

A related study, also in the US (GE Healthcare database), for years 1996-2007, found that patients with OAB treated with OAB antimuscarinics had baseline heart rate distributions similar to those with no such treatment.[13] In this study, treated patients with OAB had a higher proportion of cardiovascular comorbidity or risk factors (59%) than untreated patients (54%), including a higher proportion of hypertension, diabetes, and cerebrovascular disease. However, risk factors for cardiovascular conditions (e.g., age and sex) were not balanced among treated patients with OAB (median age, 66 years; 17% men) and untreated patients with OAB (median age, 59 years; 14% men), which may account, at least partially, for the difference.

6.1.3 Cardiovascular Endpoints

Several algorithms for the case identification of cardiovascular endpoints recorded in the CPRD have been evaluated in different studies. Studies have shown positive predictive values (PPVs) of 82%,[14] 96%,[15] and 93%[16] for acute myocardial infarction (AMI); 76%[17] and 90%[18] for ischemic stroke; and 82%[19] and 100%[17] for hemorrhagic stroke. Details are provided in Annex 2.

6.1.4 Cancer Endpoints

Cancer diagnoses recorded in the CPRD have been found to be highly reliable. One study reported PPVs of 96% for the diagnosis of lung cancer, 92% for urinary tract cancer, 96% for gastroesophageal cancer, and 98% for colorectal cancer.[20] Another study reported, among CPRD practices with data linkage to the National Cancer Data Repository (NCDR), an 83% concordance between cancer diagnoses recorded in the CPRD for a cohort of patients with diabetes and matched patients without diabetes compared with cancer diagnoses recorded for the same patients in the NCDR (excluding non-melanoma skin cancer).[21] Older age was predictive of higher discordance in a multivariable model. Using NCDR diagnoses as the reference, we estimate from data presented in this publication that the sensitivities for diagnoses of common cancers in the CPRD are as follows: breast, 97%; prostate, 99%; colorectal, 95%; lung, 91%; urinary tract, 95%; and melanoma, 96%. The investigators also used the linked Hospital Episode Statistics (HES) database to identify cancer cases and reported that 528 of the 5,797 cases recorded in the CPRD were confirmed in this additional data source, although they were not recorded in the NCDR.

Another study found that essentially all cases in the CPRD with a diagnostic code for esophageal cancer were confirmed to have had the disease; moreover, where data were available to judge the time of clinical onset, the date was within 60 days of the date

recorded in the electronic medical record in 89% of cases.[22] Similarly, in a study of calcium channel blockers and risk of cancer, among cancer patients for whom additional information was obtained directly from the patients' GPs, the diagnosis was confirmed in 95% of cases.[23] In another study using CPRD data, changes similar to those reported in national cancer statistics were observed in age-specific breast cancer incidence patterns after the introduction of a UK national screening program; although this study was an ecological (time trend) analysis, the findings provide indirect support for the validity of breast cancer diagnoses in this data source.[24] The risk of bladder cancer has also been studied in the CPRD in relation to several exposures, including acetaminophen[25] and pioglitazone.[26]

7 RESEARCH QUESTION AND OBJECTIVES

The postauthorization safety program for mirabegron is ultimately designed to determine the cardiovascular and cancer safety of mirabegron relative to other treatments for OAB. The purpose of the research presented in this report was to evaluate the suitability of the CPRD in the UK as a data source for the postauthorization safety program for mirabegron.

The specific objectives of the current study were as follows:

- Characterize users of OAB drugs (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) with respect to selected covariates.
- Describe the patterns of use of OAB drugs, including duration of treatments, drug switching, and use of medications as add-on therapy.
- Assess and confirm the processes and algorithms used to assess the cardiovascular and cancer endpoints of interest.
- Describe the availability of potential confounders in the CPRD.
- Estimate the incidence rates of cardiovascular endpoints in new users of antimuscarinic drugs by individual OAB drug and overall.
- Estimate the incidence rate ratio (IRR) of cardiovascular endpoints in users of each of the OAB drugs compared with tolterodine, a frequently used OAB drug.
- Estimate the incidence of two sex-specific, multiple-cancer endpoints (one for men and one for women) during the first year after start of treatment and during subsequent years among new users of antimuscarinic drugs used in the treatment of OAB.

The protocol and ENCePP† checklist were registered in the EU PAS Register[27] prior to the start of data collection (January 13, 2014). The study was designed and implemented in line

† ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.

with the International Society for Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiology Practices*[28]; EMA *Guidelines on Good Pharmacovigilance Practices (GVP), Module VIII – Postauthorization Safety Studies*[29]; the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology*[30]; and FDA *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Guidance*.[31] The contract between RTI Health Solutions (RTI-HS) and Astellas includes independent publication rights.

The RTI-HS study team received approval for exemption from review by the [redacted] on August 5, 2013.

CPRD [redacted] approval was received on August 30, 2013, and RTI-HS was notified of the UK National Cancer Intelligence Network's approval of the study protocol on December 5, 2013.

8 AMENDMENTS AND UPDATES

No amendments in version 1.0.

Number	Date	Section of Study Protocol	Amendment or Update	Reason
None				

9 RESEARCH METHODS

To meet the objectives listed in Section 7, this study had the following four components, which are detailed in later sections:

1. Drug utilization study (conducted in the entire study cohort):
   - Characterization of users of OAB drugs
   - Description of utilization patterns for OAB drugs
2. Validation of endpoints (conducted in the validation cohort):
   - Cardiovascular
   - Cancers
3. Study of cardiovascular disease incidence in users of antimuscarinics to treat OAB (entire study cohort), including the following:
   - Availability of potential confounders

- Measures of frequency and association for AMI, stroke, cardiovascular mortality, all-cause death, and a composite endpoint comprising nonfatal AMI, nonfatal stroke, and cardiovascular mortality (major adverse cardiovascular events [MACE])

4. Study of cancer incidence in users of antimuscarinics to treat OAB (entire study cohort), including the following:
   - Availability of potential confounders
   - Measures of frequency for the 10 most frequent cancers in the US (listed in Annex 3)

9.1 Study Design

This is a retrospective cohort study of adults newly exposed to drugs used in the treatment of OAB (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium) in the UK as reflected in the CPRD. The study had four components: a drug utilization study, a validation study of cardiovascular and cancer endpoints, a study of cardiovascular incidence, and a study of cancer incidence. The benefits of this design are that we observe the use of the study medications and the development of the endpoints in routine clinical practice using data that were collected prospectively (even if the study is conducted retrospectively on data already collected). The new user design reduces problems related to depletion of susceptibles.

9.2 Setting

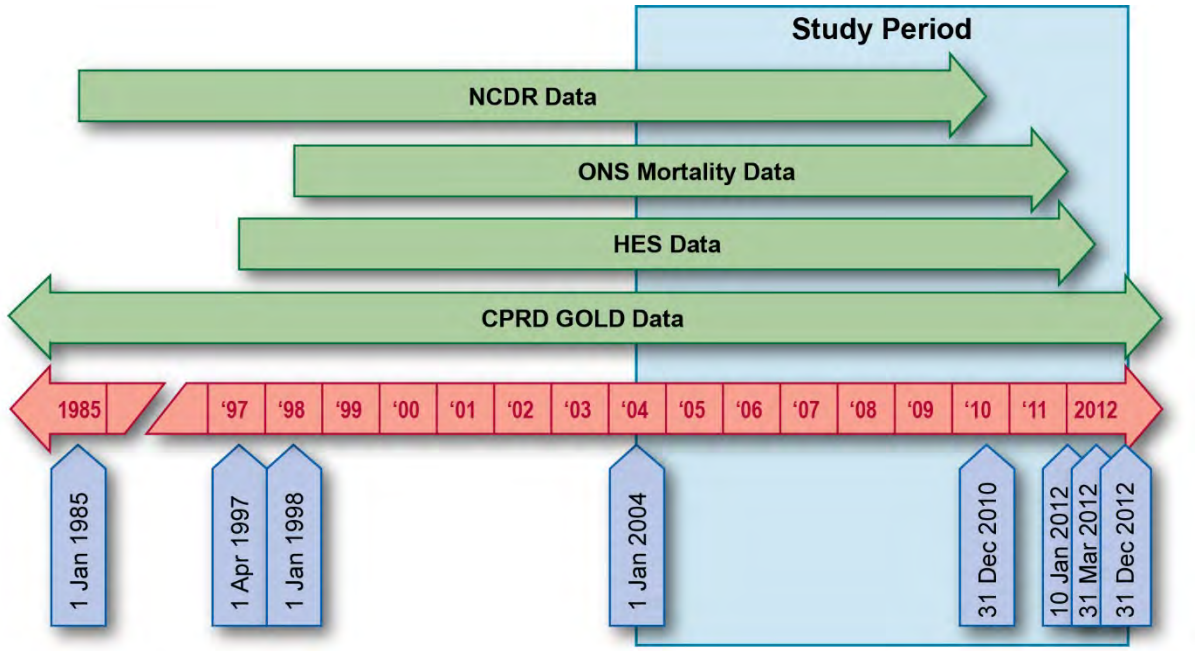
This study used information collected in the CPRD to identify the study cohorts. Study outcomes were ascertained from general practice records in the CPRD and via linkage to external data sources—HES data, the Office for National Statistics (ONS) mortality data, and data from the NCDR—for a subset of specific general practices that permit such linkage. In addition, 1,904 questionnaires were completed by GPs for validation of cardiovascular endpoints and availability of key potential confounders, and 7,079 patient electronic profiles were examined by clinical reviewers (5,593 for cardiovascular endpoints and 1,486 for cancer endpoints).

9.2.1 Linkage Process and Study Cohort

The study period was January 1, 2004, through December 31, 2012. General practice data (CPRD GOLD online database) covered the entire study period. To form the study cohort from the initial data set received from the CPRD, we excluded persons who did not have study drug prescriptions that qualified for an index prescription or who had exclusion criteria. HES coverage dates were April 1, 1997, through March 31, 2012, and ONS

mortality coverage dates were January 1, 1998, through January 10, 2012. NCDR data covered the period from January 1, 1985, through December 31, 2010 (Figure 1).

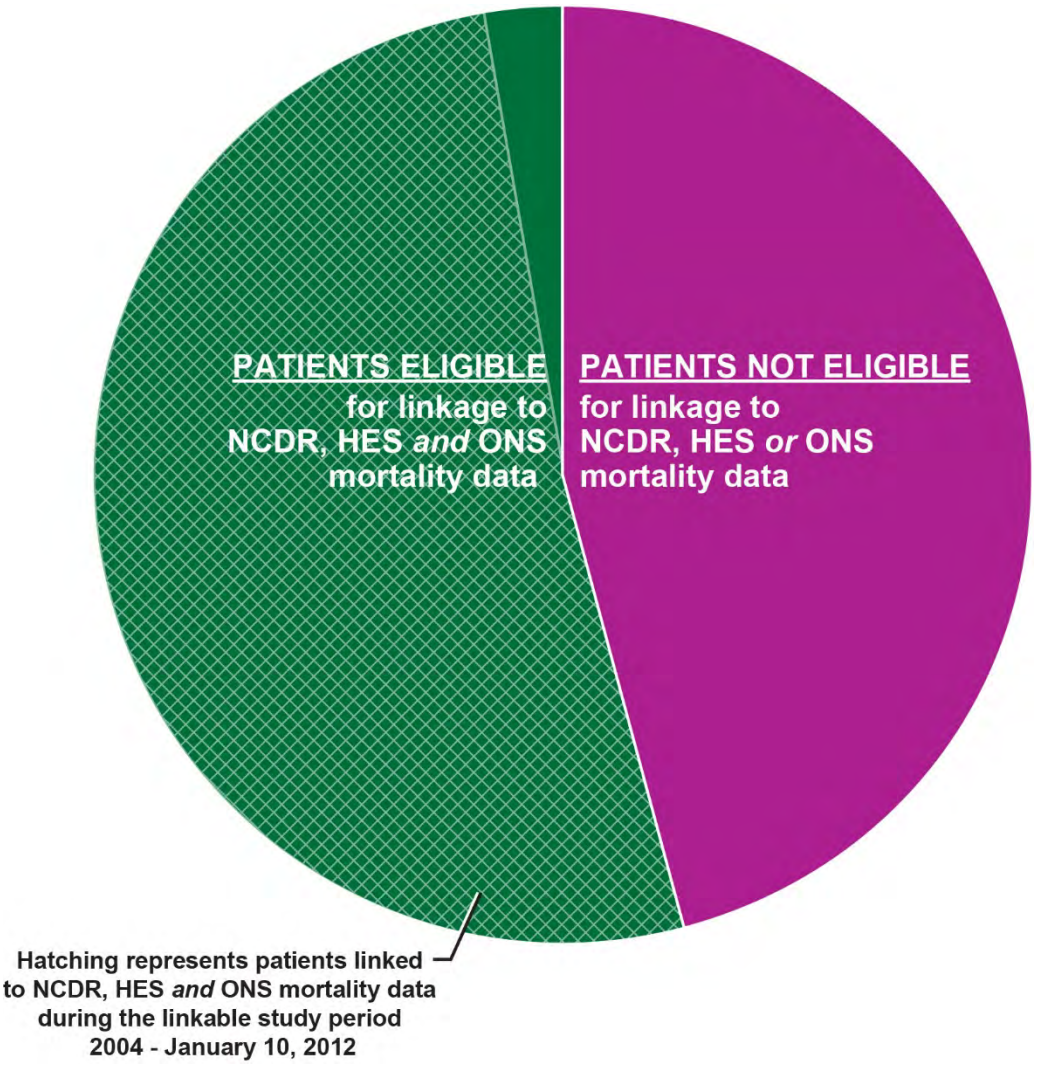
Figure 1. Data Source Coverage in Relation to the Study Period



CPRD = Clinical Practice Research Datalink; GOLD = online database of the CPRD; HES = Hospital Episode Statistics; NCDR = National Cardiovascular Data Registry (United Kingdom); ONS = Office for National Statistics (United Kingdom).

The study cohort thus comprised patients who were eligible for linkage to HES and to ONS mortality data, to only ONS mortality data, or to only HES data and some patients who were not eligible for linkage to either data source (Figure 2). Not all patients eligible for linkage to HES and to ONS mortality data were linkable to NCDR data.

Figure 2. Linkage Setting



CPRD = Clinical Practice Research Datalink; GOLD = online database of the CPRD; HES = Hospital Episode Statistics; NCDR = National Cancer Data Repository (United Kingdom); ONS = Office for National Statistics (United Kingdom).

Note: This figure is a description of the linkage setting in CPRD data. Green represents patients determined by the CPRD data holders to be eligible for linkage to data from the NCDR, ONS, and HES, while pink represents patients who are not eligible for linkage (either due to practice or individual opting out of participation in linkage). Hatched green represents patients eligible for linkage during the study period. Solid green represents the subset of eligible patients who do not have "linked data" within the study period due to the time lag between linkage with NCDR, ONS, and HES and available CPRD GOLD data.

Explanation of Linked and Linkable Terminology

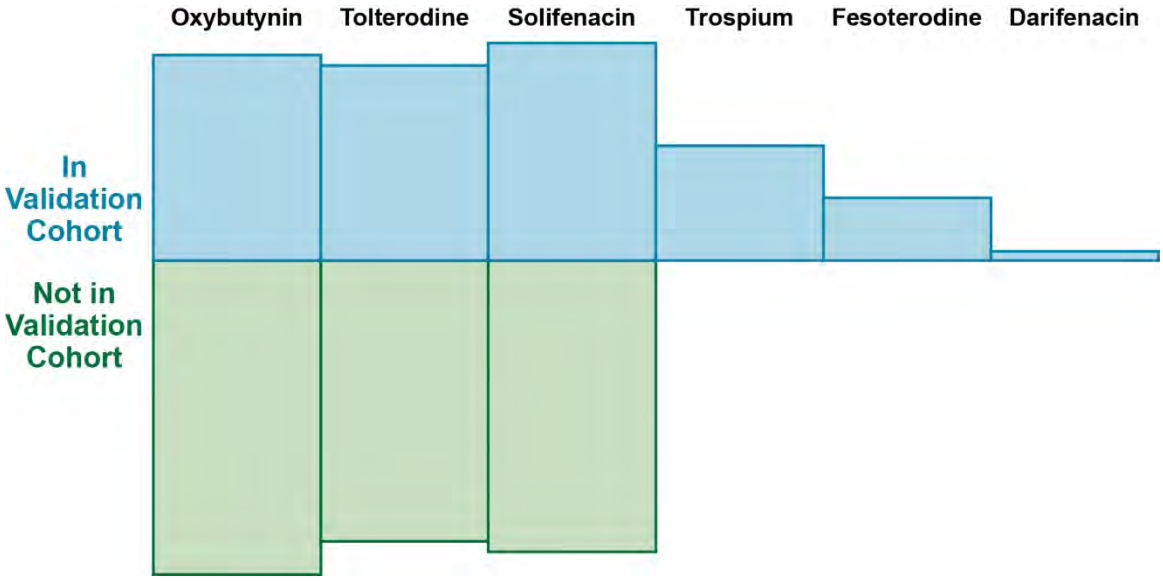
Certain patients are determined by the CPRD data holders to be "eligible for linkage," which means that they receive care in a general practice in England that contributes data to the CPRD (HES and NCDR data are available only in England), and that the practice has agreed to the data linkage. We use the term "linkable" to mean the same thing as "eligible for linkage" (in reference to either such patients or the general practice where they receive their care). Individual patients are allowed to opt out of the data linkage, so a "linkable practice" may actually have some "non-linkable patients," but only a few patients actually opt out. We also sometimes refer to "linkable person-time" because, for example, it takes approximately 2 years for NCDR data to become available (and such data were available through December 31, 2010, for the present study), so the most recent portion of patients' follow-up time in their general practice does not have corresponding information in the NCDR; therefore, patients have "linkable person-time" (before the end of 2010) followed by "non-linkable person-time" (with respect to the NCDR) if they continued to be followed in their general practice through December 31, 2012.

Once we received data for our study, data that were "linkable" had already in effect been "linked" at the individual patient level since the three data sets contain a unique patient identifier to link the data for a given patient across the three data sources (when possible). Where we discuss the data we are analyzing, our results, or the methods we used to produce our results, we will refer to "linked practices" (i.e., one that was "linkable" and for which we actually have linked data on most patients), "linked patients," or "linked person-time." For many purposes, referring to "linked practices" is specific enough (for example, when we distinguish how we analyzed data from linked practices vs. non-linked practices), but there are times when it is necessary to be more specific and refer to "linked patients" or even "linked person-time."

9.2.2 Validation Cohort

The number of events in the study cohort was large, and the time needed to conduct the clinical review components of the validation (patient profiles and GP questionnaires) with the resources available would have exceeded the time agreed for the conduct of the study. For that purpose, we approximately halved the number of events, maximizing the sample for less frequently used OAB drugs, and the clinical review of cases was performed in a sample of the study cohort (linked and non-linked). The sample consisted of all patients with a first prescription for the less frequently used OAB drugs, i.e., darifenacin, fesoterodine, or trospium (the date of that index prescription was defined as the cohort entry date for that sample) and a 33% random fraction of patients exposed only to tolterodine, solifenacin, or oxybutynin (each patient had equal probabilities of being selected within the group), also captured at the first prescription. We will refer to this as the validation cohort (Figure 3). Details on the how the validation cohort was created are presented in Section 9.3.2.

Figure 3. Stacked Histogram Showing Relationship Between the Study Cohort and the Validation Cohort



Note: The study cohort comprised all patients in the data set with an index prescription for any of the study medications for overactive bladder. The validation cohort comprised all patients in the data set with an index prescription for trospium, fesoterodine, or darifenacin, and a 33% sample of patients with an index prescription for oxybutynin, tolterodine, or solifenacin.

Different components in this CPRD study were conducted in different populations or cohorts. The drug utilization study was performed in the entire study cohort, as was the study of cardiovascular and cancer incidence, while the validation of study endpoints and covariates was conducted in the validation cohort.

9.3 Subjects

9.3.1 Study Cohort

9.3.1.1 Inclusion Criteria

Patients in the study were required to meet the following inclusion criteria:

- Have at least 12 months of continuous enrollment in a general practice for which the electronic medical records have been designated as "up-to-standard" by the CPRD, followed by a prescription for darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium, provided that agent was not prescribed during the previous 12 months.
  - The first recorded prescription that met this criterion was the patient's index prescription. Note that the patient may have had prescriptions for a different OAB drug that did not meet the eligibility criteria any time prior to the index

prescription or for the same OAB drug more than 12 months prior to the index prescription.

- Be aged 18 years or older at the time of the index prescription.

9.3.1.2 Exclusion Criteria

Patients were excluded if they met *either* of the following criteria at any time prior to the potential index prescription date:

- Had a diagnosis of cancer other than non-melanoma skin cancer (GOLD, HES, or NCDR data).
- Had a diagnosis of human immunodeficiency virus (HIV) infection (GOLD and HES data) or a prescription for an HIV medication. These patients often receive health care through specialty clinics or separate health plans, and their health service utilization might not be fully captured in the data source.

9.3.1.3 Follow-up

Follow-up started on the date of the qualifying index prescription (cohort entry) and finished at the earliest of the end of the study period (December 31, 2012), death, disenrollment from the database (i.e., patient left practice or practice stopped providing data to the CPRD), occurrence of a diagnosis listed as an exclusion criterion (including any cancer), or occurrence of an endpoint.

In the analysis of individual cardiovascular endpoints, the occurrence of the individual endpoint determined the end of follow-up for that particular endpoint, as well as for the composite cardiovascular outcome; however, follow-up for other individual cardiovascular endpoints continued. For example, in the analysis of AMI, follow-up for AMI continued after a patient had a stroke. The occurrence of any endpoint in the composite cardiovascular outcome stopped follow-up for the composite endpoint.

In analyses of cancer endpoints, the occurrence of any cancer other than non-melanoma skin cancer determined the end of follow-up. Therefore, the occurrence of any endpoint in the composite cancer outcome stopped follow-up for the composite endpoint. This was done because only the first incident study cancer was considered to be a study outcome, as the first cancer and its treatment may have modified the risk for subsequent cancers, and combining first and subsequent cancers (possibly with different risk factors) might have been inappropriate. Therefore, for example, person-time accrual for the study of breast cancer stopped after the diagnosis of lung cancer.

Double mastectomy and hysterectomy were identified through Read codes. Person-time after double mastectomy was excluded from the follow-up for breast cancer analyses since

patients who undergo this procedure for reasons other than cancer should be at very low risk for developing breast cancer subsequently. Similarly, person-time after hysterectomy was excluded from analyses of uterine cancer. However, for the analysis of the composite endpoint, if a bilateral mastectomy occurred and no breast cancer was observed, then the patient's person-time was still included after the bilateral mastectomy date because the patient was still at risk for other cancers in the composite outcome. (However, if during follow-up there was a breast cancer diagnoses after the bilateral mastectomy, then the composite cancer date was moved forward to the bilateral mastectomy date, as it was likely that the breast cancer was recorded after the procedure used to treat it.) The same reasoning was applied to hysterectomies and uterine cancer for the composite endpoint.

9.3.2 Validation Cohort Specifications

We created a validation cohort that consisted of a stratified random sample of patients with an index prescription for the most commonly prescribed drugs in the study cohort (tolterodine, oxybutynin, and solifenacin) and all patients with a qualifying prescription for the remaining drugs (darifenacin, fesoterodine, or trospium); linkage status was not taken into consideration in the sampling of patients. If the patient entered the study cohort with an index prescription for tolterodine, oxybutynin, or solifenacin and subsequently had at least one qualifying prescription during the study period for darifenacin, fesoterodine, or trospium, the first qualifying prescription for darifenacin, fesoterodine, or trospium was the patient's index prescription for inclusion in the validation cohort. This was done to ensure that all study drugs would be represented.

9.4 Variables

9.4.1 Exposure

The study drugs were darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium. No drug to treat OAB was available over the counter in the UK during the study period.

9.4.2 Endpoints and Outcomes

9.4.2.1 Cardiovascular Endpoints

Each of the following individual study endpoints was evaluated:

- AMI, including out-of-hospital coronary heart disease (CHD) deaths
- Stroke
- Cardiovascular mortality: CHD death and cerebrovascular disease death

- Composite endpoint (major adverse cardiovascular events [MACE]): nonfatal AMI, nonfatal stroke, and cardiovascular mortality
- All-cause mortality

9.4.2.2 Cancer Endpoints

The cancers observed in the mirabegron clinical development program were those that occur commonly in the general population; therefore, this study focused on the 10 most commonly occurring malignancies in the US.[32] Because several of these cancers occur exclusively (or nearly exclusively) in either males or females, the main composite cancer endpoints are sex-specific (Table 1). Overall analyses of the incidence rates for all cancers in the sex-specific composite endpoints, as well as results for study cancers individually, are also presented.

Table 1. Components of Composite Cancer Endpoints

	Sex-Specific Composite Cancer Endpoints	
Type of Neoplasia	**Males**	**Females**
Colon and rectum	Y	Y
Pancreas	Y	Y
Lung and bronchus	Y	Y
Melanoma of the skin	Y	Y
Breast (female only)	N	Y
Corpus uteri (female only)	N	Y
Prostate (male only)	Y	N
Urinary bladder	Y	Y
Kidney and renal pelvis	Y	Y
Non-Hodgkin lymphoma	Y	Y

9.4.3 Covariates

Read codes that were used to identify patients with OAB in CPRD data are listed in Annex 4. The list of other covariates, including their descriptions, is included in Annex 5.

A variety of stratified analyses were conducted. Stratified analyses included male and female patients, patients aged 65 or more years, and patients with increased cardiovascular risk. Increased cardiovascular risk was defined by the presence at baseline of one or more of the diagnoses in the first group or two or more of the diagnoses in the second group:

First group: one or more of the following:

- Diabetes (diagnostic codes or medications)
- History of myocardial infarction
- History of stroke
- History of heart failure
- Peripheral arterial disease
- Coronary heart disease
- Transient ischemic attack
- Atrial fibrillation or flutter (diagnostic codes)

Second group: two or more of the following:

- Current smoking
- Dyslipidemia (diagnostic codes)
- Hypertension (diagnostic codes)

9.5 Data Sources and Measurement

The CPRD, formerly known as the General Practice Research Database (GPRD), contains the information recorded by GPs as part of their routine clinical practice in the UK (http://www.cprd.com/intro.asp). The CPRD covers approximately 8% of the UK population and includes approximately 5.1 million active individuals who are alive and currently contribute data to the database; close to 13 million individuals have at some point been part of the CPRD.[33] The CPRD GOLD database, which is the online database of the CPRD, includes approximately 900,000 individuals aged 65 years or older, of which 500,000 are women. Patients are representative of the whole UK population in terms of age and sex.

Core data include information on diagnoses, symptoms, referrals, tests ordered, test results, prescriptions issued, and additional clinical information. Prescriptions have fields for strength and dosage. Drugs are classified following the British National Formulary, and medical data are coded in the Read coding system. The latter is very granular and is regularly updated in response to physician user requests. It has numerous codes for cancers, cardiovascular conditions, and OAB diagnosis, signs, and symptoms.

Currently, approximately 65% of the English practices contributing to the CPRD have consented to have their patient information linked, via the CPRD Division of the UK Medicines and Health Care products Regulatory Agency (MHRA), to other health care data sets via the patient's National Health Service number, sex, date of birth, and postal code.

Practices from Scotland, Wales, and Northern Ireland contributing to the CPRD do not have linkage. English practices represent approximately 75% of the practices contributing to the CPRD; therefore, linkage is an option for approximately half of the total CPRD practices and individuals.

Data on hospitalization (HES) and cause of death (ONS) were coded in ICD-10[‡] codes. Primary care data were linked with ONS death certificate data to identify all deaths occurring during the observation period among study patients for whom the linkage was available. The result of the linkage was a data set containing patient ID (identification number), practice, date of death, place of death, underlying cause of death (ICD-10 code), and all other causes of death listed on the death certificate. Dates of death in this file were checked against the dates of the study observation period to ensure that the deaths occurred during the study follow-up period. Primary care data were also linked with HES data to determine admission and discharge dates and diagnoses of all hospitalizations during the study observation period among study patients for whom the linkage was available.

9.6 Bias

Endpoints were identified electronically independently of exposure. Prescriptions for study drugs were removed from medical profiles to ensure that investigators conducting endpoint validation were blind to patients' use of study drugs. Analytical measures to minimize bias, including confounding, are described in Section 9.9.

9.7 Study Size

The study included all eligible patients and their eligible follow-up time during the study period.

9.8 Data Transformation

We encountered repeated prescription records and missing values for days' supply. Below we describe these issues and the steps taken to resolve them.

9.8.1 Repeated Prescriptions

Prescription information in the CPRD comes from prescriptions issued. At the time of issuing a prescription, situations may arise in which multiple prescription records are created for a single prescription. This can occur when the GP accidentally hits the print button more than once (which would result in multiple identical records) or when the GP issues a prescription

[‡] ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

with a blank field or a mistake and immediately creates a corrected prescription record (resulting in records that are almost identical and issued on the same date). Not surprisingly, we found duplicate prescription records, identical in all fields, including issue date. In agreement with the data custodians, one record from a set of duplicate records was retained. Further, when patients had prescriptions for the same product (as identified by codes for unique products [strength, form, commercial name]) with the same issue date, we preferentially retained records with nonmissing days' supply, which appeared chronologically later in the data and with a larger issue sequence number (the latest prescription in a sequence of repeated prescriptions). Last, if patients had more than one recorded prescription for the same drug substance and strength issued on the same date, one record was retained. If same-date prescriptions were for the same product but different strengths, we assumed that the total daily dose equaled the sum of the daily dose for both prescriptions.

Removal of duplicate records is part of the internal processing of HES data prior to release of data for use in research.[34]

9.8.2 Missing Days' Supply

When the days-of-supply field for a prescription was missing or equal to zero or days' supply could not be calculated from other variables on the prescription record, the days' supply was imputed as the modal days' supply for all prescriptions in the study cohort of the same study drug and strength with nonmissing and nonzero days' supply.

9.9 Statistical Methods

The majority of analyses were conducted using SAS software version 9.3 TS1M2 ([redacted] Stata software version 13.1 ([redacted]) was used for the analysis and graphical displays (proportional Venn diagrams) of concordance of cancer diagnoses across different data sources.

9.9.1 Main Summary Measures

We used mean and SD to describe continuous variables (e.g., age), and number and percentage to describe categorical variables (e.g., age distribution, diagnosis of hypertension). We calculated the crude and age-sex standardized incidence rate (SIR) of cardiovascular and cancer endpoints and IRRs for cardiovascular endpoints. The reference for standardization was the entire follow-up time of the study cohort from cohort entry date to end of follow-up, where end of follow-up was defined by the end of the study period, disenrollment, or death. Age groups (in years) for standardization were 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, and 85 years or older.

For crude incidence rates, we used exact Poisson confidence limits. For SIRs, we used the normal approximation to Poisson rate sums as described in Dobson et al.[35] For crude IRRs (for cardiovascular outcomes only), we constructed confidence intervals (CIs) using the methods described by Sahai and Khurshid.[36] For SIR ratios (cardiovascular outcomes only), we constructed CIs using the normal approximation as described by Newman.[37] For the multivariate-adjusted IRRs (cardiovascular outcomes only), we constructed Wald confidence limits, which make use of the normal distribution. For propensity score–based IRRs (cardiovascular outcomes only), CIs were constructed using a normal approximation as described by Rothman et al.[38]

9.9.2 Main Statistical Methods

9.9.2.1 Drug Utilization Study

Therapy Episodes

Drug therapy episodes were created by concatenating consecutive prescriptions for the same drug into a single continuous episode as long as the gap between consecutive prescriptions was not longer than 60 days. A therapy episode then referred to the period of continuous treatment with a given drug plus 7 days added to the end of the last prescription in the episode. Therapy episodes were created by examining single-drug and multiple-drug use over time, by overlapping and combining therapy episodes. The end of a therapy episode was defined by the end of treatment with a particular drug or a switch to or add-on of another OAB drug.

A switch in OAB therapy occurred when a patient stopped taking a given OAB drug and started taking a different OAB drug in an adjacent therapy episode. A switch could also occur if the patient was taking more than one OAB drug during a therapy episode and then dropped one or more of those drugs while continuing to take the other drug(s). An add-on of OAB drug occurred when the patient started taking another OAB drug while continuing the current OAB therapy.

Descriptive Analysis of Patterns of Drug Use

We first described the overall cohort and the subsets stratified by drug at cohort entry. We showed selected baseline characteristics of the study cohort at cohort entry, including age; sex; year of cohort entry; index of multiple deprivation, a relative measure of several different types of deprivation (e.g., health, education, crime, and access to services such as hospitals) in small geographic areas[39]; risk factors; and comorbidities. We described the distribution of the cohort by drug used at cohort entry for the entire cohort and for the subgroup of patients with de novo use (no use of any OAB drug in the 12 months prior to

cohort entry) and selected baseline characteristics of the study patients stratified by drug used at cohort entry.

Then, to identify the potential differences between patients eligible for linkage to HES and to ONS mortality data, to HES data only, to ONS mortality data only, or to no other data, we showed selected baseline characteristics of patients in each stratum.

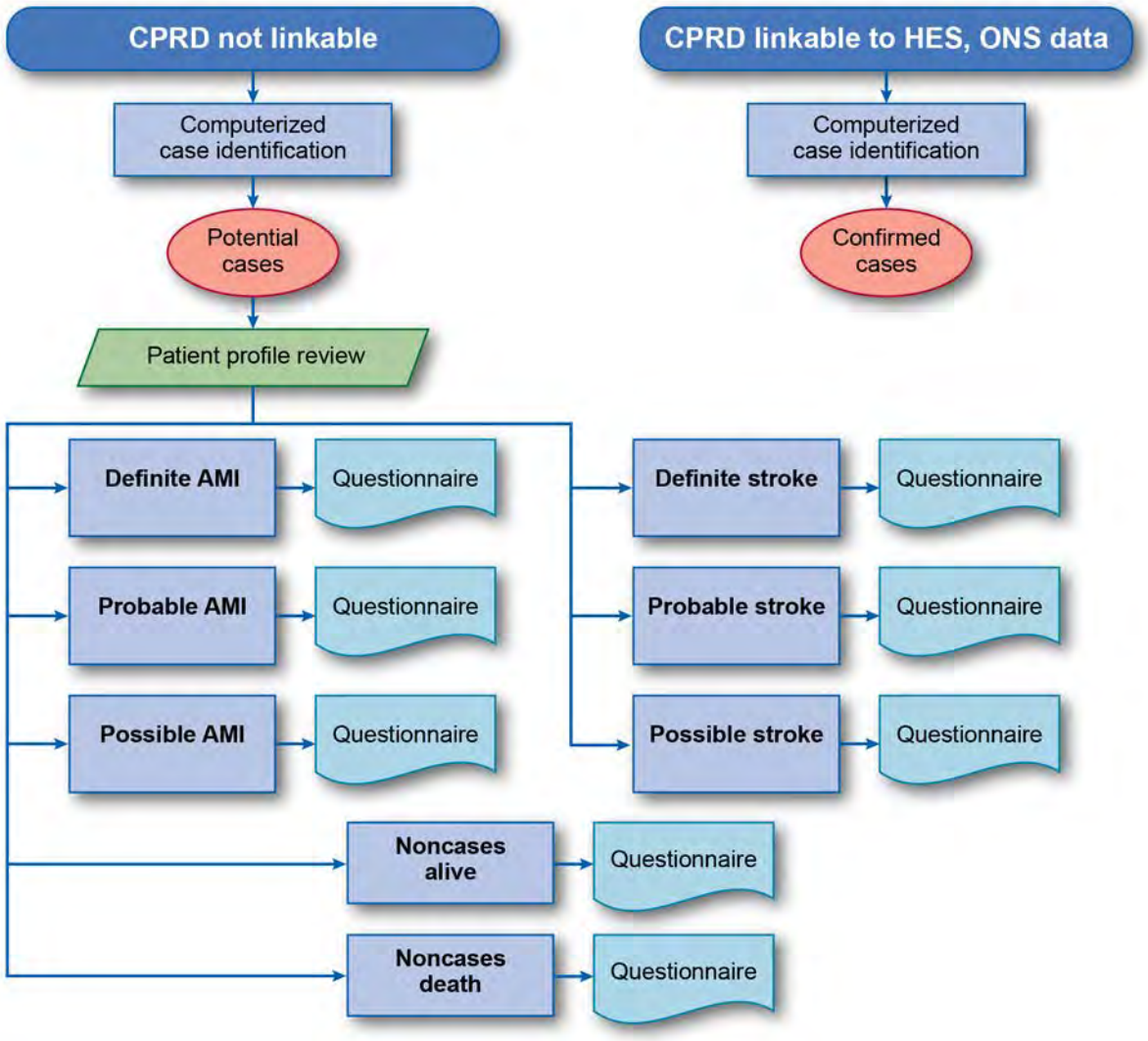
Next, we described the therapy episodes during follow-up. Information provided included the duration of the therapy episode, whether the initial dose was increased or decreased, and the reason why the therapy episode ended (drug add-on, drug switch, or lack of renewal of prescription).

Last, we described the prescriptions for the study drugs in terms of drug, strength, and duration.

9.9.2.2 Validation of Cardiovascular Endpoints

The process for identifying and validating cardiovascular endpoints is outlined in Figure 4 and described in detail in the following sections.

Figure 4. Case Validation Process for Cardiovascular Cases in the CPRD



AMI = acute myocardial infarction; CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; ONS = Office for National Statistics.

In patients from practices for which linkage to ONS mortality and HES data was available, AMI and stroke endpoints were identified from linkage with HES and with ONS mortality data, coded in ICD-10. Death status and cause of death were determined from linkage with ONS mortality data, also coded in ICD-10.

Acute Myocardial Infarction and Stroke Cases

Linkable Practices

For the subset of patients from GP practices linkable to HES data, HES data were used to determine admission and discharge dates and diagnoses of all hospitalizations during the

study observation period. All hospital episodes with a primary discharge diagnosis ICD-10 code for AMI or for stroke (see Appendix A in the statistical analysis plan, amendment 2, for a list of codes) were identified and considered to be confirmed cases. The hospital admission date was the index date. No further step in the ascertainment of AMI or stroke events using HES data was performed.

The PPV for AMI cases ascertained by primary discharge ICD-10 codes in HES has been reported to be 92%, using as a reference the AMI registry based on an international definition of registered cases.[40] HES can miss some nonfatal AMI diagnoses recorded by GPs in the database, but these cases were considered historical diagnoses because the short-term mortality of such cases was much lower than for those also recorded in HES.[40]

The underlying cause of death in ONS mortality data was also used to identify AMI and stroke cases. The same ICD-10 codes that were used to identify hospitalizations with a primary diagnosis of AMI or stroke were used to identify ONS mortality records with AMI or stroke as the underlying cause of death. Having access to ONS mortality data enabled us to capture AMI and stroke events that occurred outside of a hospital or that may have occurred in patients who were not successfully linked to HES data.

Non-linkable Practices

For the patients in practices that were not linkable to HES, AMI and stroke events were identified by using Read codes for diagnoses, test results, hospitalizations, etc. recorded by the GPs.

First, potential cases were identified and preclassified as definite, probable, or possible (in the case of AMI, possible definition 1 or possible definition 2) by a computerized algorithm based on Read codes, in accordance with the operational definitions detailed in the section Operational Definitions for Acute Myocardial Infarction and Stroke Endpoints.

Then, for cases in the validation cohort, we developed "blinded" electronic patient profiles with Read codes, prescriptions (except the study drugs), and anonymized free-text comments written by the GP (see Figure 5) in chronological order. The blinded electronic patient profiles were reviewed manually by a team of clinicians led by a cardiologist to confirm the case index date and classify potential cases based on the clinical elements listed in the section Operational Definitions for Acute Myocardial Infarction and Stroke Endpoints.

Figure 5. Free-Text Data Included in Medical Profiles of Patients With Cardiovascular Endpoints

We requested all free-text comments associated with CPRD GOLD clinical and referral records for 30 days before and after the first probable or possible (definition 1 or 2) acute myocardial infarction or the first probable or possible stroke event that occurred after the validation cohort entry date and, for patients eligible for linkage, after the period for which HES data were available and within 10 days before or after the date of death for deaths of unknown cause.

For AMI events, free text was requested if the Read code on the clinical or referral record corresponded to AMI, hospitalization, chest pain, abnormal cardiac enzymes, abnormal cardiac imaging study, thrombolytic therapy, coronary revascularization, or death.

For stroke events, free text was requested if the Read code on the clinical or referral record corresponded to stroke, hospitalization, abnormal brain imaging study, referral to a neurologist, acute treatment for stroke, thrombolytic treatment for stroke, residual damage from stroke, neurological physiotherapy, or death.

For deaths of unknown cause, free text was requested for all clinical and referral records within 10 days before or after date of death.

Results of the patient profile review were entered into an Excel spreadsheet ("scorecard") designed for the present study, with electronically populated fields for the patient identifier, cohort entry date, and endpoint date and blank fields for the reviewer's decision regarding case status, reviewer-corrected diagnosis date (if applicable), and reviewer comments. Training for the patient profile review consisted of a lecture by the clinical advisor and cardiology specialist [redacted] on details of the endpoints and endpoint definitions and discussion between the clinical advisor and each reviewer of 10 patient profiles of each type of endpoint to which the clinical reviewer was assigned. After the patient profile review, if the reviewer's decision regarding case status was unclear, the reviewer and the clinical advisor discussed the case until a consensus was reached.

Operational Definitions for Acute Myocardial Infarction and Stroke Endpoints

Based on the clinical review of patient profiles and in accordance with the following operational definitions, potential cases were reclassified into definite, probable, possible, or non-cases of AMI or stroke, as described below.

Definite, Probable, and Possible Cases of Acute Myocardial Infarction

A **definite** case of AMI was one for which there was a Read code for AMI with hospitalization and two or more Read codes or key words in free-text comments for the following events within 30 days of the AMI code [14,16]:

- Characteristic chest pain or other equivalent symptoms of myocardial ischemia[§]
- Abnormal results for cardiac enzyme(s)—e.g., CPK (creatine phosphokinase) and troponin
- Electrocardiogram with clinical signs of AMI
- Arteriogram with a recent coronary occlusion
- Administration of thrombolytic therapy
- Coronary revascularization procedure following AMI diagnosis
- Death

A **probable** case was one with an AMI code with hospitalization and/or one item in the list above within 30 days of the AMI code.

A **possible** case was one with an AMI code but no code for any of the items above (definition 1) or a case with any of the items above (except hospitalization and death) but no AMI code (definition 2). Events classified as possible AMI definition 2 cases were subsequently excluded if they were identified using only a chest pain code, if a non-coronary cause of chest pain was found within 30 days of that code and if none of the codes that were also used to identify possible AMI definition 2 cases (i.e., abnormal cardiac enzymes, abnormal cardiac imaging study, thrombolytic therapy, or coronary revascularization) were found within 30 days of the code for chest pain.

[§] Possible ischemic symptoms include various combinations of chest, upper extremity, mandibular, or epigastric discomfort (with exertion or at rest) or an ischemic equivalent such as dyspnea or fatigue. The discomfort associated with an AMI usually lasts approximately 20 minutes. Often, the discomfort is diffuse—not localized, positional, or affected by movement of the region—and it may be accompanied by diaphoresis, nausea, or syncope. However, these symptoms are not specific for myocardial ischemia. AMI may occur with atypical symptoms—such as palpitations or cardiac arrest.

Definite, Probable, and Possible Cases of Stroke

A **definite** case of stroke was one for which there was a Read code for stroke (not including transient ischemic attack) and two or more codes or key words in free-text comments for the following events (within 30 days before or after the stroke code):

- Diagnostic procedure with abnormal results (e.g., abnormal magnetic resonance imaging of brain)
- Hospitalization or referral to a neurologist
- Acute treatment: thrombolytic therapy or aspirin (ischemic stroke); embolization, clips, or other aneurysm treatments (subarachnoid hemorrhage and hemorrhagic stroke)
- Residual damage (e.g., hemiplegia, vascular dementia, aphasia, dysphagia)
- Physiotherapy (e.g., neurological physiotherapy)
- Death

A **probable** case was one with a stroke code and one of items in the listed above within 30 days before or after the stroke code.

A **possible** case was one with a stroke code and none of the items listed above.

Out-Of-Hospital Cases of Coronary Heart Disease Death

Linkable Practices

As previously described, the IDs of study cohort patients with data from linkable practices were linked with death certificate information from the ONS file to identify all deaths occurring during the observation period of the cohort. The result of the linkage was a data set containing patient ID, practice, date of death, place of death, underlying cause of death (ICD-10 code), and all other causes of death listed on the death certificate. Dates of death in this file were checked against the dates of the study observation period to ensure that the deaths occurred during the study follow-up period. Identified deaths with codes for CHD (see Appendix A in the statistical analysis plan, amendment 2, for a list of ICD-10 codes) recorded as an underlying cause of death in the ONS file and not linked to a hospitalization were considered to be confirmed out-of-hospital CHD deaths. All identified hospitalization episodes for AMI were linked with ONS mortality data to ascertain fatal AMI events. Any death occurring within 30 days after the hospital admission date for a hospitalization with a primary discharge diagnosis of AMI was considered a fatal AMI case.

Non-linkable Practices

For practices not linkable to ONS mortality data and (for patients eligible for linkage to ONS mortality data) for the period after availability of ONS mortality data, deaths during the study period were identified using the date of death provided by the CPRD in the patient data set. The CPRD assigned the value for date of death by screening the electronic medical records for Read codes indicating death, using date of death recorded in the death administration structured data area of CPRD GOLD, and identifying patients who transferred out of the practice because of death. In the validation sample, for those deaths with CHD recorded as the cause of death by the GP and for those without recorded cause of death, the electronic patient profiles (including free-text information and blinded to the OAB drug prescriptions) were generated and reviewed manually by a clinician to ascertain the potential cause of death. In the patient profile review, they were classified as (1) CHD death, (2) cardiovascular disease death, (3) other known cause of death, or (4) unknown. CHD cases were categorized as in-hospital fatal AMI or out-of-hospital CHD death. Out-of-hospital CHD deaths were classified as AMI, CHD other than AMI, or death of unknown cause with recent history of CHD.

In the GP questionnaire for the validation of AMI, we included specific questions for deaths and requested that GPs provide copies of postmortem reports, if an autopsy was performed, and copies of death certificates, if available.

We considered a patient to have died from CHD when there was (1) postmortem evidence of recent AMI, (2) a recent coronary artery occlusion or antemortem evidence of CHD in the absence of another cause of death, or (3) CHD recorded as the underlying cause of death.

All cases of hospitalized AMI identified in the non-linkable practices with a code for death from any cause recorded by the GP within 30 days after the index date of the AMI were considered fatal AMI cases. Out-of-hospital CHD deaths were included with the evaluation of the AMI endpoint, and the index date for these cases was the date of death. For cases of diagnosed AMI, either fatal or not, the index date was the date of diagnosis or hospital admission for AMI.

Validation of Cardiovascular Endpoints via Questionnaires

The validation process for events in patients registered with non-linkable practices consisted of three steps (Figure 4). In non-linkable practices, after the process of case identification and validation via electronic and manual review of electronic profiles described above, we sent a questionnaire to the GP for each randomly selected case (see selection process below) to collect information to confirm the occurrence of the event. Positive or negative

predictive values (PPVs or NPVs), as appropriate, were calculated based on the responses in the questionnaires.

For definite and probable cases and non-cases (non-AMI, non-stroke events), the objective of the validation was to confirm that the algorithms were appropriately designed. In each of these categories, 150 patients plus an additional 20% (185 in total) were randomly identified, and the classification obtained using the algorithm was compared with the classification obtained using the patient profile and GP questionnaire review. For possible cases, the objective of the validation was to assess whether validation through GP questionnaires is needed for all patients in this category for each endpoint. Patients in this category were sampled for validation. The initial electronic classification of the cases was compared with the final classification obtained after the patient profile and GP questionnaire review.

The validation process was achieved by asking the patients' GPs to review medical records and charts and complete an endpoint-specific questionnaire. There were specific questionnaires for AMI, stroke, non-case alive (patients who did not develop AMI or stroke and were alive at the end of the study period), and non-case dead (patients who did not develop AMI or stroke and had died by the end of the study period).

For analysis purposes, all probable, possible (definition 1), or definite cases were considered to be true cases if the PPV was at least 80%. Similarly, all non-cases were considered to be true non-cases if the NPV was at least 80%.

Since establishment of the CPRD (and its predecessors, the GPRD and Value Added Medical Practice), some practices have either left the CPRD or do not participate in surveys. Patients who belong to these practices were not included in the validation process.

Statistical Analysis for Cardiovascular Endpoint Validation

The response rate for the questionnaires was calculated as the number of questionnaires with valid responses received divided by the number of questionnaires sent.

Two sets of PPVs were calculated. In the first set, the PPV was calculated as the number of cases confirmed with the questionnaires, divided by the number of questionnaires that were returned to us, times 100 (to convert to a percentage), separately for AMI and stroke and for each category of definite, probable, and possible case. For the first set of PPVs, calculations were based on the electronic algorithm classification of cases (e.g., definite, probable, and possible AMI cases per the electronic algorithm). For the second set, calculations were based on the case classification after the patient profile review.

NPVs for non-case alive and non-case dead (individuals who did not have AMI or stroke and were alive or dead, respectively, at the end follow-up) were estimated as the number of

confirmed non-cases, divided by the total number of questionnaires returned in each category, times 100. NPVs were calculated only for the electronic-algorithm case classification.

For out-of-hospital CHD deaths, we reported counts and percentages from the profile-review reclassification of the potential cases of out-of-hospital CHD death assigned by the electronic algorithm to each subcategory (AMI, CHD other than AMI, or unknown cause of death with recent history of CHD).

In all cases, 95% confidence intervals were constructed using exact binomial methods.

9.9.2.3 Validation of Cancer Endpoints

The validation of cancer endpoints was conducted in the validation cohort.

Cancer endpoints were identified based on the presence of diagnostic codes in patients' electronic medical records, including CPRD GOLD, HES, and NCDR data as available, within the validation cohort. We did not include morphology or treatment Read codes in this screening step, because morphology and treatment codes are often not specific to cancer type (i.e., we would not be able to identify which type of cancer was diagnosed or treated) and because we wanted to be able to use morphology and treatment information as part of the case confirmation process when possible. See Section 9.2 for details of linkage among data sources and Section 9.2.2 for steps in the creation of the validation cohort.

Screening and validation methods available for each patient in the validation cohort depended on whether the individual's GOLD data were linked to other data sources within the UK National Health Service system. Because the end of data collection in GOLD data was later than in HES and the NCDR (due to data availability and time lag), the later periods of person-time from patients enrolled in linked practices includes information from GOLD data only. In other words, linked person-time in patients enrolled in linked practices was followed, after the end of data collection in HES and the NCDR, by some additional non-linked person-time.

Screening method 1 and type 1 provisional cases. Cancer events identified in GOLD data by the presence of diagnostic Read codes (method referred to as screening method 1 [SCR-1]) were considered type 1 provisional cases (PROV-1).

Validation method 1 and type 1 confirmed cases. All patients with a PROV-1 case had their electronic patient profiles reviewed by a clinical reviewer, including a specialist in hematology/oncology (validation method 1 [VAL-1]). Profiles incorporated patients' entire history of Read codes (including clinical diagnoses, surgical procedures, radiation therapy, and morphology codes), relevant additional clinical information (e.g., prostate-specific antigen levels, mammograms, magnetic resonance images), and prescriptions, except those

for the study OAB drugs. Our clinical oncology experience, prior experience with CPRD data, knowledge of a Quality and Outcomes Framework indicator for review of cancer patients' care,[41,42] and impressions from a pilot review of medical profiles enabled us to create a computer-based algorithm to identify a subgroup of provisional cancer cases for which free-text comments were not expected to be required to clarify the diagnosis (criteria are provided in Table 2). The medical profiles thus identified were reviewed without free-text comments (n = 1,081).

Table 2. Criteria to Select Cancer Cases When Free-Text Comments Were Not Expected to Provide Information Beyond the Information Identified by Codes

Criteria
If the first occurrence of the Read code for "cancer care review" (8BAV.00) appears on any subsequent record after the initial cancer date and no other cancer code other than a Read code for the initial type of cancer has occurred in the interim
If the initial cancer code is followed by two or more codes with Read term "Seen in oncology clinic" (9N1y800, 9N09.00) on different dates, and no other cancer code other than a Read code for the initial type of cancer has occurred in the interim, and no cancer care review code occurs on or before the date of the initial cancer
If the index cancer is breast cancer, there are no Read codes for other types of cancer in the patient's records, no cancer care review code occurs on or before the date of the initial cancer, and the patient record includes one or more entries for prescriptions of common hormonal treatments after the index cancer code (i.e., any of the following terms show up anywhere in either the Product Name or Drug Substance Name fields: aminoglutethimide, anastrozole, formestane, fulvestrant, goserelin, letrozole, tamoxifen, toremifene)
If the index cancer is prostate cancer, there are no Read codes for other types of cancer in the patient's records, no cancer care review code occurs on or before the date of the initial cancer, and the patient record includes one or more entries for prescriptions of common hormonal treatments after the index cancer code (i.e., any of the following terms show up anywhere in either the Product Name or Drug Substance Name fields: aminoglutethimide, abiraterone, bicalutamide, enzalutamide, flutamide, goserelin, leuprorelin, nilutamide)

For the remaining cancer cases, selected free-text comments (see Figure 6) were included in the medical profiles for review (405 medical profiles with free-text comments were reviewed).

Figure 6. Free-Text Data Included in Medical Profile of Patients With Cancer

- We requested up to five free-text comments from clinical and referral records within 1 year following the initial cancer date.
- Priority was first given to any events with a Read code for the initial cancer, in chronological order. If this resulted in fewer than five free-text comments being identified, then free text on additional records without Read codes for the initial cancer was selected in chronological order starting with the index date.
- If the patient had a second cancer at any point subsequent to the first cancer, we requested up to five additional free-text comments within 1 year on or following this second cancer code, using the same process to prioritize the free text around the time of the second cancer as was used around the initial cancer.
- Additionally, free text was requested on the first five records with a Read code for cancer care review and for all records with a code related to death.

PROV-1 cases were considered confirmed (type 1 confirmed cases [CONF-1]) when there was supportive evidence of a cancer diagnosis, in particular, a relevant pathology (morphology) Read code, evidence of appropriate cancer-specific therapy (surgery, radiation therapy, chemotherapy, hormonal therapy, or other targeted or biological therapy) within the period from 1 month before to 3 months after the first recorded clinical diagnostic code for the endpoint malignancy, or evidence of cancer care review by the GP. Only surgical procedures that would be used to treat cancer were considered confirmatory. For example, mastectomy was considered sufficient evidence of a diagnosis of breast cancer, but excisional biopsy (lumpectomy) was not be considered sufficient because it can be used as a diagnostic procedure or for treatment (that is, some excisional biopsy specimens show no evidence of malignancy). PROV-1 cases were also considered confirmed if subsequent clinical events (referrals, hospitalizations, or death) were associated with clinical Read codes appropriate to the cancer diagnosis. PROV-1 cases were also considered confirmed if there was an entry in the patient's electronic medical record following the first diagnostic cancer code indicating that the patient's cancer care was reviewed by the GP.[41,42] If definitive information was found indicating a provisional case did not have a diagnosis of cancer, the patient was considered a non-case. Also, when there was evidence in the medical profile that a provisional case had had cancer diagnosed prior to cohort entry, the patient was considered a non-case and his or her person-time was excluded from the study. Cases not confirmed remained provisional (PROV-1).

Each medical profile was reviewed by one physician ([redacted]), and results were entered into an Excel spreadsheet ("scorecard") designed for the present study. The scorecard included electronically populated fields for the patient identifier, cohort entry date, type of index cancer (e.g., breast) and index cancer diagnosis date, and blank fields for the reviewer's decision regarding case status (with a pull-down menu for CONF-1,

PROV-1, and non-case), reviewer-corrected type of cancer (if applicable), reviewer-corrected cancer diagnosis date (if applicable), and reviewer comments (if any). Reviewers corrected the date of diagnosis when there was clear indication that the cancer had been diagnosed before the code-based cancer diagnosis date and used clinical judgment, based on the information recorded in each provisional case's GOLD data, to determine the cancer type if there was any ambiguity.

To enhance consistency in evaluating provisional cases during the general review process, all three reviewers initially examined sets of randomly selected profiles—30 profiles without free-text comments and 20 with free-text comments (total of 50 profiles, each of which was reviewed by all three reviewers). The reviewers then discussed their validation criteria for agreement and education. During the subsequent general review process, provisional cases for which status was not clear were additionally discussed by two of the three physicians, always including the clinical advisor and oncology specialist ([redacted]), until reaching consensus. After all reviews were completed, data recorded in the scorecards were imported into SAS and incorporated into the analytical file.

Screening method 2 and type 2 and 3 confirmed cases. In the study by Boggon et al., approximately 6% of cases identified in the NCDR were not found in the CPRD.[21] Because of this finding, the NCDR was screened to find additional cases and also, when possible, to confirm cases that remained provisional after review of GOLD data or to provide supportive information for cases already confirmed in GOLD data alone. Cases identified in the NCDR (referred to as CONF-2 if they had no Read codes for cancer in GOLD data or CONF-3 if they did) were automatically considered confirmed because cancer registries perform their own independent case validation using standardized procedures including review of pathology information.[43]

Screening method 3 and type 4 confirmed cases. HES data were also used to identify additional cases (SCR-3) and to confirm or to provide supportive information about cases found in other sources. Cases with confirmatory data in the HES but not in the NCDR were designated type 4 confirmed cases (CONF-4). Since hospital discharge data are independently audited, all cases identified in HES data were considered to be confirmed.

Where there was any discrepancy between the cancer type among data sources (GOLD, NCDR, and HES) or there appeared to be uterine cancers after hysterectomy, data were reviewed by the clinical advisor ([redacted]) to determine cancer type. For cancer cases that appeared in more than one data source, the date of diagnosis was assigned as the earliest date the cancer was diagnosed in any of the sources.

Non-linked Practices

For patients from non-linked practices who were not in the validation cohort, the identification of cancers consisted of SCR-1; therefore, provisional cases identified in these practices could only be assigned a status of provisional case (PROV-1) or non-case.

In the validation cohort, the validation process for cases from non-linked practices consisted of SCR-1 followed by physician review of GOLD data; therefore, provisional cases identified in these practices could only be assigned a final status of confirmed (CONF-1), non-case, or provisional case (PROV-1).

Linked Practices

In linked practices, we applied the three screening methods to identify as many valid cases as possible. This was done in two stages: In the first stage, only the procedures in common with those used in the non-linked practices were employed (SCR-1 and physician review of GOLD data); in the second stage, additional information from the NCDR and HES were also considered in assigning final case status. These additional data sources could (1) contribute additional cases that had not previously been identified in GOLD data, (2) confirm cases that remained provisional after review of GOLD data, or (3) provide supportive information about cases already confirmed in other data sources.

To explore further the value of using several data sources to identify and validate cancer cases in this study, we examined whether each case newly identified in one of the data sources using the process described above could also be found in each of the other two data sources. The results of this analysis are presented in a series of Venn diagrams showing the numbers of cases identified in each data source and combination of data sources, overall and separately by cancer type (see Annex 6).

We did not calculate PPVs or NPVs because there is no single reference ("gold standard") data source against which to estimate the performance of the screening method applied to the GOLD data. In other words, all three data sources (GOLD, NCDR, and HES) could contribute validated (confirmed) cases to the analysis, and an individual confirmed case might be found in one, two, or all three of the data sources.

However, under the assumption that diagnoses of cancer in GOLD data in non-linked practices have approximately the same validity as in linked practices, the procedures we used will enable estimation of the extent to which cancer case finding in the study cohort is likely to be incomplete in the non-linked practices.

9.9.2.4 Covariate Validation via Questionnaire

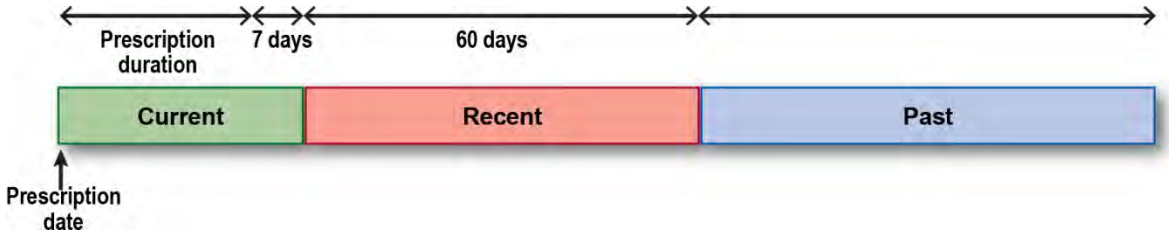
For three of the covariates—smoking, obesity (defined as body mass index ≥ 30 kg/m^2), and menopause—questions were included in the validation questionnaires sent to GPs to confirm the information obtained from the CPRD GOLD medical records. As questionnaires focused on the dates around the occurrence of cardiovascular endpoints, GPs reported the status of the patient with respect to the covariate at that time. Questionnaire data on these three covariates were compared with the latest available values for these covariates before the cohort entry date, before the endpoint date, and on the closest day before and after the endpoint date. PPVs or NPVs, as appropriate, were calculated based on the responses in the questionnaires.

9.9.2.5 Study of Cardiovascular Disease Incidence in Users of Antimuscarinics to Treat Overactive Bladder

Time at Risk and Exposure Classification

We assumed that possible cardiovascular effects of OAB drugs would present shortly after first exposure, continue during current exposure, and decline shortly after the medication is discontinued. We therefore defined three exposure categories. Figure 7 shows how current exposure to each individual drug began on the prescription issue date and continues through the days of supply plus 7 days. The 7 days are added to account for (1) the possibility that patients may forget doses and be exposed to the dispensed drug for a few days beyond the days of supply noted in the prescription and (2) delays between the prescription issuing, dispensing, and start of use. Recent exposure started the day after the period of current exposure ended and continued for 60 days, until a new episode of current exposure began or until the end of follow-up, whichever came first. Past exposure began the day after the period of recent exposure ended and ended in the same circumstances. Patients could contribute person-time to multiple drug-exposure categories (e.g., recent exposure to oxybutynin and current exposure to tolterodine).

Figure 7. Exposure Classification for Cardiovascular Endpoints



Outcome Ascertainment

In the linked practices, the analyses were performed with the first confirmed case of each outcome type (AMI or stroke) found for each patient. HES data were used to determine admission and discharge dates and diagnoses of all hospitalizations during the study observation period. All hospital episodes with a primary discharge diagnosis ICD-10 code for AMI or for stroke were identified and considered as confirmed cases. The hospital admission date is the index date. ONS death certificate data were used to identify all deaths occurring during the observation period among study patients for whom the linkage was available. The result of the linkage was a data set containing patient ID, practice, date of death, place of death, underlying cause of death (ICD-10 code), and all other causes of death listed on the death certificate. Dates of death in this file were checked against the dates of the study observation period to ensure that the deaths occurred during the study follow-up period. The underlying cause of death in ONS mortality data was also used to identify confirmed cases of AMI or stroke.

In non-linked practices and in linked practices after the end of HES data availability (i.e., after March 31, 2012), we included in the analysis all AMI and stroke events confirmed through the GP questionnaires.

For those events that were not evaluated through GP questionnaire, but were included in the patient profile review, we used the decision made by the clinical reviewer to determine whether or not an AMI or stroke event was a case. For AMI and stroke events that were not confirmed with a questionnaire or by profile review, we considered all AMI definite, probable, and possible definition 1 events and all stroke events (updated definition for definite, probable, and possible) to be cases.

For non-linked patients, the first case of each outcome type (AMI or stroke) found during the study period was used in the analyses. Among linked patients who did not have a confirmed case identified in HES data and whose study follow-up time extended past the end of HES data availability, we used the first case found during study follow-up after the end of HES data availability.

Statistical Analysis

Tables with results of analyses are located in Annex 8 and tables with the results of the cardiovascular study are identified as Table CV1, Table CV2, etc.

Descriptive Analysis

Baseline characteristics of the study cohort at the time of cohort entry are presented in Annex 8, Table CV1.

Incidence Rates

For each endpoint, person-years, event count, and crude and age-sex SIRs and 95% CIs were reported. Results are presented for all study drugs combined and for each drug. Further stratification includes strata for patients aged 65 years or older, those with increased cardiovascular risk, and for females and males. In Annex 8, Table CV2 displays results for current exposure. In Annex 8, Table CV3 shows crude and age-sex SIRs and 95% CIs stratified by number of prescriptions, cumulative exposure duration, and other exposure details. In Annex 8, Table CV4 provides information similar to that in Table CV2 for recent exposure. For crude incidence rates, we used exact Poisson confidence limits. For SIRs, we used a normal approximation to Poisson rate sums as described by Dobson et al.[35]

Incidence Rate Ratios

For crude IRRs (for cardiovascular outcomes only), we constructed CIs based on a Poisson model method described by Sahai and Khurshid.[36] For SIR ratios (cardiovascular outcomes only), we constructed CIs using the normal approximation as described by Newman.[37]

For multivariate-adjusted incidence rates (cardiovascular outcomes only), Cox regression models were used to estimate adjusted IRRs and the corresponding 95% Wald confidence limits. For each outcome, we started with a base model that included covariates for a patient's age (continuous variable) and sex, and time-varying covariates for current and recent exposure for each of the study OAB drugs. A model selection process was then performed to evaluate inclusion of the following covariates using the change-in-estimate approach[44]:

- Smoking, alcohol use, drug abuse, index of multiple deprivation quintiles (at time of cohort entry)
- Body mass index (< 20, 20 to < 25, 25 to < 30, 30 to < 40, 40+) (at time of cohort entry)
- Components of the Charlson Comorbidity Index (at time of cohort entry)
- Menopause (time-varying)
- Ever used selected medications (cardiovascular drugs, tamoxifen, letrozole, hormone replacement therapy, thyroid hormone replacement therapy, and immunosuppressive agents) (time-varying)

Covariates that changed the hazard ratio of current exposure to oxybutynin (relative to current exposure to tolterodine) or current exposure to solifenacin (relative to current exposure to tolterodine) by at least 5% (minimum absolute change 0.005) were retained in the final model for each outcome.[44]

The multivariate-adjusted IRRs were then calculated using the appropriate linear combination of model estimates to compare the current or recent use of each study drug against the current exposure to tolterodine, current exposure to other OAB drugs, and no use or past use of any OAB (Annex 8, Table CV6).

Stratified Analyses

Stratified analyses presented in this report included stratification by sex, age less than 65 years versus 65 or more years, and risk factors for cardiovascular disease.

The next section provides details of the stratified analysis component used in the propensity scores analysis.

Propensity Scores

We used logistic regression to estimate the probability of exposure to each of the study drugs in head-to-head comparisons against either tolterodine or against any of the five other OAB drugs, at cohort entry.[45] A priori, the plan was to include in the propensity score model the variables identified as potential confounders in multivariable regression analysis[46]; age and sex would be included even if not selected for the multivariable analysis. Since no variables were identified as potential confounders through the model selection process in the multivariable regression analysis, we decided to include all potential confounders as reported at the time of cohort entry, along with an additional variable to account for the year of cohort entry.

For each head-to-head comparison we performed the following analyses (for simplicity we will focus this description on the single comparison of oxybutynin users against tolterodine users). Using the subset of patients who qualified for cohort entry with a single exposure to either oxybutynin or tolterodine, the logistic model estimated the propensity score as the probability for each patient to receive oxybutynin at the time of cohort entry. Trimming was then performed, which removed patients who had a propensity score (i.e., probability of receiving oxybutynin) below the first percentile identified among the oxybutynin users. Then patients who had a propensity score above the 99th percentile based on the distribution of scores from the tolterodine users were also removed. After this trimming was performed, the resulting propensity score deciles were calculated using the distribution of propensity scores among the oxybutynin users. Oxybutynin and tolterodine users were then grouped into these deciles, and the stratified IRR comparing oxybutynin against tolterodine was calculated in the subset of patients who remained after trimming using the Mantel-Haenszel approach.[38]

These methods were then repeated to compare the four remaining OAB drugs of interest individually against tolterodine. Outside of the individual drug comparisons, we repeated

these analyses to examine each individual drug against the other five OAB drugs combined. Due to the low number of patients who qualified for cohort entry with single exposure to either darifenacin or fesoterodine, we were unable to perform the propensity score analyses for comparisons where these drugs were examined individually.

9.9.2.6 Study of Cancer Incidence in Users of Antimuscarinics to Treat Overactive Bladder

Time at Risk and Exposure Classification

For the analysis of cancer outcomes, we have assumed that the effects of OAB drugs on the incidence of cancers, if any, may continue for a long time after the medication is discontinued, as has been demonstrated for many well-known carcinogens and cancer-promoting substances (e.g., cigarette smoke, radiation, alkylating agents, estrogens). Moreover, we have assumed that stochastic transforming events at a cellular level are likely to be related to accumulated exposure, as again has been observed with carcinogens (e.g., pack-years of smoking or cumulative radiation exposure). Time at risk for each individual drug is considered to start with the first prescription for the drug at or after cohort entry and continues accruing until the end of follow-up. Patients could contribute person-time of exposure to more than one drug simultaneously. How much cumulative exposure to a given drug a patient has experienced by the time a cancer endpoint occurs is of primary interest in the cancer analyses (rather than only whether exposure to a given drug is current or not).

Outcome Ascertainment

The main analyses (see "Analysis 5" in the following section, "Statistical Analysis") were performed with confirmed cases in the linked practices and cases that were identified through electronic searches for diagnostic Read codes (SCR-1) in non-linked practices. More specifically, after exclusion of patients from the study cohort who had cancer diagnoses in either GOLD, HES, or NCDR data (and therefore could not become cases in the study), the following cases were included in the main cancer rates analyses:

- In **non-linked practices**, we included all cases identified through screening of Read codes in GOLD data.
- In **linked practices**, from patients ***in the validation cohort,*** *w*e included all cases initially identified through screening of Read codes in GOLD data that were confirmed by profile review, NCDR data, or HES data. This left the following cases initially identified through screening to not be counted as cases:
  - A total of 12 patients not confirmed to be cancer cases by profile review or by NCDR or HES data

  - One patient found by profile review not to have cancer
  - A total of 36 patients found on profile review to have had cancer before their cohort entry date

- Also, in **linked practices,** from patients ***in the validation cohort,*** we included all cases initially identified in NCDR or HES data that were not found in GOLD data.
- In **linked practices,** from patients ***NOT in the validation cohort*** (for which no profiles were reviewed), we included all cases initially identified through screening of Read codes in GOLD data (including 267 not confirmed in NCDR or HES data). We also included all cases identified in NCDR or HES data that were not found in GOLD data.

Statistical Analysis

Tables of results may be found in Annex 8, in which tables with results for cancer are named Table N1, etc.

We present counts of events, person-time, and incidence rates with 95% CIs for the composite endpoints and individual cancers for ever-exposure to individual drugs or to any drug. We also present results stratified by sex and, for some results, age (< 65 years vs. ≥ 65 years). Results include crude and age-sex SIRs (Annex 8, Tables N3). We also present results from periods of exposure to a single OAB drug (Annex 8, Tables N4). In Annex 8, Tables N5 show sex-specific incidence rates for the composite cancer endpoints in relation to several other measures of exposure to the study OAB drugs (maximum daily dose, cumulative dose, number of prescriptions, cumulative duration of use, and time since first exposure).

Per the statistical analysis plan, five groups of cases ("analyses" or case "definitions") were evaluated. The first three of these analyses were done within the validation cohort.

The first two analyses were intended to provide an estimate of the extent to which cases detected only by screening GP medical records (GOLD data) for diagnostic Read codes for the study cancers would be confirmed by expert review of individual GP medical records ("profile review"):

- Endpoint analysis 1 included all CONF-1 cases (those confirmed by profile review) from linked and non-linked practices.
- Endpoint analysis 2 used all screen-detected cases (method SCR-1) (initially designated as "provisional" or "PROV-1") from linked and non-linked practices.
- Endpoint analyses 1 and 2 were done on cancer events for both sexes combined.

In analysis 2, we ignored the results of the review of patient profiles. (Note that the order of these two analyses may appear logically reversed in the sense that the second analysis uses less available information than the first.)

By comparing the results of analyses 1 and 2, we would have an indication as to whether the reliability of screen-detected cases is similar in linked and non-linked practices. If most cases initially designated PROV-1 were subsequently confirmed as CONF-1 cases, the results of these two analyses would be similar, and analysis of cases detected by SCR-1 should be as reliable as analysis of cases confirmed by profile review. However, if a large proportion of PROV-1 cases could not be confirmed, endpoint analysis 1, which was restricted to CONF-1 cases, may have been less affected by potential case misclassification than endpoint analysis 2, which included both the confirmed (CONF-1) cases and additional cases that remained provisional (PROV-1) cases. (However, endpoint analysis 1 would likely yield less precise effect estimates than endpoint analysis 2 due to the smaller number of cases included.)

Endpoint analysis 3 started with information on cases in the linked practices in the validation cohort that was determined only from review of GP medical records (GOLD data). This analysis then used the number of final confirmed cases in the linked practices in the validation cohort to determine the additional number and proportion of cases that were identified in other linked data sources (NCDR data and HES). This "additional proportion" of cases found in data sources other than GOLD data (calculated from information in linked practices) was then used to project the "total" number of cases that might be available in non-linked practices (within the validation cohort) if sources of information comparable to the NCDR and HES databases had been available for the non-linked practices. This provided an estimate of how many cases may have been "missing" from the non-linked practices (within the validation cohort) due to the absence of NCDR and HES data:

- Among the linked practices, the difference between the initial number of CONF-1 cases and the final number of CONF-1, CONF-2, CONF-3, and CONF-4 cases combined was used to estimate the additional number of cases that could be expected in the non-linked practices if NCDR and HES data had been available for these practices. In endpoint analysis 3, the CONF-1 case number from the non-linked practices was adjusted (multiplied by a scalar obtained in the validation process) to account for the additional expected cases in the non-linked practices (if NCDR and HES data were available). The results of this analysis are presented in the subsection Estimation of Number of "Missing" Cases in Non-linked Practices in Validation Cohort (Analysis 3 in the statistical analysis plan) in Section 10.4.2.2.

Endpoint analyses 4 and 5 were intended to be done if a substantial discrepancy was found between the number of confirmed cases and the total number of cases (including both the

confirmed cases and those that remained provisional) in the validation cohort. Endpoint analysis 4 was planned to include all types of cases (all confirmed cases plus all cases that remained provisional), and endpoint analysis 5 was to include only confirmed cases and was to be the main analysis. However, since very few cases remained provisional in the validation cohort (and therefore it was expected that most provisional cases in the rest of the full study cohort were likely valid cancer cases), analysis 5 included all confirmed cases and provisional cases except for cases that remained provisional in linked practices in the validation cohort (which lacked confirmation from any of the three confirmatory data sources—GOLD profile review, NCDR, and HES—and were therefore questionable). In this report, we have emphasized incidence rates for analysis 5, which is considered the main analysis.

9.9.3 Missing Values

Handling of missing data for prescriptions is described in Section 9.8, Data Transformation.

9.9.4 Sensitivity Analyses

Sensitivity analyses for each part of the study (i.e., drug utilization study, validation of endpoints) are described in the appropriate subsection.

9.9.5 Amendments to the Statistical Analysis Plan

The amendments are summarized in Table 3.

Table 3. Summary of Amendments and Updates

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
SAP, Amendment 2	January 21, 2015	▪ Section 2, Research Strategy and Design ▪ Section 4, Endpoints ▪ Section 6, Statistical Analysis	Refinement of definition of cancer endpoints and end of follow-up. Inclusion of and specifications for additional analyses. IRR for cardiovascular outcomes for OAB drug use compared with non-use and with use of other OAB drugs. Definition of increased cardiovascular risk.	Clarify that only occurrence of the first study cancer is considered as the endpoint; occurrence of any cancer determines end of follow-up, and a patient can experience first a cardiovascular endpoint and then a cancer endpoint. Align with US Optum research database analysis.
SAP, Amendment 1	April 23, 2014	▪ Section 2, Research Strategy and Design ▪ Section 3, Exposure Classification ▪ Section 4, Endpoints ▪ Section 6, Statistical Analysis	Description of the validation process and analyses in the validation cohort (sample of the initial cohort).	Reflect revised validation process and analyses after the decision to conduct validation in a sample of the cohort instead of the full cohort.
SAP	December 16, 2013	This was the original SAP		

IRR = incidence rate ratio; OAB = overactive bladder; SAP = statistical analysis plan.

9.10 Quality Control

Quality control of the data management and analysis activities of this study were performed according to RTI-HS standard operating procedures. Programming written by one study analyst was independently reviewed by a different analyst, with oversight by a senior statistician.

Analysis data sets and program output were checked for accuracy and integrity according to standard operating procedures that include the following steps:

- Checking program logs for errors and warnings

- Checking output for errors and inconsistencies
- Running quality-control programs to verify that specifications were implemented correctly and that any output generated accurately reflects the data
- Manually reviewing output for a sample of study patients to verify the classification of observed person-time and the assignment of cases
- Checking all results tables for accuracy

10 RESULTS

Tables presenting results of the analyses are located in Annex 8.

10.1 Participants

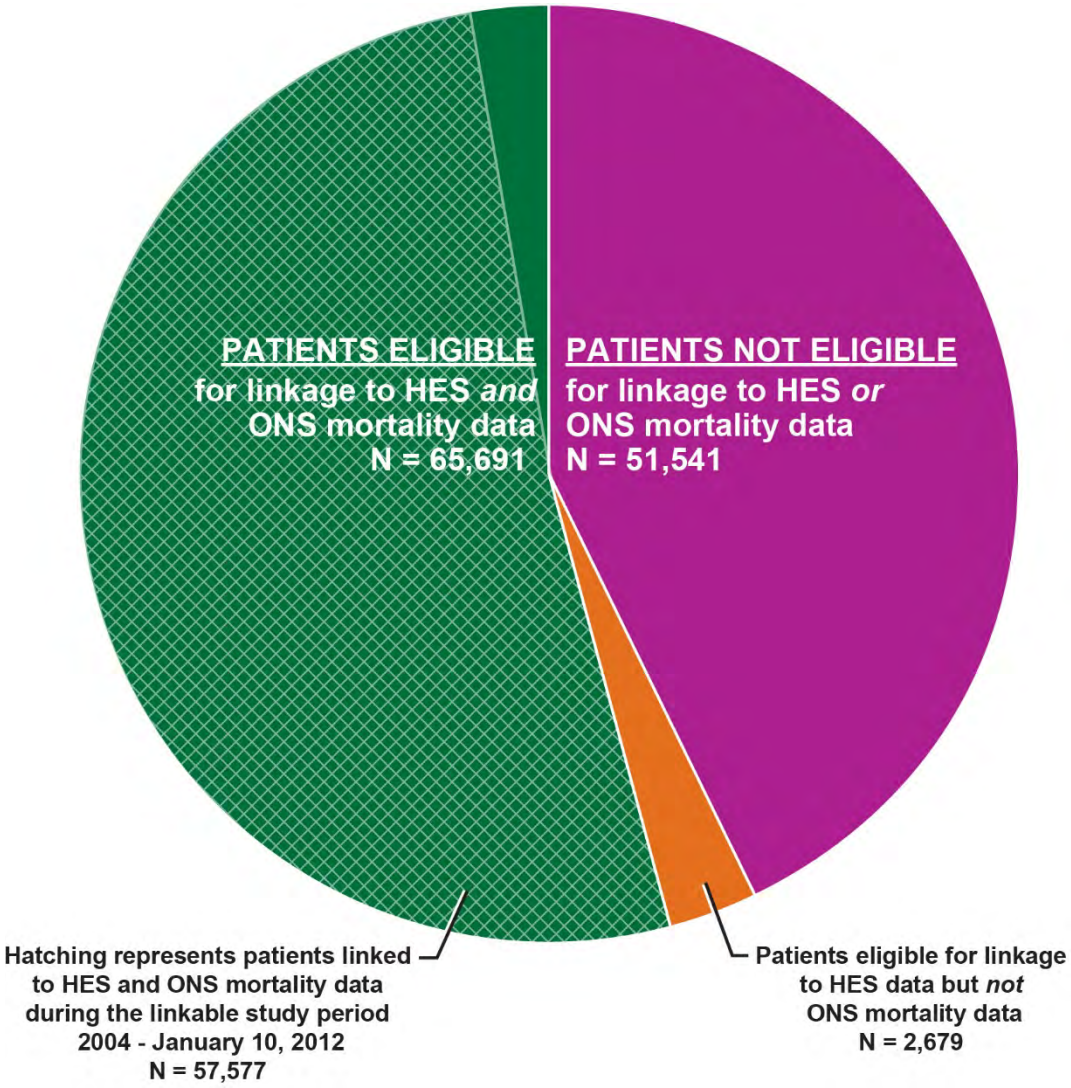
10.1.1 Study Cohort and Validation Cohort

From the initial data set received from the CPRD (n = 173,927), we excluded 37,108 persons because they did not have study drug prescriptions that qualified for index prescription; 16,860 persons because they had cancer on or prior to the cohort entry date (based on GOLD [electronic search and manual review during cancer case validation], NCDR, and HES data); 38 persons because they had HIV infection/AIDS on or prior to the cohort entry date (based on diagnostic codes in GOLD or HES data or prescriptions for HIV medications in GOLD); 8 because they had cancer and HIV infection/AIDS on or prior to the cohort entry date; and 1 because the patient ID was reported by the GP as belonging to a "test patient" created for training purposes. The study cohort thus comprised 119,912 patients, whose person-time in the study began on the date of the index prescription.

Data from the various sources covered somewhat different time periods. General practice data (GOLD data) covered the entire study period. HES data covered April 1, 1997, through March 31, 2012, and ONS mortality data covered January 1, 1998, through January 10, 2012. NCDR data covered the period from January 1, 1985, through December 31, 2010 (see Figure 1).

Of the study cohort patients, 65,691 were eligible for linkage to HES and to ONS mortality data, 1 was eligible for linkage to ONS data alone, 2,679 were eligible for linkage to HES alone, and 51,541 were not eligible for linkage to either data source (Figure 8) (see also Annex 8, Table A5). Of the 65,691 patients eligible for linkage with HES and with ONS mortality data, the person-time for 8,114 patients was not included in HES or ONS due to the lag time of posting data in these two sources, leaving 57,577 patients with data linkable to both sources (see also Section 9.2 and Figure 2).

Figure 8. CPRD GOLD Patients in the Overactive Bladder Cohort According to Linkage Eligibility to HES and to ONS Mortality Data



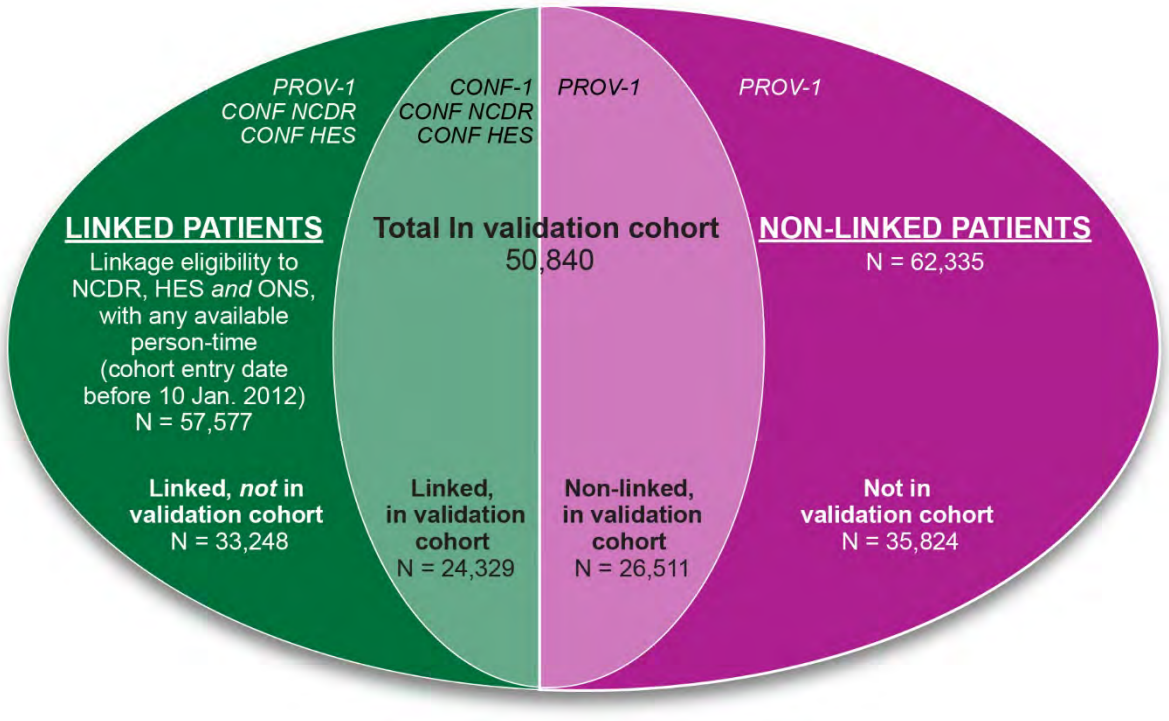
CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; ONS = Office for National Statistics.

Note: This figure describes data linkage in the study cohort. Green represents the 65,691 patients from the study cohort eligible for linkage both to HES and to ONS mortality data. Of these, person-time for 8,114 patients was not included in HES or ONS due to the lag time of posting data in these two sources (plain green), leaving 57,577 patients with data linkable to both sources (green hatching). Orange represents the 2,679 patients eligible for linkage to HES alone; 1 patient (not represented in this figure) was eligible for linkage to ONS alone. Purple represents the 51,541 patients not eligible for linkage to either data source.

Within the cohort of 119,912 patients, we selected a validation cohort that consisted of a sample of the study cohort with 50,840 patients (see Section 9.2.2 and Figure 9).

The drug utilization study and the study of cancer incidence in users of antimuscarinics to treat OAB were conducted in the cohort of 119,912 patients. The validation cohort of 50,840 patients was used to ascertain the validity of the endpoints and covariates of this study.

Figure 9. Patients in the Overactive Bladder Validation Cohort According to Eligibility for Linkage With Other Data Sources, Including Cancer Registries, and According to Case Ascertainment Method in the Study of Cancer Incidence in Users of Antimuscarinics to Treat Overactive Bladder



CONF = confirmed cases in the cancer case validation process; HES = Hospital Episode Statistics; NCDR = National Cardiovascular Data Registry; ONS = Office for National Statistics; PROV-1 = type 1 provisional cases in the cancer case validation process.

10.1.2 Modifications Triggered by Validation of Cancer Endpoints

The review of patient profiles and the comparison of findings in the three data sources conducted for the validation of cancer endpoints gave us the opportunity to identify inconsistencies in the data and correct data errors when needed. Thus, for example one cancer initially coded as breast cancer was reclassified as non-Hodgkin lymphoma based on clinical information, one case with recorded simultaneous prostate and bladder cancer was found to have bladder cancer only, one case with recorded simultaneous breast and bladder cancer was found to have bladder cancer initially, one case with recorded simultaneous lung cancer and non-Hodgkin lymphoma was found to have lung cancer initially, and two cases with recorded uterine cancer long after hysterectomy were found to have ovarian cancer. In

addition, in 601 instances, the date of a study cancer or non-study cancer diagnosis was found on clinical review of CPRD GOLD data or screening of linked data sources to have occurred before the date of cohort entry, prompting removal of the patient from the study cohort because of the exclusion of a history of cancer at cohort entry. These changes were applied to the study cohort for the drug utilization study, the study of cardiovascular disease incidence in users of antimuscarinics to treat OAB, and the study of cancer incidence in users of antimuscarinics to treat OAB.

10.2 Descriptive Data for the Study Cohort

The study cohort included 119,912 patients (Annex 8, Tables A1-A4). In 1,762 patients, the follow-up stopped due to a cancer that was not part of the study cancer endpoint. The mean duration of follow-up was 3.3 years (range, 1 day to 9 years).

The most common index prescriptions were for oxybutynin (34%), tolterodine (31%), and solifenacin (28%) (Annex 8, Table A2). Trospium was the index prescription in 5.1% of the study cohort, fesoterodine in 2.0%, darifenacin in 0.1%, and prescriptions for multiple drugs at cohort entry in 0.1%. While oxybutynin, tolterodine, solifenacin, and trospium were being prescribed at the beginning of the study period, 2004, the first prescription for darifenacin appeared in 2007, and the first prescription for fesoterodine appeared in 2008 (Annex 8, Table A3). Of study patients, 73% were exposed to a single drug during follow-up. There were 245,800 total therapy episodes (28% oxybutynin, 27% solifenacin, 26% tolterodine, and 10% polytherapy).

Of the study cohort, 70% were females (Annex 8, Table A1). The mean age at cohort entry was 62.4 years, 64.5 years for males and 61.5 years for females; 16% of the patients were between 18 and 44 years of age; and almost 50% were 65 years old or older. The mean age at cohort entry by OAB drug ranged from 60.1 years for fesoterodine to 65.3 years for darifenacin. Among patients aged 65 years or older, 66% were female. As measured by the index of multiple deprivation,[39] all socioeconomic strata were well represented in the study cohort.

At cohort entry, about 50% of study patients had a prior history of a code for OAB, from 47% in users of oxybutynin to 58% in users of darifenacin (see Annex 4 for Read codes used to identify OAB). The percentage of study patients with a prior history of OAB was 53% among those aged less than 65 years and 46% among patients aged 65 years or older. Regarding comorbidities at cohort entry, 81% (95% among patients aged 65 years or older) had diagnostic codes for hypertension or received antihypertensive treatment—the percentage was similar across users of all individual drugs, but higher for patients who entered the cohort on multiple drugs (Annex 8, Table A3); 11% (16% among patients age

65 years or older) had diabetes, also based on diagnostic codes or treatment, with no substantial variation across OAB drugs.

Regarding smoking history, 47% were never smokers, 35% former smokers, and 16% (8.7% among patients aged 65 years or older) current smokers. Information on smoking was missing for 1.2% of the study cohort, but was missing for only 0.2% of the users of the most recently introduced drugs (darifenacin and fesoterodine), possibly reflecting more complete coding of smoking over time (encouraged by smoking-related indicators for quality improvement).[47]

Regarding alcohol consumption, 14% were nondrinkers, 52% had a low or moderate alcohol intake, 18% had a high or very high intake, and 5.9% drank an unknown amount of alcohol. Percentages were similar for patients aged younger than 65 years and for patients aged 65 years or older. Information on alcohol intake was missing for 10%, and 2.9% had codes related to alcohol dependency or alcohol-related diseases. Alcohol use had some variation across individual drugs, with darifenacin having the largest percentage of nondrinkers and of alcoholism and alcohol-related diseases, and the least missing information on alcohol intake. This should be interpreted with care given the low number of users of this drug.

Coronary heart disease was present at cohort entry for 13% of the study cohort overall, 13% of oxybutynin users, 13% of tolterodine users, but 17% of darifenacin users. At cohort entry, 4.0% of the study cohort had experienced an AMI (6.0% of darifenacin users), 4.1% had experienced a transient ischemic attack (6.0% of darifenacin users), and 7.0% had peripheral vascular disease. In Annex 8, Table A1 also shows the prevalence of patients with a history of different cardiovascular conditions for the entire study cohort and stratified by age (patients aged < 65 years vs. ≥ 65 years). The prevalence of the cardiovascular conditions is systematically higher in the older group.

Menopause was recorded as present in 24% of female patients overall, but was recorded as present in only 20% of female patients aged 65 years or older.

Darifenacin users appeared to have higher cardiovascular risk profiles than users of other OAB drugs, but results should be interpreted with caution given the low numbers.

Overall, 55% of the study cohort was eligible for linkage to HES and ONS, 43% were not eligible for linkage to either data source, and data for the remaining patients (except for one patient) were eligible for linkage to HES only (Annex 8, Table A5). Disregarding the single patient who was eligible for linkage to ONS only, groups based on eligibility for linkage were similar in their age and sex distribution. Patients from linkage-eligible practices had more use of oxybutynin and less use of fesoterodine than those in practices not eligible for

linkage. The distribution of smoking, alcohol use, and measured comorbidities was generally homogeneous across groups defined by linkage eligibility, including the percentages of missing information on smoking and missing information on alcohol use.

10.3 Outcome Data

Outcome data for each component of the study are provided with the main results.

10.4 Main Results

10.4.1 Drug Utilization Study

10.4.1.1 Index Therapy Episodes

There were 119,912 index therapy episodes (one per cohort member); 33% were for oxybutynin, 31% for tolterodine, 27% for solifenacin, 4.6% for trospium, 1.9% for fesoterodine, 0.1% for darifenacin, and 2.8% for multiple drugs (Annex 8, Table A6). Note that while the index medication is the drug that was prescribed at cohort entry (Annex 8, Table A3), the index therapy episode also considered prescriptions for OAB drugs issued prior to cohort entry with days of supply that overlapped with cohort entry (these prior prescriptions did not meet eligibility criteria to be index prescriptions). Therefore, therapy episodes represent new use of a specific OAB drug but not necessarily first-ever OAB drug use.

The duration of index therapy episodes varied across individual drugs. The shortest mean (SD) duration was 5.5 (10.9) months for oxybutynin, and the longest was 8.9 (14.4) months for darifenacin. Therapy episodes comprising multiple OAB drugs had a mean (SD) duration of 1.4 (3.9) months. Focusing on the most commonly prescribed drugs, 9.4% of oxybutynin users, 4.8% of tolterodine users, and 4.4% of solifenacin users had an index therapy episode shorter than 1 month. For the three drugs, most episodes lasted between 1 and 3 months (60% of oxybutynin, 56% of tolterodine, and 53% of solifenacin therapy episodes), but 15% of oxybutynin, 21% of tolterodine, and 22% of solifenacin episodes continued beyond 9 months.

Index therapy episodes consisted of a single prescription 46% (solifenacin) to 56% (oxybutynin) of the time, and 21% (oxybutynin) to 30% (solifenacin) of index therapy episodes consisted of five or more prescriptions. In almost all index therapy episodes, the dose did not change (87% of oxybutynin index therapy episodes to 96% of tolterodine index therapy episodes).

The definition of an index therapy episode required the index prescription to be the first prescription for the individual drug in 12 months after the patient met eligibility criteria. For

index therapy episodes with the most commonly used OAB drugs (oxybutynin, tolterodine, and solifenacin), prior OAB drug use was 1.3% to 2.2%. Prior OAB drug use was present in 3.8% of patients with fesoterodine as an index prescription, 7.9% for darifenacin, and 7.3% for trospium, possibly reflecting that these drugs were sometimes prescribed as second-line treatment.

Index therapy episodes had not ended at the end of follow-up for 11% of tolterodine and trospium episodes, 13% of oxybutynin episodes, 15% of darifenacin episodes, 21% of solifenacin episodes, and 22% of fesoterodine episodes. For all index therapy episodes with all drugs, the most common reason for ending the therapy episode was discontinuation of treatment, followed by the addition of another drug. Although for most drugs, 70% to 80% of index therapy episodes ended due to therapy discontinuation, and 7% to 9% ended due to an added drug. For darifenacin index therapy episodes, 59% ended due to therapy discontinuation, and 27% ended due to an added drug.

10.4.1.2 All Therapy Episodes

There were 245,800 therapy episodes during the entire follow-up (Annex 8, Table A7). The distribution by drug was very similar to that of index therapy episodes, with 28% for oxybutynin, 27% for solifenacin, 26% for tolterodine, 5.8% for trospium, 2.8% for fesoterodine, 0.3% for darifenacin, and 10% for more than one drug.

Most therapy episodes with individual drugs ended because the drug was not renewed or refilled (89%-92% of therapy episodes of all individual drugs but darifenacin, for which the figure was 74%). The second most common reason for ending therapy episodes was an add-on of another drug. For example, 4.3% of oxybutynin therapy episodes ended when solifenacin was added to the treatment, and 3.4% when tolterodine was added. For all individual drugs but solifenacin, the most common drug added was solifenacin. For solifenacin therapy episodes, the most common drugs added were oxybutynin (2.9%) and tolterodine (2.5%). With lower numbers, solifenacin was the most common drug to which patients were switched from other OAB drugs.

In 88% of the therapy episodes, the initial dose did not increase or decrease; percentages varied by drug and varied from 82% for solifenacin to 95% for tolterodine, among the three most common drugs. When dose changed, the modification was most frequently an increase in dose for all drugs. For example, 11% of oxybutynin therapy episodes had their initial dose increased, and 4.4% had their initial dose decreased.

Over 90% of all therapy episodes were not preceded by use of another OAB drug during the previous 12 months.

10.4.1.3 Prescriptions and Route of Administration

A complete overview of prescriptions, strength, and route of administration is provided in Annex 8, Table A8. Details for the most frequently used medications are presented here. Note that patients with prescriptions for more than one strength during follow-up contributed to more than one strength category. There were 384,551 prescriptions for oxybutynin tablets, 20,918 for oxybutynin patches, and 3,576 for oxybutynin solutions. The tablet strength with the most exposed patients was 2.5 mg, and 5 mg closely followed as the second most common tablet strength.

For tolterodine, only tablets were available, with a total of 474,105 prescriptions. The most commonly prescribed strength was 4 mg, the largest available, with 81% of prescriptions. Of patients with prescriptions for a single strength of tolterodine, 75% had prescriptions for 4-mg tablets.

There were 482,576 prescriptions for solifenacin, available in tablets only; of the patients who received prescriptions for a single strength, the most common strength was 5 mg.

10.4.2 Validation of Endpoints

10.4.2.1 Cardiovascular Endpoints

Cardiovascular Endpoints

Results from the validation of cardiovascular endpoints pertain to the non-linkable practices in the validation cohort. Detailed tables displaying results of the validation analyses may be found in Annex 8; the tables for the validation of cardiovascular endpoints are named Table ValCV1 and ValCV2.

Acute Myocardial Infarction and Stroke Cases

Electronic Identification and Preclassification of Potential Cases

An electronic algorithm was initially applied to identify all instances of definite, probable, and possible AMI and stroke events. Once all events were preclassified by the algorithm, we flagged for potential patient profile review only those events that did not occur during the period of HES data availability for those patients who were eligible for linkage. Additional criteria were then applied to select the flagged events for patient profile review, as follows:

- For AMI events:
  - All definite AMI events from the full study cohort were included
  - All probable first AMI events from the validation cohort were included

  - All possible (definition 1) first AMI events from the validation cohort were included
  - All possible (definition 2) first AMI events from the validation cohort were included
- For stroke events:
  - All definite stroke events from the validation cohort were included
  - All probable first stroke events from the validation cohort were included
  - All possible first stroke events from the validation cohort were included

This left 186 definite, 203 probable, and 2,269 possible AMI events and 186 definite, 383 probable, and 157 possible stroke events for patient profile review (see Table 4).

Table 4. Patient Profiles Reviewed in Validation of Cardiovascular Endpoints

Cardiovascular Endpoint	With Free Text	No Free Text	Totals
AMI	2,313	345	2,658
Definite	—	186	186
Probable	178	25	203
Possible (definitions 1 and 2)	2,135	134	2,269
Stroke	368	358	726
Definite	—	186	186
Probable	268	115	383
Possible	100	57	157
Out-of-hospital CHD death	31	137	168
Death unknown cause	1,819	222	2,041
Totals	4,531	1,062	5,593

AMI = acute myocardial infarction; CHD = coronary heart disease.

Clinical Review of Patient Profiles

Based on the clinical review of patient profiles for the identified AMI and stroke events, these potential cases were then classified as either non-cases or as definite, probable, or possible cases. This review changed the classification of cases, increasing the number of definite and probable cases and decreasing the number of possible cases (see Annex 8, Table ValCV2a). Of 3,354 evaluated AMI and stroke events, 2,426 were reclassified as non-cases; 2,078 of these had been classified as possible AMI cases per definition 2 (with any sign or symptom included in the definition of AMI, except hospitalization and death, but no AMI code).

Some of the cardiovascular events that were included in the patient profile review were subsequently excluded from the cardiovascular validation analysis, based on new information obtained from the patient profile review of cancer endpoints or from cancer registry data. For example, the cardiovascular validation analysis did not include events of patients who were removed from the study cohort due to new evidence of cancer before cohort entry and did not include events that occurred after the end of follow-up, when follow-up time was truncated due to cancer identified after cohort entry. Also, when multiple potential AMI events were reviewed for the same patient, only the first event for the patient was counted when a second event record corresponded to the same AMI episode. Table 5 provides the numbers for the cardiovascular endpoints that were included in the cardiovascular validation analysis.

As shown in Table 5, practically all definite AMI cases (98% of 163) were confirmed as such in the patient profile review. Of 201 probable AMI cases, 42% were upgraded to definite, while 5% were considered possible cases or non-cases. Of 2,233 possible AMI cases identified by any sign or symptom included in the definition of AMI (except hospitalization and death) but no AMI code (definition 2), 93% were reclassified as non-cases. Of 186 definite stroke cases, 13% were reclassified as probable; also, 21% of definite stroke cases, 57% of probable stroke cases, and 55% of possible stroke cases were reclassified as non-cases after clinical review of the patient profile (see Table ValCV2a in Annex 8).

Table 5. Results of Validation of Cardiovascular Endpoints (Non-linked Practices, Validation Cohort)

	Question-naires Sent	Questionnaires Returned (Response Rate, %)	Case Status Confirmed by Questionnaire	Positive Predictive Value, % (95% CI)	Negative Predictive Value, % (95% CI)
Decision from original algorithm					
Acute myocardial infarction					
Definite	137	114 (83%)	112	98 (94-100)	
Probable	162	134 (83%)	123	92 (86-96)	
Possible (definition 1)	32	24 (75%)	22	92 (73-99)	
Possible (definition 2)	1,097	864 (79%)	22	2.5 (1.6-3.8)	
Stroke - original definition					
Definite	157	131 (83%)	101	77 (69-84)	
Probable	249	207 (83%)	97	47 (40-54)	
Possible	135	114 (84%)	48	42 (33-52)	
Non-cases alive[a]	185	149 (81%)	147		99 (95-100)
Non-cases dead[b]	185	146 (79%)	123		84 (77-90)
Decision from revised algorithm for stroke					
Stroke - updated definition					
Definite	120	98 (82%)	90	92 (85-96)	
Probable	107	90 (84%)	71	79 (69-87)	
Possible	48	44 (92%)	37	84 (70-93)	

	Question-naires Sent	Questionnaires Returned (Response Rate, %)	Case Status Confirmed by Questionnaire	Positive Predictive Value, % (95% CI)	Negative Predictive Value, % (95% CI)
Decision from patient profile review					
Acute myocardial infarction					
Definite	213	179 (84%)	173	97 (93-99)	
Probable	94	76 (81%)	71	93 (85-98)	
Possible (any definition)	97	77 (80%)	22	29 (19-40)	
Non-case	1,024	804 (79%)	791		98 (97-99)
Stroke					
Definite	164	137 (84%)	120	88 (81-93)	
Probable	97	83 (86%)	66	80 (69-88)	
Possible	42	36 (86%)	25	69 (52-84)	
Non-case	238	196 (82%)	161		82 (76-87)

AMI = acute myocardial infarction; CI = confidence interval; CPRD = Clinical Practice Research Datalink; GOLD = online database of the CPRD;

[a] Non-cases alive: patients without AMI or stroke in CPRD GOLD data who were alive at the end of follow-up.

[b] Non-cases dead: patients without AMI or stroke in CPRD GOLD data who had died by the end of follow-up.

Source: Table ValCV1 (Annex 8).

Questionnaires Sent to General Practitioners

A total of 2,364 validation questionnaires were submitted to the GPs. Within a 4-month period, we received 1,904 questionnaires (81% response rate). The response rate was similar for all endpoints: 80% for AMI, 83% for stroke, 81% for non-case alive, and 79% for non-case dead.

In the electronic AMI case classification, PPVs were above 90% for definite, probable, and possible (definition 1) cases. Possible AMI cases per definition 2 (with any sign or symptom included in the definition of AMI, except hospitalization and death, but no AMI code) had a PPV of 2.5% (95% CI, 1.6-3.8) (Table 5).

The electronic classification of stroke resulted in lower PPVs (Table 5), which prompted us to explore which codes were responsible for the electronic identification of the 206 potential cases that were considered non-cases (46%) after the review of the GPs questionnaires. Four Read codes were identified; none of them were diagnostic codes (Read codes 662M.00, Stroke monitoring; 662o.00, Haemorrhagic stroke monitoring; 8HTQ.00, Referral to stroke clinic; and 9N0p.00, Seen in stroke clinic). We updated the electronic stroke definitions excluding these codes.

The updated algorithm identified 139 definite stroke cases, 152 probable cases, and 53 possible stroke cases (Annex 8, Table ValCV2a). The PPV (95% CI) with the updated algorithm was 92% (85-96) for definite stroke, 79% (69-87) for probable stroke, and 84% (70-93) for possible stroke (Annex 8, Table ValCV1). The updated definition did not identify 48 cases of stroke confirmed by the GPs through questionnaires of the total 246 stroke cases confirmed by GPs (20%).

Non-cases

The NPVs for non-case alive (individuals who did not develop AMI or stroke and were alive at the end of follow-up) and for non-case dead (individuals who did not develop AMI or stroke and died during the study period) were above 80%.

Out-of-Hospital Coronary Heart Disease Death

Concordance between out-of-hospital CHD deaths identified by the electronic algorithm (categorized as AMI, CHD other than AMI, or unknown cause of death with recent history of CHD) and those identified by review of patient profiles (categorized as fatal AMI, out-of-hospital CHD death, or other cause of death) was assessed. The concordance was high (40/40) for AMI (i.e., algorithm-identified AMI cases that were categorized as fatal AMI in the patient profile review) and CHD other than AMI (90/92) (i.e., algorithm-identified CHD

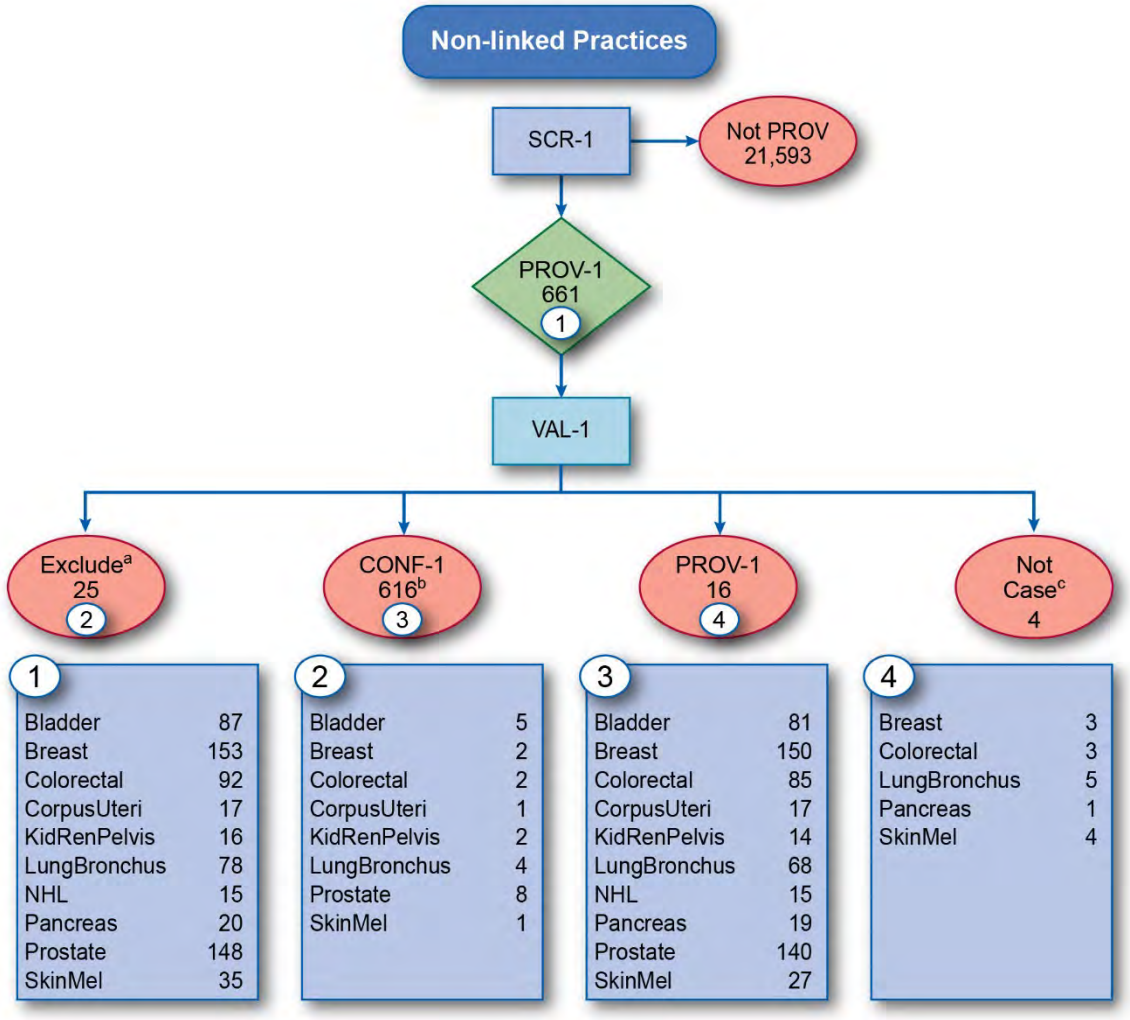
other than AMI categorized as out-of-hospital CHD death in the patient profile review). Among potential cases electronically classified as unknown cause of death with recent history of CHD, approximately 52% were categorized as fatal AMI or out-of-hospital CHD death in the patient profile review. See Annex 8, Table ValCV2b for more details.

10.4.2.2 Cancer Endpoints

Validation of Provisional Cases in Non-linked Practices

Among 22,254 patients in non-linked practices, 661 provisional cases of cancer were identified. Figure 10 is a flow diagram showing the final classification of the provisional cases based on patient profile review, as well as the counts for each type of study cancer at each step of the validation process. Overall, 616 of 661 provisional cases (93%) were confirmed. For most individual cancer types (i.e., bladder, breast, colorectal, uterus, non-Hodgkin lymphoma, pancreas, and prostate), at least 90% of provisional cases were confirmed, and at least 95% were confirmed for four cancer types: breast, uterus, non-Hodgkin lymphoma, and pancreas. The cancer with the lowest proportion of confirmed cases was melanoma (27 of 35, 77%), and less than 90% of provisional cases were confirmed for two other cancers (renal: 14 of 16, 88%; lung: 68 of 78, 87%). Twenty-five provisional cases (3.8%) were found to have evidence of a cancer diagnosed before cohort entry date; consequently, these patients were excluded from the study. Only 4 provisional cases (0.6%) were found to be non-cases.

Figure 10. Final Classification of Provisional Cancer Cases Based on Profile Review—GOLD Data. Validation Cohort, Non-linked Practices



GOLD = online database of the Clinical Practice Research Datalink in the United Kingdom; KidRenPelvis = kidney and renal pelvis; NHL = non-Hodgkin lymphoma; SkinMel = melanoma of the skin.

Note: SCR-1 was the process of screening GOLD data (GP medical records) for diagnostic Read codes. PROV-1 cases were identified in GOLD data by the procedure SCR-1. VAL-1 refers to the process of validating cases by reviewing individual patient profiles. CONF-1 cases were confirmed by VAL-1. A total of 16 PROV-1 cases remained provisional after VAL-1 because no confirmatory evidence was found in the profile.

[a] Profile review determined that the cancer event index date was before the cohort entry date.

[b] Three of the CONF-1 cases were ruled to be different study cancer than had been assigned during SCR-1. Two skin melanomas were reclassified as breast cancer, and 1 bladder cancer was reclassified as corpus uteri cancer.

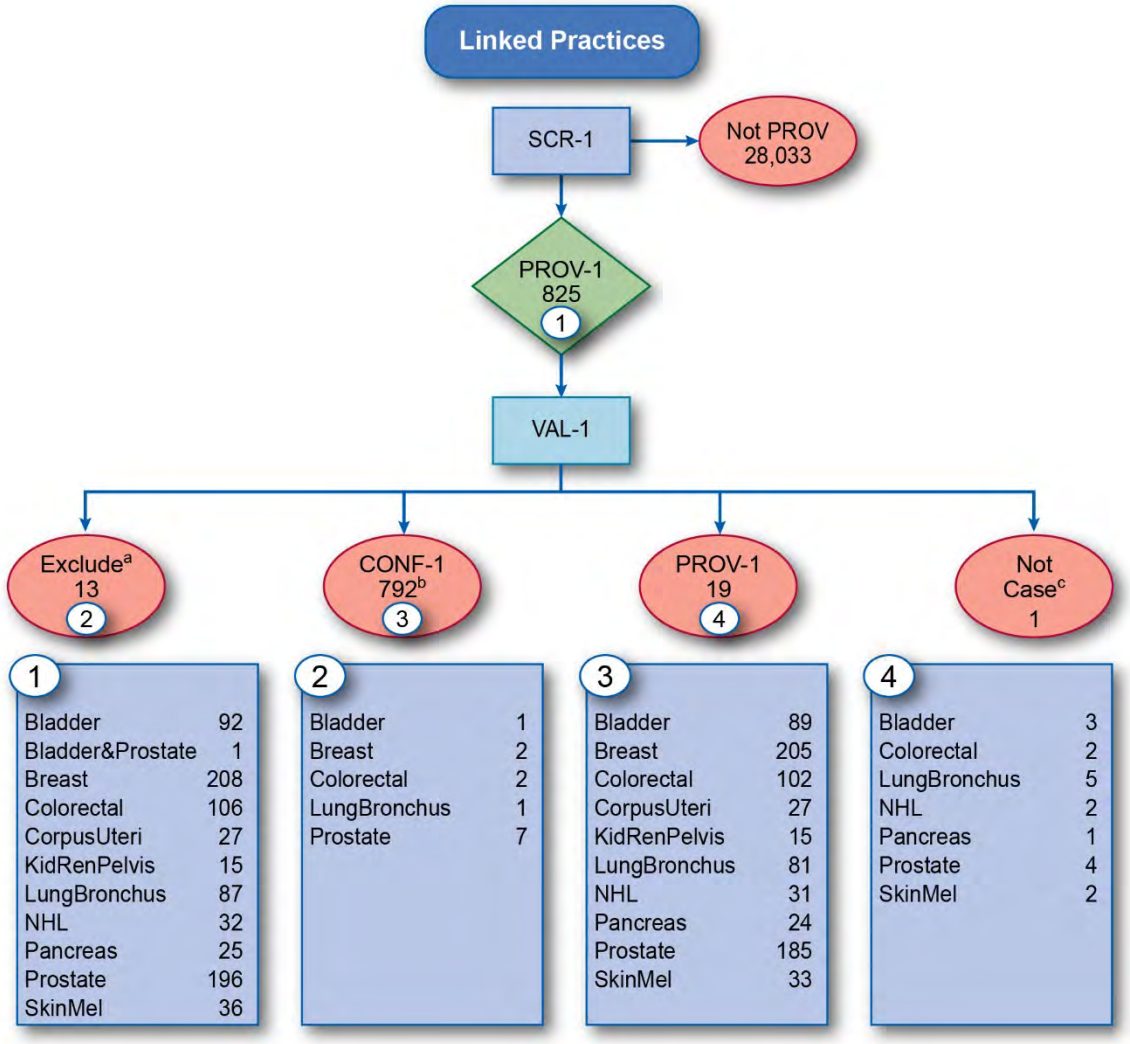
[c] Per SCR-1, 2 cases were colorectal, 1 was lung/bronchus, and 1 was skin melanoma, but classification was changed during validation. Per VAL-1, the skin melanoma and 1 colorectal cancer were deemed to be not cancer cases, and the other colorectal cancer and the lung/bronchus cancer were deemed to be not study cancers.

Validation of Provisional Cases in Linked Practices Based Only on GOLD Data

In linked practices, 825 provisional cases were identified. Note that for provisional cases identified in the linked practices, *final* case classification depended not only on profile review (GOLD data) but also on additional information found in NCDR and HES data. Also, additional cases not identified in GOLD data were identified in these data sources for patients in linked practices. *Final* classification of provisional cases identified in linked practices is described later. The information that follows here is reported to provide perspective on the results of case validation in the non-linked practices and to serve as a basis for estimating the proportion of actual cancer cases in non-linked practices that were likely to have been missed in the validation cohort because corresponding cancer registry and hospital episode data do not exist for the non-linked practices.

Figure 11 is a flow diagram showing the classification of the provisional cases based only on profile review, as well as the counts for each type of study cancer at each step of the validation process. Overall, 792 of 825 provisional cases (96%) were confirmed. For all individual cancer types, at least 90% of provisional cases were confirmed, and at least 95% were confirmed for seven cancer types: bladder, breast, colorectal, uterus, renal, non-Hodgkin lymphoma, and pancreas.

Figure 11. Final Classification of Provisional Cancer Cases Based on Profile Review—GOLD Data. Validation Cohort, Linked Practices



GOLD = online database of the Clinical Practice Research Datalink in the United Kingdom; KidRenPelvis = kidney and renal pelvis; NHL = non-Hodgkin lymphoma; SkinMel = melanoma of the skin.

Note: SCR-1 was the process of screening GOLD data (general practitioner medical records) for diagnostic Read codes. PROV-1 cases were identified in GOLD data by the procedure SCR-1. VAL-1 refers to the process of validating cases by reviewing individual patient profiles. CONF-1 cases were confirmed by VAL-1. A total of 16 PROV-1 cases remained provisional after VAL-1 because no confirmatory evidence was found in the profile.

[a] Profile review determined that the cancer event index date was before the cohort entry date.

[b] One of the CONF-1 cases initially identified as having breast as the index cancer per SCR-1 was determined to have NHL per VAL-1, and one initially identified as bladder and prostate was determined to be bladder.

[c] This was a patient identified as having skin melanoma per SCR-1, but determined not to have a study cancer per VAL-1.

Comparison of Case Validation in Non-linked and Linked Practices Based Only on GOLD Data

Overall, the proportion of provisional cases identified in non-linked practices that were confirmed based only on GOLD data (616 of 661, 93%) was slightly less than that in the linked practices (792 of 825, 96%) (difference in proportion confirmed = 2.8%; 95% CI, 0.5%–5.1%; P = 0.016). The proportions of provisional cases confirmed were at least as large in linked practices as in non-linked practices for all individual cancer types except non-Hodgkin lymphoma (non-linked: 15 of 15, 100%, vs. linked: 31 of 32, 97%) and prostate (non-linked: 140 of 148, 95%, vs. linked: 185 of 196, 94%).

Patient Profile Review for Case Validation and the Role of Incorporating Free-Text Comments Into the Patient Profile

There were 1,486 cases initially identified by the computer screening algorithm. (Note that some of these patients were eventually found to have cancer diagnosed before cohort entry based on subsequent review of NCDR data. For the purpose of this discussion, these later exclusions are not taken into account.) Of these 1,486 cases, we did not request free text on 1,077 because they met one of the criteria in Table 2.

Of the remaining 409 PROV-1 cases that were candidates to have free text obtained, we did not identify any available free text for 4, and for another 3, the patient had opted out of releasing their free text. However, of the 402 cases with free text available, 28 were found by reviewers to have had a cancer before cohort entry and were therefore excluded from the study, leaving a total of 374 cases with free text available that were eligible for participation in the study. Among these 374 cases, the reviewer decisions were 338 reclassified as CONF-1, 5 reclassified as non-cases, and 31 remained PROV-1; therefore, the proportion of PROV-1 cases with free text available that were either confirmed or determined not to be valid cases after review of the patient profiles with free text was 92%. By contrast, among the 7 PROV-1 cases that were candidates to have free text obtained but free-text was not available, the proportion that were confirmed or determined not to be valid cases after review of the patient profiles was 57% (reviewer decision was 4 reclassified as CONF-1 and 3 remained PROV-1).

Final Status of Cases in Linked Practices Using All Data Sources

Figure 12 is a flow diagram showing the final classification of cases in linked practices based on all available data sources (GOLD, NCDR, and HES). Note that in this diagram, "SCR-2" and "SCR-3" may refer to cases for which additional information was identified in NCDR or HES data, respectively, rather than to cases initially identified in these data sources (but not detected in GOLD data). A total of 1,051 cases were confirmed. Of the 19 provisional cases that remained provisional based only on review of GOLD data, 12 remained provisional after

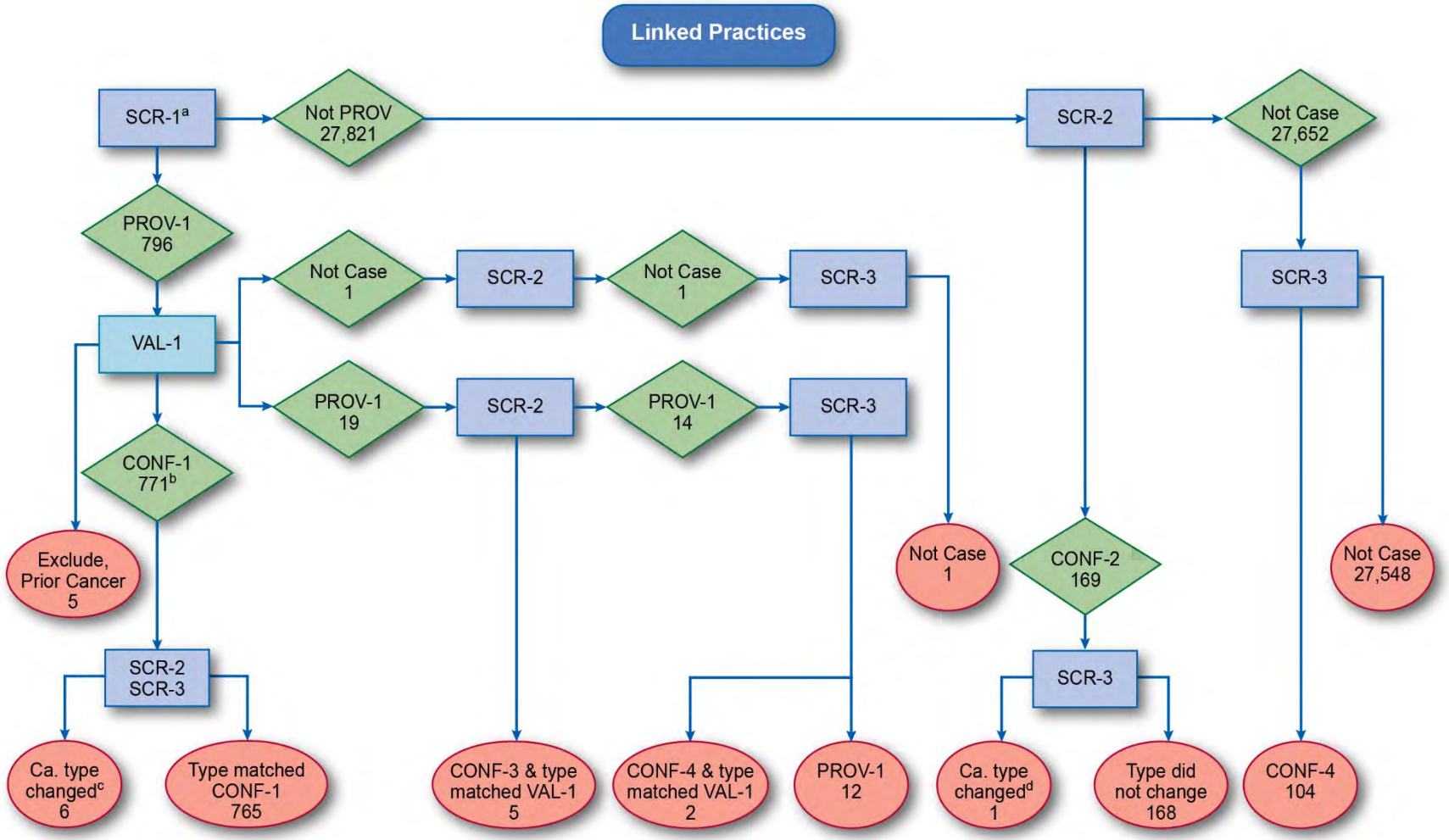
information from all data sources was used. The specific type of cancer diagnosed was changed in 7 instances based on information in either NCDR or HES data (1.0% of 705 cases identified in more than one data source; see Figure 13).

Of the 1,051 confirmed cases in linked practices, regardless of where the cases were initially found, 772 (73%) were identifiable in GOLD data, 608 (58%) in NCDR data, and 749 (71%) in HES data. Figure 13 is a Venn diagram (with the number of cases and percentage in each group) showing which data source contains each case.

Of the 1,051 confirmed cases in linked practices, 944 (90%) were identifiable in either GOLD or NCDR data; 436 of these (41% of the 1,051) were in both data sources. Altogether, 997 confirmed cases (95% of the 1,051) were identifiable in either GOLD or HES data; 524 of these (50% of the 1,051) were in both data sources. Finally, 866 confirmed cases (82% of the 1,051) were identifiable in NCDR or HES data, and 491 of these (47% of the 1,051) were in both sources.

Of all 1,051 confirmed cases, 373 (35%) were identifiable in all three data sources; 63 (6.0%) were in both GOLD and NCDR but not HES, 118 (11%) were in both NCDR and HES but not GOLD, 151 (14%) were in GOLD and HES but not NCDR, 185 (18%) were in GOLD but neither of the other two data sources, 54 (5.1%) were in NCDR only, and 107 (10%) were in HES only. Based on these results, and considering that NCDR data may not be available in the CPRD in the future, it may be concluded that if NCDR data had not been available for this study, 997 cases (95% of the 1,051 confirmed cases) would have been identified in the linked practices in this study.

Figure 12. Final Classification of Cancer Cases Based on All Available Data Sources—Validation Cohort, Linked Practices



Ca. = cancer; CPRD = Clinical Practice Research Datalink in the United Kingdom; GOLD = online database of the CPRD; Hospital Episode Statistics; ICD = International Classification of Diseases; NCDR = National Cardiovascular Data Registry.

Note: Time after a non-study cancer that was identified by PROV-1, SCR-1, SCR-2, or SCR-3 was excluded from all evaluation steps in this diagram regardless of the sequence of evaluations displayed. SCR-1 was the process of screening GOLD data (general practitioner medical records) for diagnostic Read codes. SCR-2 refers to searching NCDR data for cases using ICD codes. SCR-3 refers to searching HES data for cases using ICD codes. PROV-1 cases were identified in GOLD data by procedure SCR-1. VAL-1 refers to the process of validating cases by reviewing individual patient profiles. CONF-1 cases were confirmed by VAL-1. A total of 19 PROV-1 cases remained provisional after VAL-1 because no confirmatory evidence was found in the profile. CONF-2 refers to cases identified by SCR-2 that had not previously been identified by SCR-1. CONF-3 refers to cases that had remained provisional after profile review but that were confirmed using NCDR data. CONF-4 refers to cases identified by SCR-3 that had not previously been identified by SCR-1 or SCR-2, or that had remained provisional after profile review but were confirmed by HES data.

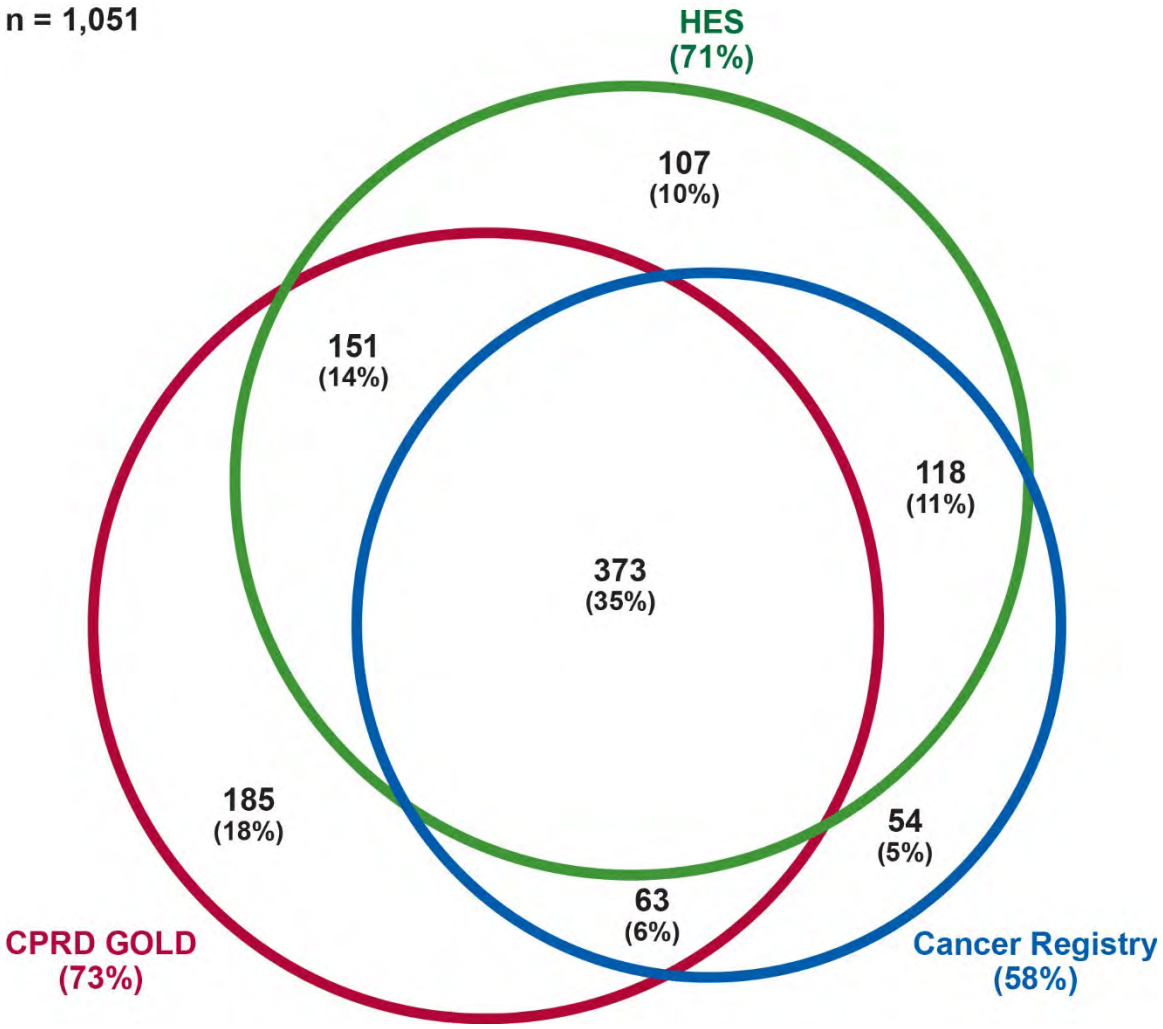
[a] A total of 241 patients were excluded prior to SCR-1 because they were identified via NCDR data as having cancer prior to cohort entry. Of these patients, 19 were classified as PROV-1 per SCR-1, and 8 were identified as having prior cancer per VAL-1.

[b] One case classified as breast cancer per SCR-1 was reclassified to non-Hodgkin lymphoma per VAL-1, and another screened as bladder plus prostate cancer was determined to be only bladder cancer.

[c] An earlier study cancer of different type was identified per SCR-2 or SCR-3.

[d] An earlier study cancer of different type was identified per SCR-3.

Figure 13. Origin of Cancer Cases by Data Source: Validation Cohort, Linked Practices, All Cases, All Cancers Combined



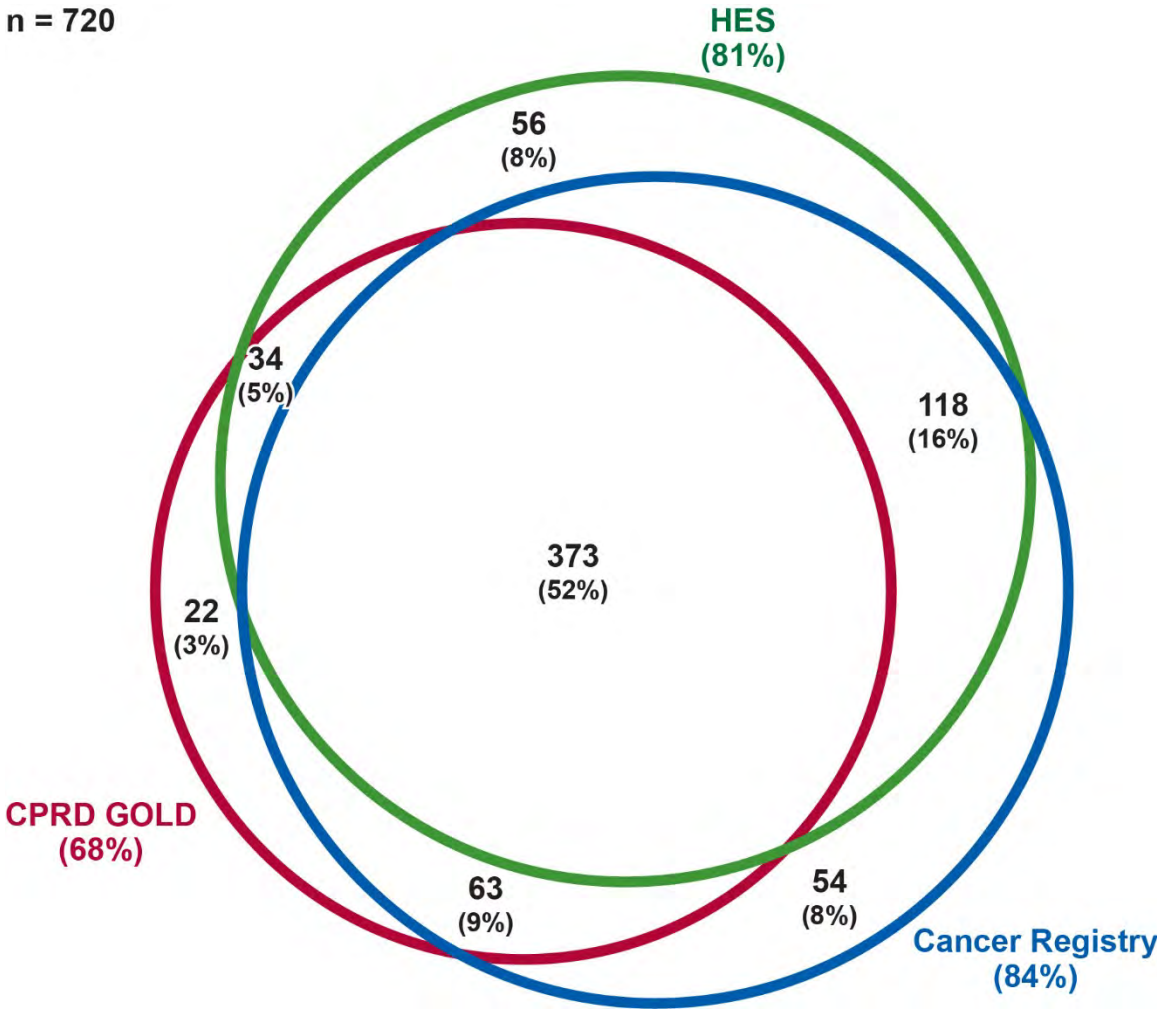
CPRD GOLD = online data from the Clinical Practice Research Datalink; HES = Hospital Episode Statistics.

This figure represents the 1,051 confirmed cases in linked practices, regardless of the data source in which the cases were initially identified. The percentages were calculated using 1,051 as the denominator.

Subgroup Analysis of Cases in Linked Practices Diagnosed Before December 31, 2010

A factor contributing to the lower overall proportion of cases identifiable in the NCDR data than in other data sources is that NCDR data used to conduct this study were available only through December 31, 2010, while follow-up for the validation cohort continued until December 31, 2012. Therefore, cases identified in GOLD or HES data during 2011 and 2012 are not expected to be identifiable in the NCDR data used to conduct this study. To account for this discrepancy, a subgroup analysis of cases diagnosed on or before December 31, 2010, was conducted. Of the confirmed cases in linked practices, 720 (69%) were diagnosed before December 31, 2010, and have the potential to be identified in the NCDR data available for this study. The subgroup analysis of these 720 patients helps to evaluate how much more concordance would have been observed for case identification among the three data sources in linked practices if the study period had been restricted to the time during which NCDR data were available. The results of this subgroup analysis are shown in a Venn diagram (with number of cases and percentages of the total) in Figure 14.

Figure 14. Origin of Cancer Cases by Data Source: Validation Cohort, Linked Practices, Subgroup of Cases Diagnosed During NCDR Data Availability, All Cancers Combined



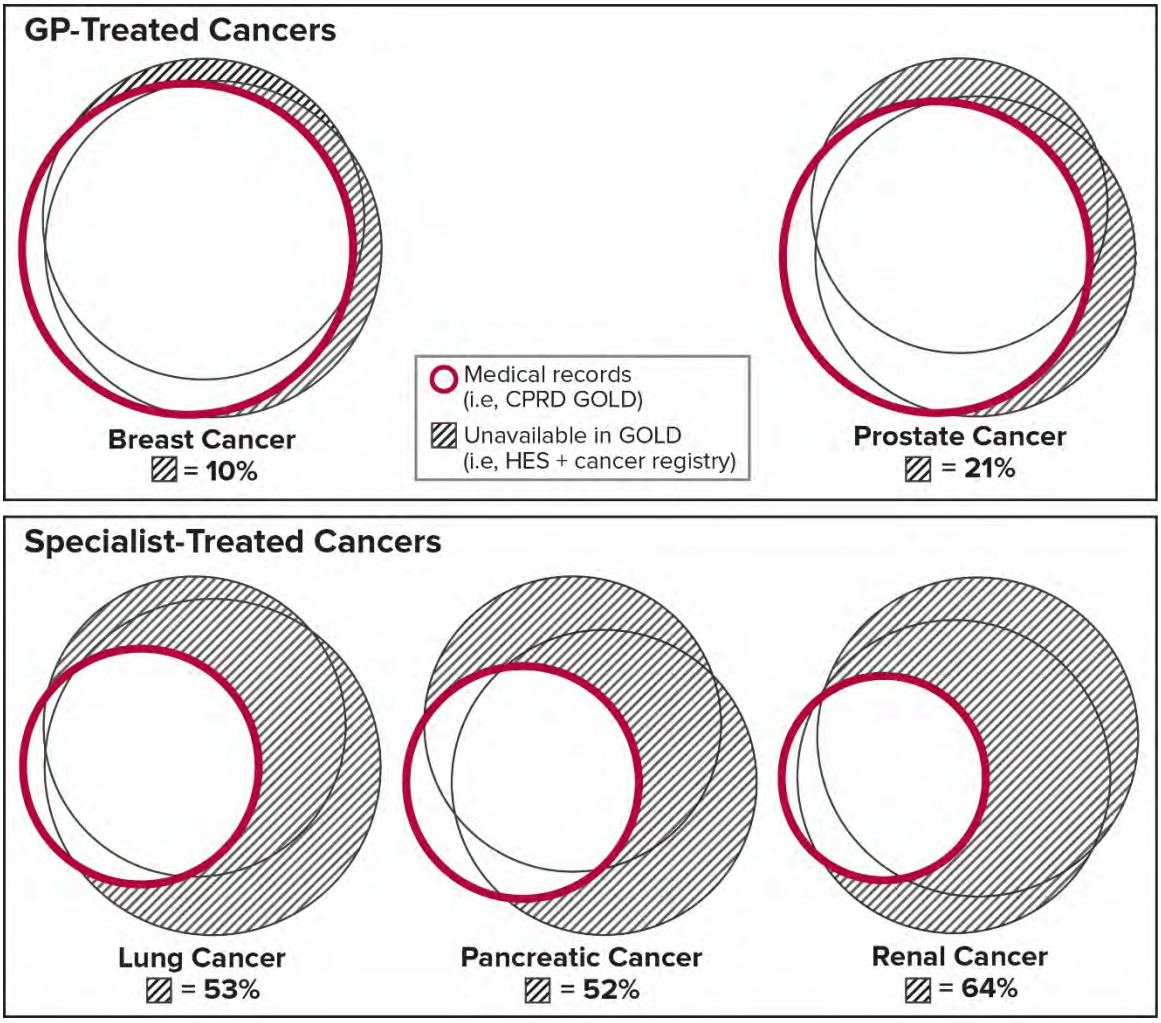
CPRD GOLD = online data from the Clinical Practice Research Datalink; HES = Hospital Episode Statistics; NCDR = National Cardiovascular Data Registry.

Of the 720 confirmed cases in this subgroup analysis, 664 (92%) were identifiable in either GOLD or NCDR data; 436 of these (61% of the 720) were in both data sources. Altogether, 666 cases (93% of the 720) were identifiable in either GOLD or HES data; 407 of these (57% of the 720) were in both data sources. Finally, 698 confirmed cases (97% of the 720) were identifiable in NCDR or HES data, and 491 of these (68% of the 720) were in both sources.

Of the 720 confirmed cases in this subgroup analysis, 373 (52%) were identifiable in all three data sources; 63 (8.8%) were in both GOLD and NCDR, but not HES; 118 (16%) were in both NCDR and HES, but not GOLD; and 34 (4.7%) were in GOLD and HES, but not NCDR. Finally, 22 (3.1%) were in GOLD but neither of the other two data sources; 54 (7.5%) were in NCDR only; and 56 (7.8%) were in HES only.

Similar Venn diagrams for each of the study cancer types are shown in Annex 6. It is apparent from these data that the concordance of case identification in GOLD data with the other data sources is greater for those cancers for which GPs regularly provide prescriptions for treatment (i.e., breast cancer and prostate cancer) than for the other study cancers (Figure 15). In other words, the percentage of cases not identifiable in GOLD data is lowest for these cancer types. For example, for breast cancer, only 14 of 144 cases (9.7%) were not identifiable in GOLD data; for prostate cancer, only 31 of 151 cases (21%) were not identifiable in GOLD data. The proportions of cases not identifiable in GOLD data were considerably higher for the other cancer types evaluated, particularly renal (18 of 28, 64%), pancreatic (11 of 21, 52%), and lung (48 of 91, 53%), for which more than half of the cases would not have been identifiable if only GOLD data had been available.

Figure 15. Selected Cancers by Main Treating Physician: Percentage of Cases Not Identifiable in GOLD: Linked Practices, Complete Overlap Study Period (2004-2010)



CPRD GOLD = online data from the Clinical Practice Research Datalink; GP = general practitioner; HES = Hospital Episode Statistics.

Estimation of Number of "Missing" Cases in Non-linked Practices in Validation Cohort (Analysis 3 in the Statistical Analysis Plan)

Using only GOLD data (including profile review), 792 cases in the validation cohort were confirmed in linked practices, and 1,051 (1.33 times as many) were confirmed using all available data sources (including NCDR and HES data). In non-linked practices in the validation cohort, 616 cases were confirmed based only on GOLD data (i.e., the only data available). If analogous NCDR and HES data had been available for the non-linked practices, and assuming that the proportion of additional cases that would have been identified in the non-linked practices was similar to the proportion actually identified in the linked practices if such data sources existed, an estimated total of 1.33 × 616 = 819 cases would have been confirmed in the non-linked practices. In the non-linked practices (in the validation cohort), the difference between 819 "projected" total cases and 661 screen-detected cases (158 cases) is an estimate of the number of cases that may be "missing" from the current validation cohort in the non-linked practices (under the assumption mentioned previously). Based on the preceding analyses, and assuming that diagnostic patterns in non-linked practices are similar to those observed in linked practices, it is expected that the types of cancer among these "missing" cases in non-linked practices would likely be disproportionately cancers of the kidney, lung, and pancreas, and that the numbers of "missing" cases of breast and prostate cancer would be proportionately lower.

In calculating a more refined estimate of the total number of cases (including those missed in the non-linked practices) (Annex 8, Table N Additional 3), a different scalar factor for each cancer type and for the overall composite outcome was applied. The scalar factor was calculated in the validation cohort using linked practices and the subgroup of cases diagnosed during NCDR data availability as the ratio between all confirmed cases (CONF-1, CONF-2, CONF-3, CONF-4) and cases confirmed only by CPRD GOLD data (CONF-1). Using a scalar factor of 1.46 derived for the overall composite outcome, the number of cases for the composite outcome in this analysis increased from 1,397 to 2,045 cases. Had the number of cases been estimated separately by type of cancer, the overall number of estimated events would have been 2,085.

10.4.2.3 Validation of Covariates

Detailed tables displaying results of the validation analyses may be found in Annex 8; the tables for the validation of covariates are named Table ValCov1 and ValCov2.

Smoking. Information on smoking in the CPRD GOLD database was missing for only 3 patients (0.17% of 1,731 questionnaires with information on smoking). In Annex 8, Tables ValCov1 shows the agreement between the information on smoking in the CPRD GOLD database and the responses from the questionnaires. Based on CPRD GOLD data on the

closest day *before* the endpoint date, 287 patients (17%) were current smokers, 709 (41%) were former smokers, and 732 (42%) were never smokers (Annex 8, Table ValCov1b). In comparing CPRD GOLD data with information from GP questionnaires, 84% of patients who identified as current smokers in CPRD GOLD data were also current smokers according to GP questionnaires; 77% who were identified as former smokers in CPRD GOLD data were also former smokers according to GP questionnaires, and 97% who were identified as never smokers in CPRD GOLD data were also never smokers according to the GP questionnaires. This level of concordance was seen for different types of GP questionnaires (AMI, stroke, non-case alive, non-case death). CPRD GOLD data and questionnaires sent to GPs correlated better when the information on covariates was obtained for the date closest to and before the endpoint date.

Obesity (body mass index ≥ 30 kg/m^2). Information on obesity was missing for 26% of the 1,713 questionnaires with information on obesity when using only information from the CPRD GOLD database on the closest date *before* the endpoint date. In Annex 8, Tables ValCov2 shows the correlation between the information on obesity in the CPRD GOLD database and the responses from the GP questionnaires. For 78% of patients with missing data in the CPRD GOLD database, obesity information was provided on the returned GP questionnaire. Of the patients classified as obese according to the CPRD GOLD database, 82% were confirmed through the GP questionnaire, and of the patients who were not obese (body mass index < 30), 92% were confirmed through the GP questionnaire (Annex 8, Table ValCov2b).

Menopause. Pre/postmenopausal status was not correctly identified using CPRD GOLD data. Tables ValCov2 in Annex 8 shows the correlation between the information on menopause in the CPRD GOLD database and the responses from the GP questionnaires. Of patients with recorded codes for menopause in the CPRD GOLD database before the endpoint date, 83% were confirmed by their GPs as having gone through menopause prior to the endpoint date, but 3.6% were reported to be premenopausal (Annex 8, Table ValCov2b). Of patients without recorded codes for menopause in the CPRD GOLD database before the endpoint date (assumed premenopausal based on electronic data), 12% were confirmed as premenopausal, but 77% were reported by their GPs to have gone through menopause.

History of AMI was included in the AMI questionnaire sent to GPs. History of AMI according to CPRD GOLD data before the endpoint date was confirmed by the GP questionnaires in 70% of the cases, and absence of a history of AMI was confirmed in 96% of the cases (Annex 8, Table ValCov2b).

History of stroke was included in the stroke questionnaire sent to GPs. History of stroke according to CPRD GOLD data before the endpoint date was confirmed by the GP questionnaires in 44% of the cases, and absence of history of stroke was confirmed in 88% of the cases (Annex 8, Table ValCov2b).

10.4.3 Study of Cardiovascular Disease Incidence in Users of Antimuscarinics to Treat Overactive Bladder

The study of cardiovascular disease incidence in patients treated with OAB antimuscarinic drugs was conducted in the full study cohort, including all 119,912 patients from both linked and non-linked practices. Of these patients, 1,983 had an AMI, 2,184 had a stroke, and 2,097 died of cardiovascular causes (1,126 CHD death or 1,007 cerebrovascular disease deaths; please note that the two causes could be listed in a patient's death certificate). A total of 4,728 patients experienced an event included in the MACE definition. Of the 119,912 patients who used one of the OAB drugs studied, 9,487 died of any cause.

The characteristics of the study patients and the prevalence of cardiovascular risk factors according to the presence or absence of the different endpoints are summarized in Annex 8, Table CV1. As in the overall cohort, 70% of the study patients without the event were female, and almost 70% were aged 55 years or more. Patients with any of the endpoints were older, and the proportion of males was greater than among patients without any of the endpoints.

Overactive bladder was present in 50% of the patients without a cardiovascular endpoint. This prevalence was lower in patients who had a cardiovascular event (45%) or died (41%).

In patients who did not develop any of the cardiovascular endpoints, the prevalence of hypertension was 80%; the prevalence of diabetes was 11%; and 16% were current smokers, 35% former smokers, and 48% nonsmokers. In this group, information on smoking status was not available for 1.2% of the patients. In contrast, patients with a cardiovascular endpoint had a greater prevalence of hypertension (96%) and diabetes (19%). There were fewer nonsmokers among those that presented with a cardiovascular endpoint.

The proportion of patients with a previous history of cardiovascular disease or transient ischemic attack was greater in those who developed a cardiovascular endpoint than in those who did not. In those without a cardiovascular endpoint, history of AMI was present in 3.7% of the patients, compared with 13% of those with MACE; history of stroke was present in 6.4% of the patients without a cardiovascular endpoint, compared with 20% of those with MACE; and history of transient ischemic attack was present in 3.7% of the patients without a cardiovascular endpoint, compared with 12% of those with MACE.

The prevalence of dyslipidemia in patients who did not develop a cardiovascular endpoint was 13%, the prevalence of atrial fibrillation was 5.3%, and the prevalence of hemiplegia was 1.4%. In patients who met the criteria for MACE, the prevalence of dyslipidemia was 17%, the prevalence of atrial fibrillation was 17%, and the prevalence of hemiplegia was 4.1%.

Menopause was recorded as present in 24% of female patients who did not develop a cardiovascular endpoint, in 14% of cases that developed any of the cardiovascular endpoints, and in 8.7% of the deceased cases.

Body mass index was recorded for 67% of the patients without a cardiovascular endpoint, for 65% of those with a cardiovascular endpoint, and for 60% of deceased patients. In approximately 25% of the patients overall, the body mass index was recorded as 30 kg/m^2 or more.

History of alcohol use was recorded for 90% of the patients without a cardiovascular endpoint and for 86% of deceased patients.

Health services utilization was similar whether or not a patient developed a cardiovascular endpoint. Patients without a cardiovascular endpoint had a mean number of 11 outpatient visits and one hospitalization during the year prior to cohort entry; they were prescribed 1 study OAB drug and had, on average, 12 study OAB drug prescriptions during the study period. They had been enrolled in the CPRD database a mean of 9 years previous to cohort entry and were followed for a mean of 3 years.

The high cardiovascular risk definition was met by 43% of the patients without a cardiovascular endpoint, and by 71% of those who developed a cardiovascular endpoint.

In Annex 8, Tables CV2a-CV2e summarize the incidence rates of the different cardiovascular endpoints for current exposure to the different medications overall and stratified by age less than 65 years, female sex, presence of cardiovascular risk factors, and combinations of these variables. Annex 8, Tables CV4a-CV4e are similar but are for recent exposure to each OAB drug.

For AMI, the SIR (95% CI) in cases per 1,000 person-years was 4.90 (4.53-5.29) for current use of any OAB drug and 6.07 (5.28-6.94) for recent use. Of the three most commonly used OAB drugs, the SIR (95% CI) was lowest for current use of solifenacin, 4.00 (3.41-4.67), and greatest for oxybutynin, 5.94 (5.16-6.80). For tolterodine, the SIR (95% CI) was 5.01 (4.39-5.68) for current use and 5.97 (4.69-7.50) for recent use. The SIR (95% CI) was greater than the average for current use of any OAB drug among people aged more than 65 years, 8.02 (7.38-8.71); for OAB drug use among males, 7.69 (6.83-

8.63); for males aged more than 65 years with current exposure to any OAB drug, 11.19 (9.85-12.66); and for males with high cardiovascular risk with current exposure to any OAB drug, 10.29 (8.67-12.07). Details are available in Annex 8, Tables CV2a and CV4a.

For stroke, the SIR (95% CI) in cases per 1,000 person-years was 6.00 (5.60-6.43) for current use of any OAB drug and 6.42 (5.61-7.32) for recent use. Of the three most commonly used OAB drugs, the SIR (95% CI) per 1,000 person-years was lowest for current use of solifenacin, 5.12 (4.45-5.87), and greatest for oxybutynin, 6.76 (5.94-7.65). For tolterodine, the SIR (95% CI) was 6.34 (5.63-7.10) for current use and 6.70 (5.33-8.31) for recent use. The SIR (95% CI) was greater than the average for current use of any OAB drug among people aged more than 65 years, 10.18 (9.45-10.95); for people with high cardiovascular risk with current exposure to any OAB drug, 7.86 (7.19-8.57); for OAB drug use among males, 7.67 (6.81-8.60); for males aged more than 65 years with current exposure to any OAB drug, 11.71 (10.34-13.21); and for males with high cardiovascular risk with current exposure to any OAB drug, 9.69 (8.42-11.09). Details are available in Annex 8, Tables CV2g and CV4g.

When analyzing overall mortality, the SIR (95% CI) in cases per 1,000 person-years for current use of any OAB drug was 19.87 (19.13-20.63) and higher for recent use 40.60 (38.53-42.76). Among the three most commonly used OAB drugs, the SIR (95% CI) per 1,000 person-years was lowest for current use of solifenacin, 15.37 (14.18-16.64), and greatest for oxybutynin, 25.61 (24.00-27.30). For tolterodine, the SIR was 19.21 (18.00-20.49) for current use and 42.82 (39.25-46.62) for recent use. The SIR (95% CI) was greater than the average for current use of any OAB drug among people aged more than 65 years, 34.69 (33.35-36.08); for people with high cardiovascular risk with current exposure to an OAB drug, 24.77 (23.60-25.99); for OAB drug use among males, 28.12 (26.47-29.85); for males aged over 65 years with current exposure to any OAB drug, 43.43 (40.76-46.22); and for males with high cardiovascular risk with current exposure to any OAB drug, 33.32 (30.83-35.95). Similar patterns of variations within groups of medications and patient characteristics can be seen when cardiovascular mortality and its two components CHD death and cerebrovascular mortality were analyzed (see Annex 8, Tables CV2c, CV2d, CV2e, and CV4c, CV4d, and CV4e). For current use of any OAB drug, the SIR (95% CI) per 1,000 person-years was 4.53 (4.18-4.90) for cardiovascular mortality, 2.63 (2.36-2.91) for CHD death, and 1.99 (1.76-2.24) for cerebrovascular disease death.

We included the composite endpoint MACE to be analyzed in case the effect of OAB drugs was homogeneous on the components of MACE (Annex 8, Tables CV2f and CV4f). The SIR (95% CI) in cases per 1,000 person-years was 12.19 (11.61-12.80) for current use of any OAB drug and 15.59 (14.31-16.96) for recent use. Among the three most commonly used OAB drugs, the SIR (95% CI) per 1,000 person-years was lowest for current use of

solifenacin, 9.82 (8.88-10.84), and greatest for oxybutynin, 14.32 (13.10-15.62). For tolterodine, the SIR (95% CI) was 12.63 (11.63-13.69) for current use and 16.40 (14.21-18.83) for recent use. The SIR (95% CI) was greater than the average for current use of any OAB drug among people aged more than 65 years, 20.60 (19.55-21.68); for people with high cardiovascular risk with current exposure to OAB drugs, 16.09 (15.11-17.12); for OAB drug use among males, 17.58 (16.26-18.97); for males aged over 65 years with current exposure to any OAB drug, 26.48 (24.38-28.70); and for males with high cardiovascular risk with current exposure to any OAB drug, 22.96 (20.76-25.30).

In Annex 8, Tables CV3, show the SIRs for each of the cardiovascular endpoints, for each of the medications in relation to the number of prescriptions, cumulative duration of use of the medication, and time since first exposure. No evident relationship can be clearly established with any of the endpoints or medications.

10.4.3.1 Incidence Rate Ratios

The effect of exposure to each of the OAB drugs compared with current use of tolterodine in the five cardiovascular endpoints studied is shown in Annex 8, Tables CV5, CV6, and CV7. Tables CV5a-CV5e (Annex 8) show crude and standardized (by age and sex) IRRs for the different cardiovascular endpoints with tolterodine as the reference for current exposure to OAB drugs. Table CV6 (Annex 8) shows the sex- and age-adjusted IRR of exposure to each of the OAB drugs studied for the different cardiovascular endpoints, as no other candidate variables met the requirements for inclusion in multivariate Cox regression models. It is a summary table of three analyses, the first using current use of tolterodine as the comparator, the second using current use of any other OAB drug as the comparator, and the third using periods of no/past use of OAB drugs as the comparator. Tables CV7.a-CV7.j (Annex 8) show IRRs from the propensity score analysis. Selected results from the study of cardiovascular disease incidence in users of antimuscarinics to treat OAB are presented in Table 6.

The point estimates for the IRRs for AMI, stroke, cardiovascular mortality, MACE, and overall mortality for current exposure to oxybutynin were consistently greater than 1 in the various analyses performed using different adjustments (standardization, individual covariate selection, and propensity score models) and comparators (tolterodine, any other OAB, and no use of any OAB drugs). In contrast, the point estimates for IRRs for AMI, stroke, cardiovascular mortality, MACE, and overall mortality for current exposure to solifenacin were all lower than 1.

Table 6. Selected Results From the Study of Cardiovascular Disease Incidence in Users of Antimuscarinics to Treat Overactive Bladder From Multivariate Analysis

Current Exposure and Endpoint	Adjusted Incidence Rate Ratio (95% Confidence Interval) for Each Endpoint for the Current Exposure Compared With…		
	Current Use of Tolterodine (Propensity Score Analysis)	Current Use of Any Other Study Drug (Multivariate Analysis)	Current Use of Any Other Study Drug (Propensity Score Analysis)
Current use of tolterodine			
AMI	Ref.	1.23 (0.80-1.89)	1.17 (0.98-1.39)
Stroke	Ref.	1.13 (0.85-1.51)	1.12 (0.96-1.31)
Coronary heart disease death	Ref.	0.89 (0.62-1.28)	1.12 (0.89-1.41)
Cerebrovascular disease death	Ref.	1.42 (0.93-2.16)	1.17 (0.90-1.51)
Cardiovascular mortality	Ref.	1.11 (0.80-1.56)	1.16 (0.98-1.38)
MACE	Ref.	1.06 (0.87-1.30)	1.15 (1.03-1.28)
Overall mortality	Ref.	1.10 (0.92-1.31)	1.04 (0.96-1.14)
Current use of oxybutynin			
AMI	1.20 (0.98-1.46)	1.43 (0.93-2.21)	1.36 (1.15-1.61)
Stroke	1.12 (0.94-1.34)	1.19 (0.89-1.60)	1.17 (1.00-1.37)
Coronary heart disease death	1.36 (1.05-1.75)	1.18 (0.82-1.70)	1.60 (1.29-2.00)
Cerebrovascular disease death	1.37 (1.03-1.82)	2.01 (1.33-3.06)	1.70 (1.32-2.19)
Cardiovascular mortality	1.34 (1.11-1.62)	1.50 (1.07-2.10)	1.64 (1.38-1.93)
MACE	1.14 (1.01-1.30)	1.18 (0.96-1.44)	1.25 (1.12-1.39)
Overall mortality	1.26 (1.14-1.38)	1.49 (1.24-1.78)	1.38 (1.27-1.50)
Current use of trospium			
AMI	0.93 (0.64-1.35)	1.37 (0.84-2.26)	0.98 (0.70-1.37)
Stroke	0.96 (0.70-1.33)	1.16 (0.81-1.68)	1.06 (0.79-1.41)

Current Exposure and Endpoint	Adjusted Incidence Rate Ratio (95% Confidence Interval) for Each Endpoint for the Current Exposure Compared With…		
	Current Use of Tolterodine (Propensity Score Analysis)	Current Use of Any Other Study Drug (Multivariate Analysis)	Current Use of Any Other Study Drug (Propensity Score Analysis)
Coronary heart disease death	1.15 (0.73-1.80	1.15 (0.72-1.85)	1.22 (0.81-1.83)
Cerebrovascular disease death	0.86 (0.49-1.49)	1.64 (0.95-2.86)	1.22 (0.78-1.90)
Cardiovascular mortality	1.02 (0.72-1.45)	1.39 (0.92-2.10)	1.25 (0.92-1.69)
MACE	1.03 (0.82-1.29)	1.24 (0.96-1.59)	1.13 (0.93-1.38)
Overall mortality	1.12 (0.94-1.33)	1.36 (1.10-1.68)	1.16 (1.00-1.35)
Current use of solifenacin			
AMI	0.64 (0.50-0.82)	0.91 (0.59-1.42)	0.71 (0.58-0.87)
Stroke	0.70 (0.56-0.88)	0.89 (0.66-1.20)	0.78 (0.65-0.93)
Coronary heart disease death	0.49 (0.33-0.71)	0.45 (0.30-0.68)	0.44 (0.33-0.61)
Cerebrovascular disease death	0.45 (0.28-0.73)	0.59 (0.37-0.95)	0.46 (0.31-0.66)
Cardiovascular mortality	0.46 (0.34-0.62)	0.51 (0.35-0.74)	0.44 (0.34-0.56)
MACE	0.65 (0.56-0.76)	0.78 (0.64-0.96)	0.70 (0.61-0.80)
Overall mortality	0.68 (0.60-0.77)	0.84 (0.70-1.01)	0.67 (0.60-0.74)

AMI = acute myocardial infarction; MACE = major adverse cardiovascular event; OAB = overactive bladder.

Note: Multivariate analysis adjustment was done as described in methods section. Model adjusted for age at cohort entry and sex.

The propensity score was estimated through logistic regression using patients who experienced single exposure to either oxybutynin or tolterodine at cohort entry. These models adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Annex 8, Table CV1. After trimming approximately 1% of extreme values in each tail, patients were grouped into propensity score strata defined by deciles of the propensity score distribution in patients receiving the comparison (as opposed to the reference) medication at entry. Stratified incidence rate ratios estimated in propensity score analyses were calculated using the Mantel-Haenszel approach.

Please note that the comparator "any other OAB drug" is a shifting comparator including different OAB drugs in each comparison. As result, incidence rate ratios are not directly comparable across OAB drugs.

Source: Annex 8, Tables CV6 and CV7.

Propensity score–adjusted IRRs for AMI, stroke, cardiovascular mortality, MACE, and overall mortality were calculated for the different medications. Propensity scores were used for trimming the exposure cohorts using the 99th percentile (any OAB group) and the first percentile (tolterodine group). We stratified using deciles of the propensity score calculated among the tolterodine patients and calculated the stratified relative risk using the Mantel-Haenszel approach. Detailed results of the analysis stratified and adjusted by propensity scores are shown in Annex 8, Table CV7.

10.4.4 Study of Cancer Incidence in Users of Antimuscarinics to Treat Overactive Bladder

10.4.4.1 Description of Patient Characteristics

In Annex 8, Table N1 shows characteristics of patients in the study cohort stratified by the presence of the outcome. Of the 119,912 persons in the study cohort, 4,117 developed a study cancer endpoint. Since an additional 1,762 patients had their follow-up terminated when they developed a non-study cancer (yielding a total of 5,879 study and non-study cancers combined), the study cancers accounted for 70% of all incident cancers in the study cohort. See the description of the methods in Section 9.9.2.6.

Among the 4,117 patients with a study cancer endpoint, the most common cancers were of the prostate (n = 932), female breast (n = 886), colon/rectum (n = 545), bladder (n = 534), and lung (n = 495). Males represented 30% of the persons without cancer but 47% of those with cancer endpoints. For the cancers that are not sex-specific, the proportion of males was highest among the patients with bladder cancer and lowest in those with skin melanoma. Over two-thirds of the cancers appeared in patients aged at least 65 years at cohort entry; over 90% appeared in patients aged at least 55 years at cohort entry. The age distribution in patients with melanoma of the skin and breast cancer was slightly shifted toward younger ages. The distribution of socioeconomic status (measured through the index of multiple deprivation) was very similar for patients who did and did not develop a cancer endpoint.

A diagnosis of OAB was recorded in 50% of patients without a cancer endpoint. Among patients who experienced a cancer endpoint, 44% had a recorded diagnosis of OAB. The proportion of women with breast cancer who had an OAB diagnosis was 62%, and for uterine cancer it was 60%. In contrast, among men with a diagnosis of prostate cancer, 28% had a recorded diagnosis of OAB. A higher percentage of patients with cancer had exposure to the study drugs prior to cohort entry than patients without cancer.

Current smoking at cohort entry was 16% for the entire cohort, but former smoking was more common in patients who later developed cancer (43%) than in patients who did not

develop cancer (35%). Current smoking was present at cohort entry in 42% of patients who later developed lung and bronchus cancer. Information on smoking was missing for 1.2% of patients without a cancer endpoint and in 1.3% of those with cancer. The distribution of body mass index was similar in patients with and without cancer; information was missing in 33% of each group. Patients who developed corpus uteri cancer were more commonly obese (body mass index ≥ 30 kg/m^2) than others. The distribution of alcohol intake was generally similar in patients who did or did not develop cancer, with similar distributions of missing amount of alcohol (5.2% and 6.0%, respectively) and missing information (9.4% and 10%, respectively). Overall, 52% of patients had a low-moderate intake of alcohol. Patients with prostate cancer had a slightly different distribution, with fewer nondrinkers, more heavy drinkers, and less missing information.

Only 2 patients in the cohort had codes indicating the presence of *BRCA1* or *BRCA2* mutations, and they did not develop cancer. A total of 21 women had codes for bilateral mastectomy (1 developed colorectal cancer; note that cancer prior to the date of the index prescription was an exclusion criterion). Recorded family history of cancer had a similar distribution in patients with and without cancer. For all cancers evaluated, less than 3% of patients had a recorded family history of cancer, which suggests an underrecording of family history of cancer in these data, because the population prevalence of a family history of common cancers is appreciably higher than 3%.[48,49] Eleven patients had recorded exposure to radiation prior to cohort entry and did not develop cancer. Less than 1% of the patients had exposure to tamoxifen or letrozole prior to cohort entry. Although women with cancer had higher use of hormonal replacement therapy prior to cohort entry (42% vs. 36% for women without cancer), the distribution across study cancers was relatively similar. The use of immunosuppressant drugs was similar in patients with and without cancer (1.2% vs. 1.1%, respectively); the distribution across cancers varied, but calculations were based on a very low number of cases.

The prevalence of hypertension (as determined by diagnoses and/or medication use) was 80% in patients without a study cancer endpoint and 90% in those with a study cancer endpoint. Differences in prevalence of hypertension by cancer type mirrored the age distribution of the study cancers. Diabetes (as determined by diagnoses and/or medication use) was present in 11% of patients with no study cancer endpoint and 16% of those with the any cancer endpoint. As before, prevalences generally mirrored the age distribution of the subgroups stratified by study cancer, but a higher prevalence was seen in patients who later received a diagnosis of corpus uteri or pancreatic cancer. Cardiovascular morbidity at baseline (e.g., history of AMI or stroke) was more common in patients who developed cancer.

Health services utilization in the year prior to cohort entry was similar in patients with and without cancer. Mean time from enrollment to cohort entry was similar in patients with and without cancer (9 years).

10.4.4.2 Analysis of Cancer Incidence Rates by Ever-Exposure to Study Drugs

A total of 4,117 cancer events were observed during 399,365 person-years of follow-up contributed by 119,859 study patients. For individual study drugs, ever-exposed person-time ranged from 1,696 person-years for darifenacin and 9,881 person-years for fesoterodine to 155,883 person-years for oxybutynin and 191,057 person-years for tolterodine. The number of cancer events observed during ever-exposed follow-up time ranged from 17 for darifenacin and 89 for fesoterodine to 1,736 for oxybutynin and 1,930 for tolterodine. Note that the sum of the number of cancer events associated with ever-exposure to individual study drugs is greater than the total number of events for exposure to any OAB drug because an event may occur in a patient with ever-exposure to more than one study drug. Similarly, the person-years accumulated for ever-exposure to individual study drugs are not mutually exclusive.

The crude incidence rate estimate in an analysis of all study cancers was 10.31 per 1,000 person-years (95% CI, 10.00-10.63) (Annex 8, Table N3.a5). (All subsequent incidence rates [95% CIs] are expressed per 1,000 person-years with males and females combined unless sex-specific rates are quoted.) Cancer incidence rates were standardized to the age-sex distribution of the person-time contributed by all cohort members (hereafter referred to as SIRs). SIRs (95% CIs) for ever-exposure were similar across study drugs, ranging from 9.78 (7.82-12.07) for fesoterodine to 10.88 (10.38-11.41) for oxybutynin.

SIRs (95% CIs) for the composite cancer endpoints in analysis 5 were more than twice as high for males, 16.92 (16.17-17.70), as for females, 7.69 (7.37-8.02) (Annex 8, Table N3.a5). Among males, SIRs (95% CIs) for ever-exposure to individual study drugs ranged from 15.33 (14.32–16.40) for tolterodine to 19.82 (8.33, 39.42) for darifenacin. Among females, SIRs (95% CIs) for ever-exposure to individual study drugs ranged from 6.70 (3.04–12.74) for darifenacin to 7.97 (7.46–8.51) for oxybutynin.

SIRs (95% CIs) by study drug for individual study cancer endpoints ranged from 0.31 (0.26–0.37) for renal cancer (Annex 8, Table N3.j5) to 8.23 (7.71–8.77) per 1,000 male person-years for prostate cancer (Annex 8, Table N3.h5). Except for several instances in which very few cases occurred and estimates were quite imprecise, SIRs for a given cancer type were generally similar among the various study drugs, and 95% CIs for the SIRs overlapped. Prostate cancer was a notable exception; for this cancer, the SIR (95% CI) for use of oxybutynin, 8.71 (7.87-9.61), was higher than that for use of tolterodine, 7.22 (6.53-7.97). Of note, the calendar years of cohort entry for oxybutynin users at entry were

nearly evenly distributed throughout the study period, while those for tolterodine were weighted substantially toward the earlier years of the study (Annex 8, Table A3). This would likely result in proportionately more oxybutynin person-time being contributed within the first few years after cohort entry than tolterodine person-time, a point that will be discussed further in Section 11.3.

SIRs (95% CIs) were higher for males than for females for all study cancers that affect both sexes except for melanoma, for which the male SIR was 0.43 (0.32–0.57) and the female SIR was 0.46 (0.39–0.55). SIRs were also consistently higher for the older age group (≥ 65 years) than the younger group (< 65 years) for all study cancers combined and for the individual study cancers.

The SIR (95% CI) for prostate cancer noted above is quite high, almost 4 times higher than the SIR for colorectal cancer among males exposed to any OAB drug, 2.06 (1.80-2.34) (Annex 8, Table N3.b5), and more than 4 times higher than the SIR for lung cancer in the same group, 1.89 (1.64-2.16) (Annex 8, Table N3.d5). Moreover, prostate cancer accounted for nearly half of the study cancers identified among males (932 of 1,917 events). Also of note is that the SIR for bladder cancer among males, 2.87 (95% CI, 2.57-3.20) (Annex 8, Table N3.i5), was higher than the SIRs for colorectal cancer and lung cancer among males, and that bladder cancer represents approximately one-third of study cancers other than prostate cancer among males (325 of 985 non–prostate cancer events). Although not as striking as the results for prostate cancer, this would be a higher incidence of bladder cancer than expected relative to the incidences of colorectal or lung cancer in the general population. These findings have been evaluated further in analyses described in Sections 10.4.4.3 and 10.4.4.4, and an interpretation is provided in Section 11.3.

Analysis 1 (which included only cases in the validation cohort that were identified in GP records; NCDR and HES data were ignored) and analysis 2 (which included all provisional cases in the validation cohort that were identified in GP records; again ignoring NCDR and HES data) are also shown. Overall, in analysis 1, there were 1,397 events among 50,816 patients contributing 161,852 person-years of follow-up, and the SIR (95% CI) for both sexes combined was 8.56 (8.11-9.02) (Annex 8, Table N3.a1). Similarly, in analysis 2, the overall SIR was 8.82 (8.37-9.29) (Annex 8, Table N3.a2). Sex- and age-specific results for the study cancers overall and by study drug follow similar patterns to those described above.

Analysis 4 included all confirmed and provisional cases from the entire study cohort and used all data sources to identify cases, including the information obtained during patient profile review of GP records. Therefore, the total number of cases is greater than for analysis 5 (4,129 rather than 4,117). Since the person-time for analysis 4 is the same as for

analysis 5, incidence rates for analysis 4 are slightly higher than for analysis 5, but the differences are not apparent within the level of precision of results presented. Overall, the SIR for all study cancers in both sexes combined in this analysis was 10.34 (95% CI, 10.03-10.66) (Annex 8, Table N3.a4), which is the same as the result for analysis 5 except for the change in the upper confidence bound after rounding off (Annex 8, Table N3.a5).

10.4.4.3 Analysis of Cancer Incidence Rates by Ever-Exposure to a Single Study Drug

In Annex 8, Tables N4 show results of analyses restricted to cohort members who had exposure to a single OAB drug during their observed follow-up time; table numbering follows the same pattern as described at the beginning of Annex 8 for Tables N3. Again, analysis 5 is the main analysis and will be discussed here first.

A total of 3,095 cancer events were observed during 301,139 person-years of follow-up contributed by 117,077 patients (Annex 8, Table N4.a5). Results related to single exposure to the individual study drugs were generally similar to those for ever-exposure to the study drugs because more than 75% of the total person-time in the study consisted of person-time ever exposed to only a single study drug (301,139 person-years of 399,365 person-years).

For individual study drugs, person-time accumulated by patients exposed to a single study drug (Annex 8, Table N4.a5) ranged from 233 person-years for darifenacin and 3,093 person-years for fesoterodine to 95,010 person-years for oxybutynin and 120,060 person-years for tolterodine. The number of cancer events observed among patients with exposure to a single study drug ranged from 3 for darifenacin and 33 for fesoterodine to 1,072 for oxybutynin and 1,199 for tolterodine.

The SIR (95% CI) for the overall composite cancer endpoint in the subgroup of patients with exposure to a single study drug was more than twice as high for males, 17.22 (16.37-18.11), as for females, 7.60 (7.23-7.99) (Annex 8, Table N4.a5). Among males with single study drug exposures, the incidence rate for exposure to individual study drugs ranged from 14.22 (11.03-18.05) for trospium to 19.75 (1.51-73.99) for darifenacin (based on 2 cases). The next highest SIR for males was associated with single use of oxybutynin, 19.57 (18.01-21.24). Among females, the incidence rate for single study drug exposure ranged from 5.84 (0.15-32.52) for darifenacin (based on 1 case) to 8.36 (4.76-13.53) for fesoterodine.

In an analysis of all study cancers combined, the SIR estimate associated with exposure to a single study drug was 10.33 per 1,000 person-years (95% CI, 9.97-10.70) (Annex 8, Table N4.a5). SIRs (95% CIs) for single exposures were similar across study drugs, ranging from 9.81 (1.68-29.51) for darifenacin to 11.18 (7.63-15.79) for fesoterodine.

In Annex 8, Tables N4.b5-N4.k5 show SIRs for individual study cancer endpoints overall, by study drug, and by sex. SIRs (95% CIs) ranged from 0.32 (0.26-0.39) for renal cancer to 8.58 (7.98-9.21) per 1,000 male person-years for prostate cancer. In general, SIRs for a given cancer type were similar among the various study drugs. SIRs (95% CIs) were higher for males than for females for all study cancers that affect both sexes except for melanoma, for which the male SIR was 0.43 (0.31–0.59) and the female SIR was 0.46 (0.38–0.57). Again, SIRs were consistently higher for older patients (≥ 65 years) than for the younger age group (< 65 years).

The other analyses (case definitions) followed the same pattern as described in the beginning of Annex 8, with essentially similar SIRs for analyses 4 and 5 and somewhat lower SIRs for analyses 1 and 2 (for the same reasons as discussed in Section 10.4.4.2).

10.4.4.4 Analysis of Cancer Incidence Rates by Other Measures of Exposure to Overactive Bladder Medications

Beyond ever-exposure and single-exposure, we explored the relation of cancer incidence to several quantitative measures of exposure to OAB drugs, including maximum daily dose, cumulative dose, number of prescriptions, cumulative duration of use, and time since first exposure. For a drug prescribed to be taken (1) at a single daily dose by all patients, (2) on a continuous basis, (3) indefinitely, and (4) with prescriptions written for one specific duration (e.g., 30 days), there will be a perfect correlation between cumulative dose, number of prescriptions, cumulative duration of use, and time since first exposure, and these measures can be used interchangeably to specify cumulative exposure. To the extent that there is variability in the four prescribing factors listed above (e.g., change in daily dose, prescriptions written for either 30 or 90 days, or any intermittent use), there will be a lower correlation among these four measures. In general, when exposure to a drug causes an increased risk of cancer, the risk increases with increasing cumulative exposure (although, conditional on the cumulative dose achieved, it may be expected to decrease toward the background level after exposure ends). Therefore, the main focus here is on cumulative dose, with the other measures providing supporting or complementary information. In Annex 8, Table N5 presents SIRs (case definition 5) for the sex-specific composite cancer endpoints stratified by categories of each of these measures; SIRs for males are presented first for each study drug, followed by SIRs for females for each study drug.

For males exposed to oxybutynin, the SIRs (95% CIs) for the composite cancer endpoint were seen to *decrease* with increasing cumulative exposure, from 20.79 (18.62-23.15) for ≤ 200 mg to 18.09 (16.12-20.23) for 200-1,000 mg to 15.72 (13.50-18.20) for > 1,000 mg. A similar pattern was seen in the other measures that are expected to be somewhat correlated with cumulative dose. The most striking decrease in SIR in relation to

any of these measures was seen with time since first exposure, where the SIR for more than 365 days since first exposure to oxybutynin (14.24; 95% CI, 12.96-15.62) was only approximately one-third of that for 1 to 45 days since first exposure (41.50; 95% CI, 32.64-52.02) (Annex 8, Table N5). This decrease in cancer incidence with increasing time since first exposure indicates a temporal relation between cohort entry and cancer risk; this phenomenon is further explored in Section 10.4.4.5. By contrast, there is no substantial difference among SIRs stratified by maximum daily dose.

Similar patterns were observed for composite cancer SIRs among males for each of the study OAB drugs (except for darifenacin, for which decreases in SIRs with increasing cumulative dose and time since first exposure were not evident based on a total of 8 cases) (Annex 8, Table N5).

For females exposed to oxybutynin, there was no evident trend in the composite cancer endpoint incidence in relation to cumulative dose or any of the other measures that are expected to be somewhat correlated with cumulative dose (Annex 8, Table N5). There was also no apparent association between cancer incidence and maximum daily dose (Annex 8, Table N5). The same findings were observed for the other study OAB drugs; although an association between increasing cancer SIR and increasing cumulative dose or duration of darifenacin is suggested, these estimates are quite imprecise (based on 8 cases), and CIs overlap broadly (Annex 8, Table N5).

10.4.4.5 Other Analyses

As noted in Section 10.4.4.2, we observed higher-than-expected incidences of bladder and prostate cancer in males in this study, as well as decreasing rates of these cancers in relation to increasing time since starting OAB drugs. We therefore evaluated the timing of diagnosis of these (and the other study) cancers in relation to the time since cohort entry, as prespecified in the statistical analysis plan. The rationale for this is that genitourinary cancers may cause symptoms similar to those of OAB and therefore the rates of such cancers might be influenced by protopathic or detection bias during the period soon after the start of treatment with OAB drugs. Annual cancer incidence rates stratified by 6-month period since cohort entry, with 95% CIs, are shown in Table 7. Rates are shown for both sexes combined except for sex-specific cancers. The bladder cancer incidence rate (95% CI) was greater in earlier periods after cohort entry: 3.42 (2.96-3.94) for 6 months or less since cohort entry, 1.51 (1.19–1.88) for > 6 to 12 months since cohort entry, and close to 1 or less for most intervals of longer duration since cohort entry. The prostate cancer incidence rate was 19.34 (17.30-21.55) for 6 months or less since cohort entry, 8.28 (6.88–9.88) for > 6 to 12 months since cohort entry, and decreased more gradually thereafter to plateau at

lower values. Incidence rates stratified by 6-month periods since cohort entry for other cancers did not show this pattern.

Figures depicting cancer incidence rates (sex-specific and overall) stratified by 6-month intervals after cohort entry are shown in Annex 7. Patterns similar to those discussed in the preceding paragraph are seen for the sex-specific incidence rates for bladder cancer. By contrast, for the other study cancers, incidence rates are generally more uniform among 6-month strata after cohort entry (rather than showing a higher rate during the early period of follow-up than during later periods).

Table 7. Cancer Incidence Rates by Time Since Cohort Entry at 6-Month Intervals

Time Since Cohort Entry (Months)	Colon and Rectum			Pancreas			Lung and Bronchus		
	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 6	79	1.39	(1.10, 1.74)	15	0.26	(0.15, 0.44)	79	1.39	(1.10, 1.74)
> 6 to 12	56	1.11	(0.84, 1.44)	16	0.32	(0.18, 0.51)	60	1.19	(0.91, 1.53)
> 12 to 18	63	1.41	(1.08, 1.80)	15	0.34	(0.19, 0.55)	46	1.03	(0.75, 1.37)
> 18 to 24	44	1.12	(0.81, 1.50)	18	0.46	(0.27, 0.72)	40	1.01	(0.72, 1.38)
> 24 to 30	51	1.47	(1.09, 1.93)	10	0.29	(0.14, 0.53)	47	1.35	(1.00, 1.80)
> 30 to 36	44	1.45	(1.05, 1.94)	6	0.20	(0.07, 0.43)	42	1.38	(0.99, 1.86)
> 36 to 42	47	1.77	(1.30, 2.35)	14	0.53	(0.29, 0.88)	35	1.31	(0.92, 1.83)
> 42 to 48	23	1.00	(0.63, 1.50)	6	0.26	(0.10, 0.57)	29	1.26	(0.84, 1.81)
> 48 to 54	25	1.26	(0.81, 1.85)	5	0.25	(0.08, 0.59)	21	1.05	(0.65, 1.61)
> 54 to 60	34	2.00	(1.38, 2.79)	10	0.59	(0.28, 1.08)	20	1.17	(0.72, 1.81)
> 60 to 66	24	1.67	(1.07, 2.48)	6	0.42	(0.15, 0.91)	17	1.18	(0.69, 1.89)
> 66 to 72	17	1.42	(0.83, 2.28)	3	0.25	(0.05, 0.73)	17	1.42	(0.83, 2.28)
> 72 to 78	15	1.55	(0.87, 2.55)	3	0.31	(0.06, 0.90)	9	0.93	(0.42, 1.76)
> 78 to 84	11	1.43	(0.72, 2.56)	4	0.52	(0.14, 1.33)	7	0.91	(0.37, 1.88)
> 84 to 90	4	0.70	(0.19, 1.80)	2	0.35	(0.04, 1.27)	12	2.11	(1.09, 3.68)
> 90 to 96	7	1.80	(0.72, 3.71)	3	0.77	(0.16, 2.26)	7	1.80	(0.72, 3.71)
> 96 to 102	1	0.45	(0.01, 2.51)	2	0.90	(0.11, 3.25)	4	1.80	(0.49, 4.61)
> 102 to 108	0	0.00	(0.00, 4.96)	0	0.00	(0.00, 4.96)	3	4.03	(0.83, 11.79)
Total	545	1.36	(1.25, 1.48)	138	0.35	(0.29, 0.41)	495	1.24	(1.13, 1.35)

Time Since Cohort Entry (Months)	Melanoma of the Skin			Breast (Female)			Corpus Uteri (Female)		
	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 6	26	0.46	(0.30, 0.67)	134	3.37	(2.82, 3.99)	32	1.09	(0.74, 1.54)
> 6 to 12	26	0.51	(0.34, 0.75)	114	3.20	(2.64, 3.84)	21	0.81	(0.50, 1.23)
> 12 to 18	21	0.47	(0.29, 0.72)	102	3.22	(2.62, 3.91)	14	0.61	(0.33, 1.02)
> 18 to 24	14	0.35	(0.19, 0.60)	84	2.99	(2.39, 3.70)	11	0.54	(0.27, 0.97)
> 24 to 30	18	0.52	(0.31, 0.82)	64	2.58	(1.98, 3.29)	12	0.68	(0.35, 1.18)
> 30 to 36	15	0.49	(0.28, 0.81)	75	3.42	(2.69, 4.29)	15	0.96	(0.54, 1.59)
> 36 to 42	11	0.41	(0.21, 0.74)	61	3.17	(2.42, 4.07)	6	0.44	(0.16, 0.96)
> 42 to 48	10	0.43	(0.21, 0.80)	51	3.05	(2.27, 4.01)	7	0.60	(0.24, 1.23)
> 48 to 54	4	0.20	(0.05, 0.51)	39	2.70	(1.92, 3.69)	3	0.30	(0.06, 0.87)
> 54 to 60	7	0.41	(0.17, 0.85)	42	3.39	(2.44, 4.58)	3	0.35	(0.07, 1.02)
> 60 to 66	13	0.90	(0.48, 1.54)	37	3.52	(2.48, 4.85)	4	0.55	(0.15, 1.41)
> 66 to 72	5	0.42	(0.14, 0.98)	17	1.95	(1.13, 3.11)	2	0.33	(0.04, 1.21)
> 72 to 78	2	0.21	(0.02, 0.74)	28	3.93	(2.61, 5.68)	3	0.62	(0.13, 1.81)
> 78 to 84	2	0.26	(0.03, 0.94)	9	1.59	(0.73, 3.03)	1	0.26	(0.01, 1.46)
> 84 to 90	5	0.88	(0.29, 2.05)	16	3.81	(2.18, 6.19)	1	0.35	(0.01, 1.97)
> 90 to 96	2	0.51	(0.06, 1.86)	6	2.10	(0.77, 4.57)	0	0.00	(0.00, 1.92)
> 96 to 102	0	0.00	(0.00, 1.66)	6	3.67	(1.35, 8.00)	1	0.92	(0.02, 5.12)
> 102 to 108	1	1.34	(0.03, 7.49)	1	1.81	(0.05, 10.07)	0	0.00	(0.00, 9.98)
Total	182	0.46	(0.39, 0.53)	886	3.10	(2.90, 3.31)	136	0.67	(0.56, 0.79)

Time Since Cohort Entry (Months)	Prostate (Male)			Urinary Bladder		
	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 6	327	19.34	(17.30, 21.55)	194	3.42	(2.96, 3.94)
> 6 to 12	123	8.28	(6.88, 9.88)	76	1.51	(1.19, 1.88)
> 12 to 18	100	7.69	(6.26, 9.36)	53	1.19	(0.89, 1.55)
> 18 to 24	66	5.80	(4.49, 7.38)	45	1.14	(0.83, 1.53)
> 24 to 30	64	6.50	(5.01, 8.30)	33	0.95	(0.65, 1.34)
> 30 to 36	47	5.52	(4.06, 7.35)	25	0.82	(0.53, 1.21)
> 36 to 42	54	7.32	(5.50, 9.55)	26	0.98	(0.64, 1.43)
> 42 to 48	26	4.09	(2.67, 6.00)	22	0.95	(0.60, 1.44)
> 48 to 54	33	6.05	(4.17, 8.50)	19	0.95	(0.57, 1.49)
> 54 to 60	24	5.17	(3.31, 7.70)	7	0.41	(0.17, 0.85)
> 60 to 66	15	3.86	(2.16, 6.37)	8	0.56	(0.24, 1.09)
> 66 to 72	18	5.60	(3.32, 8.86)	6	0.50	(0.18, 1.09)
> 72 to 78	15	5.83	(3.26, 9.61)	8	0.82	(0.36, 1.63)
> 78 to 84	6	2.96	(1.09, 6.45)	5	0.65	(0.21, 1.52)
> 84 to 90	7	4.70	(1.89, 9.69)	1	0.18	(0.00, 0.98)
> 90 to 96	4	3.89	(1.06, 9.95)	2	0.51	(0.06, 1.86)
> 96 to 102	3	5.12	(1.06, 14.96)	3	1.35	(0.28, 3.95)
> 102 to 108	0	0.00	(0.00, 19.41)	1	1.34	(0.03, 7.49)
Total	932	8.23	(7.71, 8.77)	534	1.34	(1.23, 1.46)

Time Since Cohort Entry (Months)	Kidney and Renal Pelvis			Non-Hodgkin Lymphoma		
	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 6	20	0.35	(0.22, 0.54)	26	0.46	(0.30, 0.67)
> 6 to 12	18	0.36	(0.21, 0.56)	17	0.34	(0.20, 0.54)
> 12 to 18	9	0.20	(0.09, 0.38)	15	0.34	(0.19, 0.55)
> 18 to 24	13	0.33	(0.18, 0.56)	18	0.46	(0.27, 0.72)
> 24 to 30	5	0.14	(0.05, 0.34)	7	0.20	(0.08, 0.42)
> 30 to 36	12	0.39	(0.20, 0.69)	11	0.36	(0.18, 0.65)
> 36 to 42	12	0.45	(0.23, 0.79)	11	0.41	(0.21, 0.74)
> 42 to 48	5	0.22	(0.07, 0.51)	5	0.22	(0.07, 0.51)
> 48 to 54	8	0.40	(0.17, 0.79)	7	0.35	(0.14, 0.72)
> 54 to 60	3	0.18	(0.04, 0.51)	4	0.23	(0.06, 0.60)
> 60 to 66	6	0.42	(0.15, 0.91)	1	0.07	(0.00, 0.39)
> 66 to 72	2	0.17	(0.02, 0.60)	7	0.59	(0.24, 1.21)
> 72 to 78	7	0.72	(0.29, 1.49)	5	0.52	(0.17, 1.20)
> 78 to 84	2	0.26	(0.03, 0.94)	4	0.52	(0.14, 1.33)
> 84 to 90	2	0.35	(0.04, 1.27)	3	0.53	(0.11, 1.54)
> 90 to 96	0	0.00	(0.00, 0.95)	1	0.26	(0.01, 1.43)
> 96 to 102	1	0.45	(0.01, 2.51)	2	0.90	(0.11, 3.25)
> 102 to 108	0	0.00	(0.00, 4.96)	0	0.00	(0.00, 4.96)
Total	125	0.31	(0.26, 0.37)	144	0.36	(0.30, 0.42)

CI = confidence interval; CONF = confirmed; PROV = provisional.

Note: Cancer definition 5 comprised all provisional (PROV-1) cases from non-linked practices and CONF-1, CONF-2, and CONF-4 cases from linked practices.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Protopathic bias and/or detection bias are plausible explanations for higher incidence rates of bladder and prostate cancers during the early period after cohort entry, and especially during the first 6 months after starting OAB drug treatment, than in subsequent periods. Although depletion of susceptibles is another potential explanation for a drop in incidence of a disease during follow-up in pharmacoepidemiology studies, such an interpretation requires that there is a causal relation between the exposure and disease of interest. In view of the rapid appearance of excessive bladder and prostate cancers after cohort entry in the present study and the typically longer time course for development and growth of these cancers, such a causal explanation seems improbable.

10.5 Adverse Events and Adverse Reactions

For studies in which the research team used data only from automated health care databases, according to the International Society for Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,

> *"Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines."*[28]

Thus, reporting of individual cases is not required, and the analysis of adverse reactions is based upon aggregated data that are presented in the final study report.

According to the EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products*,

> *"For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarized in the final study report."*[50]

Module VIII – Post-Authorisation Safety Studies, of the same document echoes this approach.[29] The new legislation further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health care records, it may not be feasible to make a causality assessment at the individual case level.

11 DISCUSSION

11.1 Key Results

Validation efforts in this study were based on various sources of information, including registries, hospital discharge diagnoses, and clinical review of electronic primary care records (5,593 for cardiovascular endpoints and 1,486 for cancer endpoints), complemented by information provided on questionnaires sent to GPs, who checked medical records. These questionnaires had a response rate of 81%, which yielded 1,904 assessable questionnaires and allowed estimation of PPVs and NPVs with good precision.

The validation of electronic algorithms to identify AMI supports the usefulness of the algorithms used. PPVs were above 90% for definite, probable, and possible cases when definition 1 (only codes for AMI were present) was used. Possible AMI cases with definition 2 (no codes for AMI were present) had a PPV of 2.5% (95% CI, 1.6%-3.8%) (Section 9.9.2.2).

The electronic algorithm used for stroke ascertainment resulted in lower PPVs, none higher than 80%. During clinical review of patient profiles of unconfirmed cases, the following Read codes, none of them diagnostic codes, were found to be frequent: 662M.00, Stroke monitoring; 662o.00, Haemorrhagic stroke monitoring; 8HTQ.00, Referral to stroke clinic; and 9N0p.00, Seen in stroke clinic. We updated the electronic stroke definitions excluding these codes, and the PPVs rose to 92% (95% CI, 85%-96%) for definite stroke, 79% (95% CI, 69%-87%) for probable stroke, and 84% (95% CI, 70%-93%) for possible stroke. The updated algorithm did not identify 48 cases of stroke confirmed by the GPs through questionnaires out of the total 246 stroke cases confirmed by GPs (20%).

The NPV for non-case alive (individuals who did not develop AMI or stroke and were alive at the end of follow-up) was 99% (95% CI, 95%-100%) and for non-case dead (individuals who did not develop AMI or stroke and died during the study period) was 84% (95% CI, 77%-90%). This means that among non-case deaths, 16% were due to an AMI or stroke.

The stroke definition in CPRD GOLD data had a lower sensitivity than the stroke definition used for identifying stroke cases in linked practices using HES and ONS data. For stroke, the SIR (95% CI) in cases per 1,000 person-years was 6.00 (5.60-6.43) for current use of any OAB drug compared with 7.8 (7.1-8.5) in linked practices (preliminary report). It also affected the MACE endpoint—the SIR was 12.19 (11.61-12.80) for current use of any OAB drug in the study cohort and 14.7 (13.8-15.7) in the analysis performed in linked practices only (preliminary report)—and it affected cardiovascular mortality—the SIR was 4.53 (4.18-4.90) for current use of any OAB drug in the study cohort and 6.9 (6.2-7.5) in linked practices only (preliminary report). For AMI, the SIR was 4.90 (4.53-5.29) for current use of

any OAB drug in the study cohort and 4.3 (3.8-4.8) in linked practices (preliminary report). When analyzing overall mortality, the SIR for current use of any OAB drug was 19.87 (19.13-20.63) in the study cohort and 19.9 (18.8-21.1) in the linked practices (preliminary report).

The validation of cancer endpoints indicates that a very high proportion of cases of cancer identified in GP records by screening for diagnostic Read codes are confirmed by the clinical review of case profiles (chronologic GP medical record entries) or, in linked practices, by linkage to NCDR or HES data. The main limitation of identifying cancer cases in GP records is that a relatively high proportion of cases with cancer types for which GPs do not typically prescribe treatment themselves (lung, pancreatic, and renal) are not recorded compared with those for which GPs commonly prescribe hormonal therapies (breast, prostate). Whether this limitation affects relative risks in safety studies requires further study, but a lower proportion of cases of a given cancer type identified in non-linked practices would, at a minimum, result in more imprecise effect estimates than a higher proportion of cases of the same cancer in linked practices. Stratified analysis by linkage status could be considered to evaluate this impact.

Dregan and colleagues [20] compared diagnoses of cancers in four sites (lung, urinary tract, gastroesophageal, and colorectal) between GPRD[**] records and NCDR data in a cohort of 42,556 individuals registered in linked practices. They identified a total of 5,923 cancers: 5,216 (88%) in both sources, 494 (8.3%) in NCDR data only, and 213 (3.6%) in GP records only. PPVs were 96% for lung cancer, 92% for urinary tract cancer, 97% for gastroesophageal cancer, and 98% for colorectal cancer, but these calculations are based on NCDR data as the "gold standard" and with the assumption that cancer diagnoses observed only in GP records are false-positives. Our screening with Read cancer diagnosis codes followed by review of individual profiles (GP medical records) identified 185 cases (18% of 1,051 confirmed cases in the validation cohort) that were present only in the GP (CPRD GOLD) data. In addition, 151 cases (14% of 1,051 confirmed cases in the validation cohort) were identified in GP records (CPRD GOLD data) and also in HES data but not in NCDR data. In the analysis restricted to diagnosis dates before December 31, 2010 (during linked person-time in the NCDR data), these proportions were smaller: 22 cases (3.1% of 720 confirmed cases) were present only in GP records (CPRD GOLD data), and 34 cases (4.7% of 720 confirmed cases) were identified in GP records (CPRD GOLD data) and also in HES data but not in the NCDR data. Nevertheless, it is evident from our review that cases in GP records that do not appear in NCDR data are not all false-positives.

[**] The General Practice Research Database (GPRD) was the forerunner of the Clinical Practice Research Datalink (CPRD).

Boggon and colleagues [21] similarly reported a relatively high concordance (83%) between cancers recorded in the linked NCDR and those coded in GPs records in the GPRD (among a cohort selected to study antidiabetes medications). A majority of cases not found in the NCDR in their study (528 of 967 = 55%) were present in linked hospital records or death certificates. They also reported that among 5,676 NCDR cases, 5,335 (94%) were found in the GPRD. Thus, it is apparent that although the cancers identified in GP records, NCDR data, and HES data overlap considerably, some cases are found only in a subset of these sources. They reported that a larger number of cases were recorded in the NCDR than in the GPRD for colorectal, lung, genitourinary, and pancreatic cancers. Although our study cohort and methods used to screen for and validate cases in the present study differ from those of Boggon and colleagues, we confirmed that the overlap among the three main data sources used to identify cancers varies by cancer type and that different periods/lag times of data availability of each source have to be taken into account in study design.

A minor difference in validation results between the linked and non-linked practices is that a higher proportion of cases were excluded in the non-linked practices (25 of 661, 3.8%) than in the linked practices (13 of 825, 1.6%) because there was evidence of a cancer diagnosis preceding cohort entry in the patient's profile (despite lack of a diagnostic Read code that would have been detected automatically during cohort formation). This may be at least in part a result of the fact that HES data were used in the original process of cohort formation (for linked practices), and some patients in linked practices may have been excluded from the study based only on cancer diagnoses recorded in HES data before what would otherwise have been their cohort entry date. Some of the patients in non-linked practices who were excluded based on profile review might have had cancer diagnoses identified in their hospital data if such a linkage had existed for these practices, but since these data were not available, the chance of finding a preexisting cancer during profile review (GP records) was probably somewhat higher than for patients in the linked practices.

SIRs of cancer for the individual OAB drugs did not differ considerably. Cancer incidence rates were generally similar among the study OAB drugs whether analyzed as ever-exposed or as single-drug–exposed. If also the situation in other study populations, this opens the possibility of forming an aggregated exposure classification ("other OAB drugs") in a comparative study of a new OAB drug.

A relatively high incidence rate of certain genitourinary cancers (bladder and prostate) during the first year after initiating treatment for OAB symptoms could be related to protopathic or detection bias. In our view, the distinction between these forms of bias is essentially that in protopathic bias, the patient's symptoms are due to the cancer that is already present but undiagnosed, while in detection bias, the symptoms are not due to the cancer that is already present but undiagnosed, but rather they prompt further evaluation

that leads to its diagnosis. This distinction is not likely to be made reliably with the data available in a study such as this one, which uses limited medical record information. Methods to alleviate these biases, such as excluding the period immediately after initiating OAB treatment from consideration or simulating rates based on extrapolation back in time from later observations, may be considered in future studies.

The observed incidence rate (95% CI) per 1,000 person-years of the overall composite endpoint for the 10 cancers studied was 16.92 (16.17–17.70) in males and 7.69 (7.37–8.02) in females. Since these 10 cancers represent approximately 70% of all cancers observed in the study cohort, it is expected that the incidence rate of all cancers in the study cohort (study cancers plus all other cancers not studied) would be approximately 43% higher (1/0.7 = 1.43) than those we estimated for the study cancers. Such extrapolated rates for all cancers (calculated to be 24.2 per 1,000 person-years in males in males and 11.0 in females) are well below the peak sex-specific incidence rates for all cancers (other than non-melanoma skin cancer) among individuals aged 85 or more years in the UK in 2009-2011, which are 35.4 per 1,000 person-years in males in males and 21.4 in females.[51] Although this provides some evidence that the cancer incidence rates estimated in the present study are not implausibly high in relation to expected rates, more precise assessment of observed rates relative to expected rates in the present study cohort would require estimation of adjusted IRRs based on the observed age and sex distribution of the study cohort and the expected cancer incidence rates from UK cancer registries.

Regarding bladder cancer in particular, the observed incidence rate during the first year after cohort entry in the present study was 2.52 (95% CI, 2.23–2.84) per 1,000 person-years in males. This rate is similar to the highest age-specific incidence rate among males in the general UK population (i.e., 2.6 per 1,000 person-years among those aged ≥ 85 years).[52] The rate of bladder cancer during the first year of follow-up among males in the present study is unexpectedly high considering that the study cohort also included men in age groups younger than 85 years (for whom bladder cancer incidence rates in the general UK population are lower). Moreover, the SIR of bladder cancer among males observed in the present study (2.87 per 1,000 person-years) was higher than the rates observed among males for other cancers that occur more commonly than bladder cancer in the general population (e.g., the SIR among males in the present study was 1.89 per 1,000 person-years for lung cancer and 2.06 per 1,000 person-years for colorectal cancer). Considering these results, it is reasonable to conclude that the observed incidence rates for bladder cancer in this study are higher than expected, particularly during the first year after cohort entry and particularly in males. Together with the unexpectedly high rate of bladder cancer observed early in follow-up, the marked decrease in bladder cancer incidence after the first year of follow-up is consistent with the likelihood that protopathic

and/or detection bias play a considerable role in the observed incidence rates of bladder cancer in this study, particularly among males.

Detection bias for bladder cancer has been reported in another context, for example, as a confounder of the association between pioglitazone exposure in patients with diabetes mellitus and the diagnosis of bladder cancer.[53] Testing for proteinuria was more common among patients treated with pioglitazone than among patients receiving other treatments for diabetes, and the odds of a positive test for proteinuria and of having a full urinalysis within the next 6 months were also higher. Positive and negative proteinuria test results were directly and inversely related to the risk of having bladder cancer diagnosed, and adjustment for positive and negative proteinuria testing slightly reduced the magnitude of an observed association between pioglitazone and bladder cancer diagnosis (from 1.38 per 1,000 person-years to 1.28 per 1,000 person-years with > 4 years exposure). We have not further investigated the possibilities of detection bias or protopathic bias in the present study by evaluating the use of diagnostic tests in patients who initiate treatments for OAB symptoms.

The prostate cancer incidence rate (95% CI) was 14.17 (12.89-15.54) per 1,000 person-years for less than for 1 year since cohort entry, 6.81 (5.81–7.93) for 1 to less than 2 years since cohort entry, and then decreased more gradually. Incidence rates for other cancers stratified by number of years since cohort entry did not show this pattern. This observation suggests that protopathic and/or detection bias also play a role in the observed incidence of prostate cancer in this study.

The methods used to screen for and confirm cancer cases in electronic data sources generally and the CPRD in particular have varied among published studies. Rañopa and colleagues[54] conducted a literature review to ascertain methods used to identify cases of three commonly occurring cancers in UK primary care databases (THIN, QRESEARCH, and the CPRD). These investigators found that methods used in studies to identify breast, colorectal, and prostate cancers in these electronic data resources relied on only diagnostic codes in 57 of 84 studies (68%) and used additional evidence (e.g., chemotherapy) in the other 27 studies (32%). However, authors of few studies provided the cancer code list or made codes directly available to other researchers (such as by posting the list online). Among 28 study code lists obtained by Rañopa and colleagues, all included malignant neoplasm diagnostic codes, but they varied in whether they contained other codes such as those for in situ neoplasms, morphology designations, history of cancer, or secondary, suspected, or borderline cancer. In the present study, we focused on diagnostic codes recorded by GPs in the initial screening of their records and relied on related codes (treatment, morphology, and cancer care review), as well as independent data sources (NCDR and HES), to confirm cases. More sensitive methods of screening for possible

cancers (e.g., including a wider array of codes in the algorithm) inevitably would result in more false-positive cases or cases that cannot be confirmed by other evidence, and the priority for the present study (in preparation for a pharmacoepidemiology safety study) was to identify cases with a high probability of being true cases (within the constraints of available resources). Although absolute cancer incidence rates may be somewhat underestimated by this approach, it is expected that the relative risk estimation will be more accurate if fewer false-positive cases are included in the study.

Information on smoking in the CPRD GOLD database was unknown for only 3 of 1,731 patients for which GP questionnaires were available. On the closest day before the endpoint date, 732 (42%) were never smokers, 709 (41%) were former smokers, and 287 (17%) were current smokers. In comparing CPRD GOLD data with information from GP questionnaires, among never smokers, 97% were never smokers according to the GP questionnaires; among former smokers, 77% were former smokers according to GP questionnaires; and among current smokers, 84% were current smokers according to GP questionnaires. The level of concordance was similar for different types of data collection questionnaires (AMI, stroke, non-case alive, non-case death). CPRD GOLD data and GP questionnaires correlated better when the information on covariates was obtained for the date closest before the endpoint date in the CPRD GOLD database.

For obesity, CPRD GOLD data could not provide information for 26% of the patients when information was provided for the date closest before the endpoint date. Of those, 77% had information provided on the GP questionnaire. Of the patients classified as obese according to CPRD GOLD data, 82% were confirmed through the GP questionnaire, and absence of obesity was confirmed by the GP questionnaire for 92% of the patients.

CPRD GOLD data did not accurately classify pre/postmenopausal status. Of the patients classified as postmenopausal according to CPRD GOLD data, 3.6% were premenopausal based on GP questionnaires; 12% of those classified as premenopausal were confirmed by the GP questionnaire, and 77% of those classified as premenopausal in the CPRD GOLD database had their status changed to postmenopausal based on GP questionnaire information.

History of AMI according to CPRD GOLD data was confirmed by the GP questionnaire in 70% of the cases, and absence of history of AMI was confirmed in 96%. History of stroke according to CPRD GOLD data was confirmed by the GP questionnaire in 44% of the cases, and absence of history of stroke was confirmed in 88%.

Contrary to the study of cancer incidence in users of antimuscarinics to treat OAB, SIRs for cardiovascular endpoints for the individual OAB drugs differed. Among the three most commonly used OAB drugs, the incidence of each of the cardiovascular endpoints (AMI,

stroke, cardiovascular mortality, overall mortality, and MACE) was lowest for solifenacin and greatest for oxybutynin. The SIR (95% CI) of the composite endpoint MACE was lower for current use of solifenacin, 9.82 (8.88-10.84), and greater for oxybutynin, 14.32 (13.10-15.62).

Point estimates of the IRRs for AMI, stroke, MACE, overall mortality, and cardiovascular mortality for current exposure to oxybutynin were consistently greater than 1 in analyses using different comparators (tolterodine, use of other OAB drugs, and non-use of OAB drugs). In contrast, point estimates for IRRs for AMI, stroke, MACE, overall mortality, and cardiovascular mortality for current exposure to solifenacin were lower than 1.

11.2 Limitations

The main limitation of this study is related to the data sources. As the data include records from health care in routine clinical care settings, data are not necessarily clean, as shown by the presence of duplicated prescription records, likely due to repeated issue-and-print orders at the GP office at the time of patient visits. Also, linked data sources (NCDR and HES) are available only for practices in England, so some additional cancer cases are likely to have been missed in the substantial number of non-linked practices included in the CPRD (more so for cancers not routinely treated by GPs and less so for breast and prostate cancer, for which GPs commonly prescribe medications). While this would be expected to lower estimated cancer rates in non-linked practices, it is unknown whether it would affect relative risk estimation, which is the primary ultimate goal of this research.

Exposure information, including drug-use and treatment patterns, is derived from prescriptions issued, which the patient might not have filled and followed. We created definitions for therapy episodes, including treatment add-ons and switches, based on our clinical training and knowledge of patients, but we may not have captured the reality of drug treatments. For example, we found a relatively high percentage of treatment add-ons, which is surprising given that all study drugs are antimuscarinics and have a shared mechanism of action. It is possible that some of them actually represent treatment switches. This is supported by the observation that solifenacin was the drug most patients added on or switched to. We will review these definitions for the core studies.

We used three sources of information to identify cardiovascular endpoints: HES and ONS for linked practices and CPRD GOLD data for non-linked practices. The algorithms used in the CPRD GOLD database to identify AMI had a PPV greater than 90% and lower limit of the 95% CI above 80% for definite AMI, probable AMI, and possible AMI definition 1. Therefore, we included in the analysis of incidence rates and IRRs all cases identified through these definitions. The algorithm for possible AMI definition 2 (based only on compatible signs and

symptoms, but not AMI codes) performed poorly (PPV 2%). For the above-mentioned analysis, we included only the confirmed cases identified using possible AMI definition 2. For future studies, we propose to use all algorithms except possible AMI definition 2, because no further validation would be required.

The original stroke algorithms did not reach a PPV higher than 80% for any of the definitions, therefore we updated them. In the incidence rate and IRR analyses, we included all cases identified with the updated algorithms plus cases identified through the original algorithms and confirmed through the clinical review and GP questionnaires. Among the updated algorithms, only the updated definite stroke algorithm met the 80% threshold of the lower limit of the 95% CI; however, this algorithm missed 20% of the cases confirmed by GP questionnaires. Therefore, we propose for future studies using the updated definite stroke algorithm and validating via GP questionnaire all potential cases identified through the original and more sensitive stroke algorithms that were not classified as definite stroke using the updated definition.

While the algorithms for non-case alive performed satisfactorily, 16% of the patients classified as non-case among patients who died were found to have an AMI or stroke. If the goal of a study were to estimate the incidence of AMI or stroke in the study population, to avoid missing these cases, validation of all deaths of unknown cause would be required. However, if the resulting case misclassification were non-differential with respect to the exposure (the misclassification is equally present in users of each medication), the IRRs comparing exposures would be valid.

The stroke algorithm based on Read codes used in CPRD GOLD data in non-linked practices had a lower sensitivity than the stroke algorithm based on ICD codes used for identifying stroke cases in linked practices using HES and ONS data. This resulted in an underestimate of the incidence rates of stroke, the MACE endpoint, and cardiovascular mortality. For AMI, in linked practices, ascertainment of endpoints using only HES and ONS data did not include all out-of-hospital sudden cardiac deaths and was less sensitive than the algorithm used to identify AMI in CPRD GOLD data only in non-linked practices, which includes out-of-hospital sudden cardiac deaths.

The multivariate-adjusted IRRs (age-sex standardized, Cox proportional hazards models, or propensity score–stratified analysis) were calculated to compare the current or recent use of each study drug against the current exposure to tolterodine and to other OAB drugs. One of the comparators selected, "any other OAB drug," was a shifting comparison group that included different OAB drugs in each comparison. As result, IRRs obtained from these analyses are not directly comparable since each OAB drug is compared with a different

group of OAB drugs. The only situation in which this would not be a limitation would be if all OAB drugs had the same risk for the event in each analysis.

We identified cancer cases based on diagnostic Read codes. While the coding system includes codes for morphology (e.g., Read code BB5..11, "[M] Adenocarcinoma") and treatment (e.g., Read code 8BAD.00, "Chemotherapy"), only diagnostic codes permit identification of the type of cancer, which is of interest for this study. Instead, these codes were used, along with codes related to cancer care, to confirm the presence of cancer in medical profiles. It is possible that some GPs recorded their patients' cancer using only morphology or treatment codes and the associated free-text field. We would not be able to identify such patients in GP records as having cancer. We found that 32% of the 720 study cancer cases occurring during person-time were linked to the NCDR (i.e., cases diagnosed before December 31, 2010) were not found in CPRD GOLD data (Figure 14), which is a higher proportion than reported by Boggon and colleagues[21] (6%, used Read codes or free-text comments indicating cancer or cancer treatment to identify cases in CPRD GOLD data) and Dregan and colleagues [20] (9%, used diagnostic, morphology, and other Read codes).

It has been suggested that the treatment of prostate and bladder cancer may result in bladder irritability that may be treated with OAB drugs.[55-57] Given the eligibility criteria in our study, a patient with a cancer diagnosis followed by a prescription for a study drug would not enter the cohort due to the cancer diagnosis. If the prescription were recorded before the cancer diagnosis (inaccuracies in the dating of events in the CPRD have been noted in this and other studies), this would help explain the increased detection of these cancers shortly after treatment initiation. Although it is possible, we believe this incorrect recording of dates of cancer diagnosis and prescriptions would not explain more than a small part of the trends we found.

However, the data source is also a strength of this study. The CPRD records the routine health care of a sizeable proportion of the population of the UK; the UK population gets most of its health care through the government-run health care system and is thus highly complete. The discrepancy between the cancer cases identified in the three available data sources, previously noted as a limitation, highlights the importance of having access to all three data sources. A study based on only one of the three data sources would miss a non-negligible proportion of cases while (spuriously) looking stronger.

Another strength of this study is that we compared users of different OAB drugs rather than users and non-users (our comparisons to non-use actually represent periods of non-use in patients who previously used OAB drugs). As mentioned in the literature review section, patients with OAB have a larger prevalence of cardiovascular comorbidities than persons without such a diagnosis. Further, there are suggestions that treated patients with OAB may

have an increased cardiovascular risk compared with untreated patients with OAB. On the other hand, we have shown that the distribution of cardiovascular risk factors is relatively similar across users of different OAB drugs, with the possible exception of darifenacin. Therefore, comparisons between users of OAB drugs are expected to be more robust to baseline differences in cardiovascular risk. Regarding cancer risk, we have shown that detection of bladder and prostate cancer is increased soon after initiation of OAB treatment. Studies comparing OAB drug users with non-users (either with or without OAB) may interpret this risk as caused by the treatment itself.

11.3 Interpretation

In this cohort of 119,912 patients with prescriptions for OAB drugs, the majority of patients were female (70%); approximately 50% were aged 65 years or older; most patients (73%) used a single drug during follow-up; and 28% of the therapy episodes were with oxybutynin, 27% with solifenacin, and 26% with tolterodine. The observed exposure patterns are well suited to detecting acute toxicities for individual OAB drugs.

The validation of electronic algorithms used to identify AMI supports the usefulness of the algorithms used. For stroke, the original algorithm used to ascertain stroke cases resulted in lower PPVs, none higher than 80%. The updated stroke definitions, which excluded codes for referral to stroke clinic or stroke monitoring but not for incident stroke, increased the PPV considerably but failed to identify 20% of the stroke cases confirmed by GPs through questionnaires. In the validation of cancer endpoints, the majority of cancers in GP records were confirmed by profile review or other data sources. This fact was seen in linkable practices and non-linkable practices. A substantial proportion of cancers in linkable practices would have been missed without data from the NCDR and HES, and it is likely that a meaningful proportion of cancers was missed in non-linkable practices.

Incidence rates of bladder cancer and prostate cancer were greater in earlier periods after cohort entry. In contrast, risk of other cancers did not show this effect of time since cohort entry. Patterns of change in incidence rate over time since cohort entry must be considered in etiologic studies of cancer risk related to use of OAB drugs. Protopathic bias and/or detection bias are plausible explanations for higher incidence rates of bladder and prostate cancers during the first 2 years, and especially the first 6 months, after starting OAB drug treatment than in subsequent periods. This may also account for the somewhat higher incidence of prostate cancer seen in users of oxybutynin at cohort entry than in users of tolterodine—this apparent association is probably confounded by the different distributions of person-time since cohort entry between users of these two drugs (see Section 10.4.4.1).

SIRs of cancer for the individual OAB drugs did not differ considerably. Cancer incidence rates were generally similar among the study OAB drugs whether analyzed as ever-exposed or as single-drug–exposed. These findings support the possibility to consider forming an aggregated exposure classification ("other OAB drugs") in a comparative study of a new OAB drug.

Cardiovascular endpoints were evaluated in the study cohort. Contrary to the study of cancer incidence in users of antimuscarinics to treat OAB, SIRs of cardiovascular outcomes for the individual OAB drugs differed. Among the three most commonly used OAB drugs, the incidence of each of the endpoints was lowest for solifenacin and greatest for oxybutynin; the incidence for tolterodine was in between these values.

Multivariate analyses estimated the point estimates of the IRRs for AMI, stroke, MACE, overall mortality, and cardiovascular mortality for current exposure to oxybutynin. The point estimates were consistently greater than 1, irrespective of the comparator used (tolterodine, any other OAB drug, or non-use of OAB drugs). In contrast, point estimates for age- and sex-adjusted IRRs for AMI, stroke, MACE, overall mortality, and cardiovascular mortality for current exposure to solifenacin were all lower than 1. These results should be considered with caution until the effect is replicated in the validation studies to be conducted in other data sources.

For the comparative study of cardiovascular safety endpoints of the new OAB treatment mirabegron, the choice of comparator will depend on the results obtained from the validation studies conducted in the other data sources.

11.4 Generalizability

Eligibility criteria were defined to identify the widest possible population of new users of OAB drugs with good-quality data. Findings of the drug utilization and patient characterization component are generalizable to the rest of the UK. The results of the endpoint validation component apply to the CPRD system and possibly to other UK health databases with the same coding systems and linkages. Results on the risk of events are intended to be scientifically generalizable to all patients using these medications.[58]

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

In this cohort of 119,912 new users with at least one prescription for an OAB drug, the majority were females, almost 50% were aged 65 years or older, and most patients used only one drug during follow-up. The observed exposure patterns are well suited to detecting acute adverse events for individual OAB drugs. For effects potentially driven by moderate- to long-term exposure or with a lag time for clinical manifestation, the ability to detect adverse effects will depend on the length of drug use and follow-up for each individual OAB drug.

Validation efforts in this study were based on various sources of information, including registries, hospital discharge diagnoses, and clinical review of (7,079) electronic primary care records supplemented with information provided by GPs through questionnaires based on medical records. The GP questionnaires had a response rate of 80%, which yielded 1,904 assessable questionnaires and allowed estimation of PPVs and NPVs with good precision.

The validation of electronic algorithms to identify AMI supported the usefulness of the algorithms used. PPVs were above 90% for definite, probable, and possible cases when definition 1 was used. Possible AMI cases identified with only codes for signs or symptoms of AMI, in the absence of a diagnosis of AMI, (definition 2) are unlikely to be confirmed cases of AMI. For stroke, the original electronic algorithm used resulted in lower PPVs, none of which were higher than 80%. We updated the electronic stroke definitions, excluding codes for visits to stroke clinics or stroke monitoring (but not for incident stroke), and the PPV rose to 92% for definite stroke. However, the updated definition did not identify 20% of stroke cases confirmed by the GPs. Individuals without AMI or stroke in CPRD GOLD data who were alive at the end of follow-up were 99% non-cases, but 16% of those who died during the study period were reported by their GPs to have had an AMI or stroke. For future studies, we recommend using all algorithms except the one for possible AMI definition 2. No further validation would be required. For stroke, we recommend using the updated definite stroke algorithm and validating via GP questionnaires all potential cases identified through the original and more sensitive stroke algorithms that were not classified as definite stroke using the updated definition.

The majority of cancer endpoints in GP records were confirmed by profile review or other data sources. This was seen in linkable practices and non-linkable practices. Data from the NCDR and HES allow identification of a substantial proportion of cancers in linkable practices that are likely to be missed in non-linkable practices. Protopathic bias and detection bias are plausible explanations for higher incidence rates of bladder and prostate cancers during the first 2 years after starting an OAB drug than in subsequent periods. These findings

complicate investigation of any potential causal relation between exposure to OAB drugs and prostate or bladder cancer.

Information on smoking in the CPRD GOLD database was fairly complete and accurate. Information on obesity was present and fairly accurate for three-fourths of the patients. The definitions used to identify menopause, history of AMI, and history of stroke in CPRD GOLD data did not have high PPVs.

SIRs of cancer for the individual OAB drugs did not differ considerably. Cancer incidence rates were generally similar among the study OAB drugs whether analyzed as ever-exposed or as single-drug–exposed.

In contrast to the study of cancer incidence in users of antimuscarinics to treat OAB, SIRs of cardiovascular endpoints for the individual OAB drugs differed. Point estimates of the IRRs for AMI, stroke, MACE, overall mortality, and cardiovascular mortality for current exposure to oxybutynin were all of moderate size and greater than 1 in analyses using different comparators. In contrast, point estimates for the IRRs for AMI, stroke, MACE, overall mortality, and cardiovascular mortality for current exposure to solifenacin were lower than 1.

The results suggest the possibility of forming an aggregated exposure classification ("other OAB drugs") for the comparative study of cancer incidence in relation to use of the new OAB treatment mirabegron. For the comparative study of cardiovascular safety endpoints for the new OAB treatment mirabegron, the choice of comparator will depend on the results obtained from the validation studies to be conducted in the other data sources.

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2. Validation Studies Conducted in the CPRD

Table A-1. Acute Myocardial Infarction

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Varas-Lorenzo C, Garcia-Rodriguez LA, Perez-Gutthann S, et al. Hormone replacement therapy and incidence of acute myocardial infarction. A population-based nested case-control study. Circulation. 2000;101(22):2572-78	1991-1995	▪ 50-74 years old at cohort entry ▪ Female	Baseline: ▪ Cardiovascular or cerebrovascular diseases ▪ Cancer ▪ Coagulopathies ▪ Vasculitis ▪ Alcohol-related diseases Censor if in follow-up: ▪ Cardiovascular or cerebrovascular diseases ▪ Cancer ▪ Coagulopathies ▪ Vasculitis ▪ Alcohol-related diseases	81.56 (79.31-83.62)
García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation. 2004;109(24):3000-6	1997-2000	▪ 50-84 years old on January 1, 1997 ▪ 2 years of enrollment with a general practitioner ▪ 1 year since first prescription	Baseline: ▪ Cancer ▪ Patients 70 years old and older with scarce contact with general practitioner Censor if in follow-up: ▪ Cancer ▪ 85 years old	95.92 (91.71-98.33)

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Hammad TA, McAdams MA, Feight A, et al. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. Pharmacoepidemiol Drug Saf. 2008;17(12):1197-201	1997-2004	▪ 40-84 years old at cohort entry ▪ GPRD quality-related criteria ▪ 1 year of baseline information	Baseline: ▪ Prior AMI	92.60 (88.30-95.70)

AMI = acute myocardial infarction; CI = confidence interval; GPRD = General Practice Research Database, forerunner of the Clinical Practice Research Datalink in the United Kingdom; OXMIS = Oxford Medical Information Systems (coding system).

Table A-2. Stroke

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value
Arana A, Varas C, González-Pérez A, Gutiérrez L, Bjerrum L, García Rodríguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. Menopause. 2006 Sep-Oct;13(5):730-6	1991-1997	▪ 50-59 years old at cohort entry ▪ Females	Baseline: ▪ Cardiovascular diseases ▪ Neoplasms ▪ Coagulopathies ▪ Vasculitis ▪ Alcohol-related diseases Censor if in follow-up: ▪ Cardiovascular diseases ▪ Neoplasms ▪ Coagulopathies ▪ Vasculitis ▪ Alcohol-related diseases ▪ 70 years old	Ischemic stroke: 76% Hemorrhagic stroke: 100%
Ruigómez A, Martín-Merino E, Rodríguez LA. Validation of ischemic cerebrovascular diagnoses in The Health Improvement Network (THIN). Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):579-85	2000-2004	▪ 40-84 years old in 2000-2004 ▪ 2 years of enrollment with general practitioner	Baseline: ▪ Cerebrovascular diseases ▪ Cancer Censor if in follow-up: ▪ Cancer ▪ 85 years old	First recorded ischemic stroke: 90% (95% CI, 79-97)

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value
Gaist D, Wallander MA, González-Pérez A, García-Rodríguez LA. Incidence of hemorrhagic stroke in the general population: validation of data from The Health Improvement Network. Pharmacoepidemiol Drug Saf. 2013 Feb;22(2):176-82	2000-2008	▪ 20-89 years old ▪ Enrollment status, permanent or dead ▪ 2 years of enrollment with general practitioner ▪ 1 year since the first computerized prescription ▪ At least one visit to general practitioner in the previous 2 years	Baseline: ▪ A diagnosis of intracerebral hemorrhage or subarachnoid hemorrhage before cohort entry ▪ 70+ years old at the start of follow-up with follow-up longer than 1 year and no records in THIN during follow-up Censor if in follow-up: ▪ 90 years old Computer-identified cases were discarded after manual review if: ▪ They were secondary to traumatic injury ▪ They were ischemic instead of hemorrhagic ▪ Not first episode ▪ The patient had cancer or subdural hemorrhage ▪ The episode took place while the patient was hospitalized	Subarachnoid hemorrhage: 91% Intracerebral hemorrhage: 73% Analyses modifying some parts of the outcome definition are also presented; lower confirmation rate in some groups of patients receiving anticoagulant therapy

PPV = positive predictive value.

Annex 3. Incidence Rates for Cancer Endpoints

Incidence Rates for Cancer Endpoints per 100,000 Person-years in Patients of All Ages and Those Aged ≥ 65 Years, by Sex, United States

	All Ages[a]		Aged ≥ 65 Years[b]	
Type of Cancer	**Males**	**Females**	**Males**	**Females**
Colon and rectum	54.0	40.2	255.3	191.0
Pancreas	13.8	10.8	76.3	62.0
Lung and bronchus	76.4	52.7	435.8	289.6
Melanoma of the skin	27.2	16.7	125.6	46.4
Breast (female)	—	124.3	—	421.3
Corpus uteri	—	23.5	—	84.8
Prostate	154.8	—	742.2	—
Urinary bladder	37.0	8.9	222.4	51.1
Kidney and renal pelvis	20.7	10.5	91.2	44.3
Non-Hodgkin lymphoma	23.8	16.3	109.4	75.3
Total per 100,000	**407.7**	**303.9**	**2,058.2**	**1,265.8**

[a] SEER Cancer Statistics Review 1975-2009. Table 1.4. Age-adjusted SEER incidence and U.S. death rates and 5-year relative survival (percent) by primary cancer site, sex and time period. Incidence rates are age-adjusted to the 2000 US Standard Population (19 age groups). Available at: http://seer.cancer.gov/archive/csr/1975_2009_pops09/results_merged/sect_01_overview.pdf. Accessed August 13, 2015.

[b] SEER website Fast Stats – Statistics stratified by age. Data for 2009. Incidence rates are age-adjusted to the 2000 US Standard Population (19 age groups). Available at: http://seer.cancer.gov/faststats/selections.php?#Output. Accessed January 31, 2013.

Annex 4. Read Codes Used to Identify Overactive Bladder

Read Codes Used to Identify Overactive Bladder

Read Code	Description
16F..00	Double incontinence
1A22.00	Enuresis
1A22000	Nocturnal enuresis
1A22011	Bedwetting
1A22100	Daytime enuresis
1A23.00	Incontinence of urine
1A24.00	Stress incontinence
1A24.11	Stress incontinence - symptom
1A25.00	Urgency
1A25.11	Urgency of micturition
1A26.00	Urge incontinence of urine
1A27.00	Urge to pass urine again shortly after finishing voiding
3940.00	Bladder: incontinent
7B33800	Insertion retropubic device stress urinary incontinence NEC
7B33C00	Insertion retropubic dev fem stress urinary incontinence NEC
7B42111	Insertion of Kaufman prosthesis for male incontinence
7B42113	Insertion of Rosen prosthesis for male incontinence
E276.00	Non-organic enuresis
E276000	Non-organic primary enuresis
E276100	Non-organic secondary enuresis
E276z00	Non-organic enuresis NOS
Eu9y000	[X] Non-organic enuresis
K165300	Detrusor instability
K165400	Unstable bladder
K16V100	Overactive bladder
K16y400	Irritable bladder
K16y411	Detrusor instability
K16y412	Unstable bladder
K198.00	Stress incontinence
K586.00	Stress incontinence - female
Kyu5A00	[X] Other specified urinary incontinence
R083.00	[D] Incontinence of urine
R083000	[D] Enuresis NOS
R083100	[D] Urethral sphincter incontinence
R083200	[D] Urge incontinence
R083z00	[D] Incontinence of urine NOS
R086200	[D] Urgency of micturition

NEC = not elsewhere classified; NOS = not otherwise specified.

Annex 5.
Patient Characteristics

Characteristic	Description/Notes
Patient sex	Patient's sex
Birth year	Patient's year of birth
Region	Value to indicate where in the UK the practice is based. The region denotes the Strategic Health Authority for practices within England, and the country, i.e., Wales, Scotland, or Northern Ireland, for the rest
Age on cohort entry date	
Index of multiple deprivation (IMD) 2010 quintile	If a patient did not have a reported IMD quintile, we used the IMD quintile provided at the practice level
BRCA1 and *BRCA2* mutations reported in medical record	Based on Read codes in CPRD GOLD data
Body mass index grouping at cohort entry	Based on calculations from height and weight recorded, with additional clinical details (first priority) or Read codes in GOLD data (second priority, categorical); selected the most recent values in the 3 years prior to the cohort entry date Categories: < 20 (underweight) 20 - 25 (normal weight) 25 - 30 (overweight) 30 - 40 (obese) 40+ (severely obese)
Smoking status at cohort entry	Based on additional clinical details or Read codes in GOLD data over the entire medical history prior to cohort entry. If patient was identified as a current smoker, set to 1. If patient was identified as a former smoker, set to 2. If the patient was identified as a nonsmoker, then set to 3. However, if later on in their medical record this patient was identified as either being a former smoker or current smoker, we updated this patient to being a former smoker (2). If multiple smoking classifications were reported on the same date, then we reported the minimum of the classifications Categories: 1 = Current 2 = Former 3 = Nonsmoker
History of alcohol use at cohort entry	Using additional clinical details or Read codes in GOLD data over the entire medical history prior to cohort entry. If multiple reported values, kept the maximum. If a patient was classified as a Drinker - unknown quantity, we continued on in the medical record until identifying an amount. If no amount was found, the category was left as Drinker - unknown quantity. If a patient was classified as a Nondrinker, but later in their medical record reported to be a Drinker (either unknown quantity or an amount) the classification was updated. 1 = Low-moderate intake (1-6 units/wk) 2 = Heavy or very heavy intake (7+ units/wk) 3 = Drinker - unknown quantity 4 = Nondrinker

Characteristic	Description/Notes
Menopause at or before cohort entry	Based on Read codes in GOLD data
Hypertension at or before cohort entry	Based on additional clinical details and diagnostic Read codes in GOLD data. If from additional clinical details, thresholds are diastolic ≥ 90 or systolic ≥ 140.
Dyslipidemia at or before cohort entry	Based on diagnostic Read codes in GOLD data
History of acute myocardial infarction (AMI) at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
History of stroke at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
History of transient ischemic attack at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
History of coronary heart disease at of before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
History of heart failure at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
History of peripheral artery disease or peripheral vascular disease at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Diabetes at or before cohort entry	Based on diagnostic Read codes in GOLD data or ICD-10 codes in HES data Because we were trying to identify patients with increased cardiovascular risk, we included codes for type I, type 2, and secondary diabetes, and other types of diabetes (e.g., "Secondary pancreatic diabetes mellitus", "Cystic fibrosis related diabetes mellitus"). Gestational diabetes was not included.
Atrial fibrillation at or before cohort entry	Based on Read codes for diagnoses or ECG (electrocardiogram) findings in GOLD data or ICD-10 codes in HES data
Family history of cancer (melanoma) using the entire medical record	Based on Read codes for family history of this condition and additional clinical details on family history in GOLD data
Family history of cancer (colon or rectum) using the entire medical record	Based on Read codes for family history of this condition and additional clinical details on family history in GOLD data
Family history of cancer (lung and bronchus) using the entire medical record	Based on Read codes for family history of this condition and additional clinical details on family history in GOLD data
Family history of cancer (prostate) using the entire medical record	Based on Read codes for family history of this condition and additional clinical details on family history in GOLD data

Characteristic	Description/Notes
Family history of cancer (breast) using the entire medical record	Based on Read codes for family history of this condition and additional clinical details on family history in GOLD data
Family history of cancer (corpus uteri) using the entire medical record	Based on Read codes for family history of this condition and additional clinical details on family history in GOLD data
Alcohol abuse and related diseases at or before cohort entry	Based on Read codes explicitly specifying that diseases were alcohol related in GOLD data or ICD-10 codes in HES data (e.g., ICD-10 code K70.3, Alcoholic cirrhosis of liver)
Drug abuse at or before cohort entry	Based on Read codes in GOLD data
Chronic obstructive pulmonary disease (COPD) at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Dementia at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Hemiplegia and paraplegia at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Liver disease at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Peptic ulcer disease at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Acute renal disease at cohort entry and up to 1 year prior	Based on Read codes in GOLD data or ICD-10 codes in HES data
Chronic renal disease at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data. This variable included codes for kidney diseases that generally affect kidney function and codes for impaired function, acute kidney impairment, chronic kidney impairment, dialysis (hemodialysis and peritoneal dialysis) and transplant. Non-kidney genitourinary conditions and wounds to the kidney were not included. Codes that did not clearly describe an acute cause were included among codes for chronic renal disease.
Rheumatological disease at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Dialysis at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Gout at or before cohort entry	Based on Read codes in GOLD data
Overactive bladder (OAB) at or before cohort entry	Based on Read codes in GOLD data
Organ transplantation at or before cohort entry	Based on Read codes in GOLD data or ICD-10 codes in HES data
Polycystic ovary syndrome at or before cohort entry	Based on Read codes in GOLD data

Characteristic	Description/Notes
Endometrial polyps or other benign growths of the uterine lining at or before cohort entry	Based on Read codes in GOLD data
Exposure to radiation at or before cohort entry	Based on Read codes in GOLD data
Drugs	Based on prescriptions in GOLD data ▪ OAB drugs (any time, 5 years, and 1 year before cohort entry) ▪ Hormone replacement therapy (any time before cohort entry) ▪ Tamoxifen (any time before cohort entry) ▪ Letrozole (any time before cohort entry) ▪ Thyroid hormone replacement (any time before cohort entry) ▪ Nitrates, digoxin, and drugs to treat angina (any time before cohort entry) ▪ Lipid-lowering drugs (any time before cohort entry) ▪ Nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) (any time before cohort entry) ▪ Low-dose aspirin and other antiplatelets (any time before cohort entry) ▪ Antihypertensives (any time before cohort entry) ▪ Immunosuppressive agents (any time before cohort entry) ▪ Antiarrhythmic drugs (any time before cohort entry) ▪ Thrombolytic therapy (any time before cohort entry) ▪ Warfarin (any time before cohort entry) ▪ Obesity treatment (any time before cohort entry)
Health services utilization: Number of outpatient visits in the year before cohort entry	Number of records with type identifying outpatient visits (maximum 1 visit per day) in GOLD data. These values identify office visits; an accurate accounting of outpatient hospital visits is possible in GOLD data
Health services utilization: Number of hospitalizations in the year before cohort entry	Number of records for hospital admissions and visits to the emergency room in Read codes in GOLD data. Among patients linkable to HES, we kept only values that occurred outside of the date associated with the end of the HES linkage (March 31, 2012). In patients linkable to HES, within the period of HES linkage, the number of records on or in the year before cohort entry. Counting each date only once, summed the number of hospitalization visits recorded.
Health services utilization: Number of sigmoidoscopies/colonoscopies in the year before cohort entry	Based on Read codes in GOLD data (maximum 1 procedure per day)
Health services utilization: Number of mammography visits in the year before cohort entry	Based on Read codes in GOLD data (maximum 1 procedure per day)

Characteristic	Description/Notes
Increased cardiovascular risk at baseline	Defined by the presence of one or more of the diagnoses in the first group or two or more of the second group of diagnoses at baseline (using diagnoses as defined above) One or more of the following ▪ Diabetes (diagnostic codes or medications) ▪ Prior history of myocardial infarction ▪ Prior history of stroke ▪ Prior history of heart failure ▪ Peripheral arterial disease ▪ Coronary heart disease ▪ Transient ischemic attack ▪ Atrial fibrillation or flutter (diagnostic codes) Two or more of the following ▪ Current smoking ▪ Dyslipidemia (diagnostic codes) ▪ Hypertension (diagnostic codes)

Annex 6. Origin of Cancer Cases by Data Source: Validation Cohort, Linked Practices, Subgroup of Cases Diagnosed During NCDR Data Availability, Individual Cancer Types

List of Figures

Figure 6-1. Bladder Cancer Proportional Venn Diagram

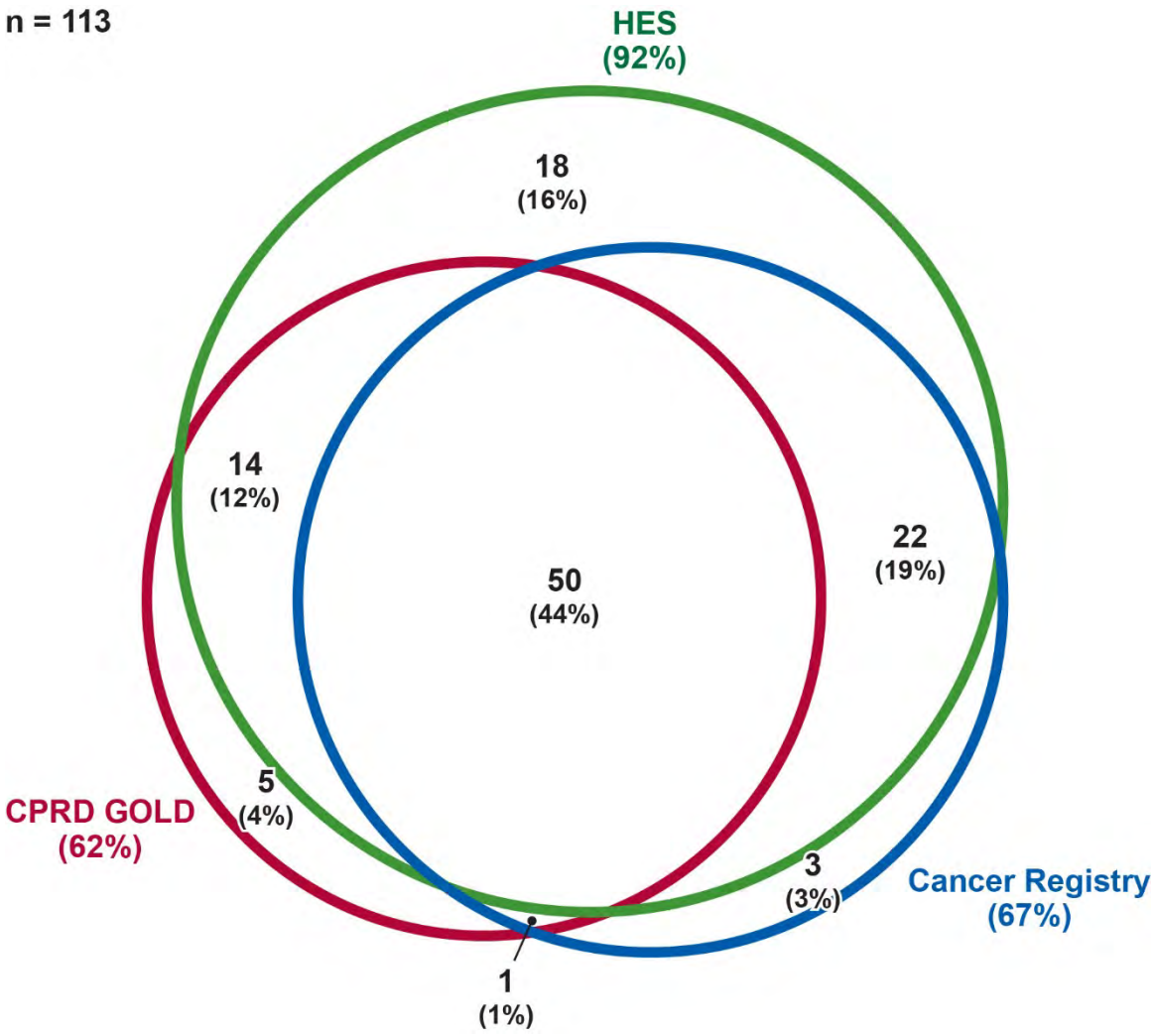


Figure 6-2. Breast Cancer Proportional Venn Diagram

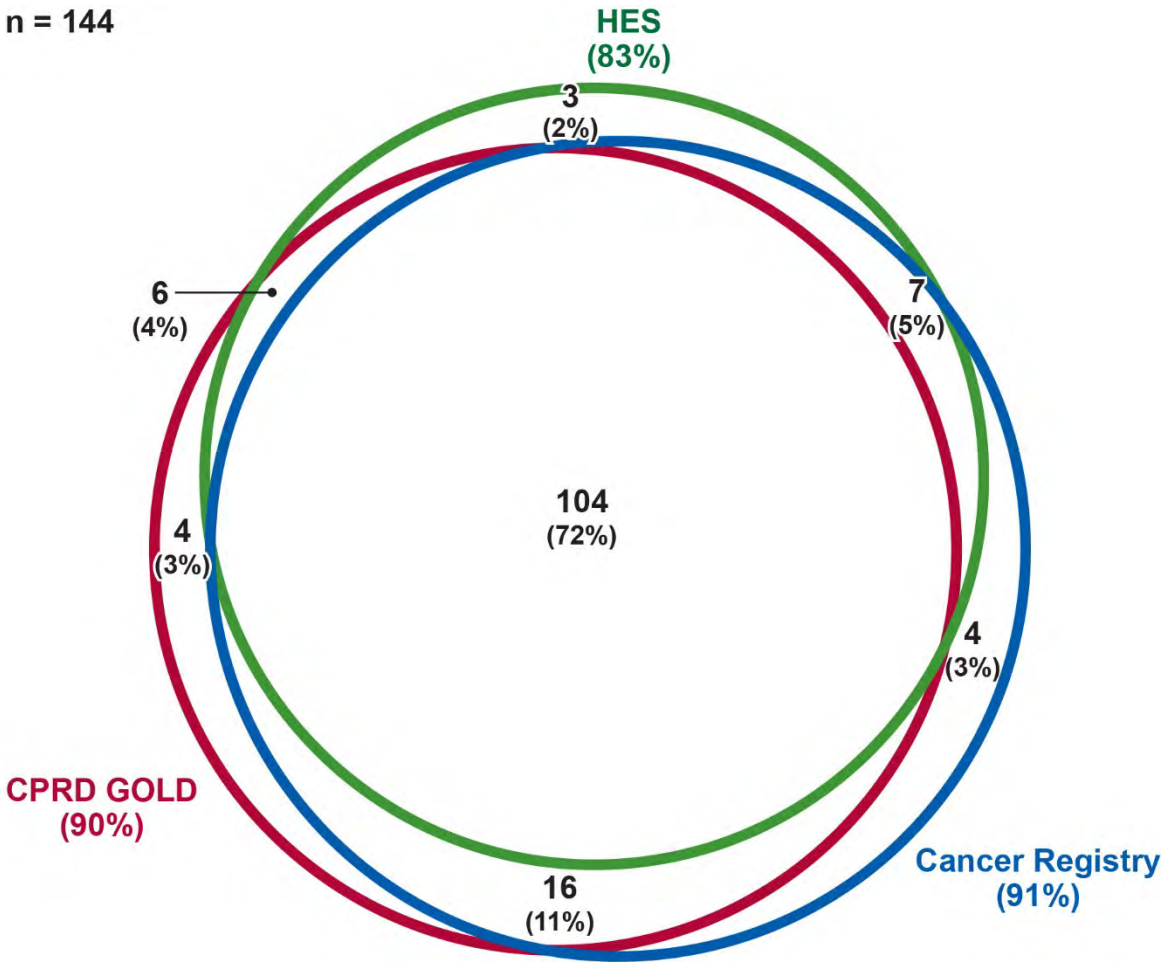


Figure 6-3. Colorectal Cancer Proportional Venn Diagram

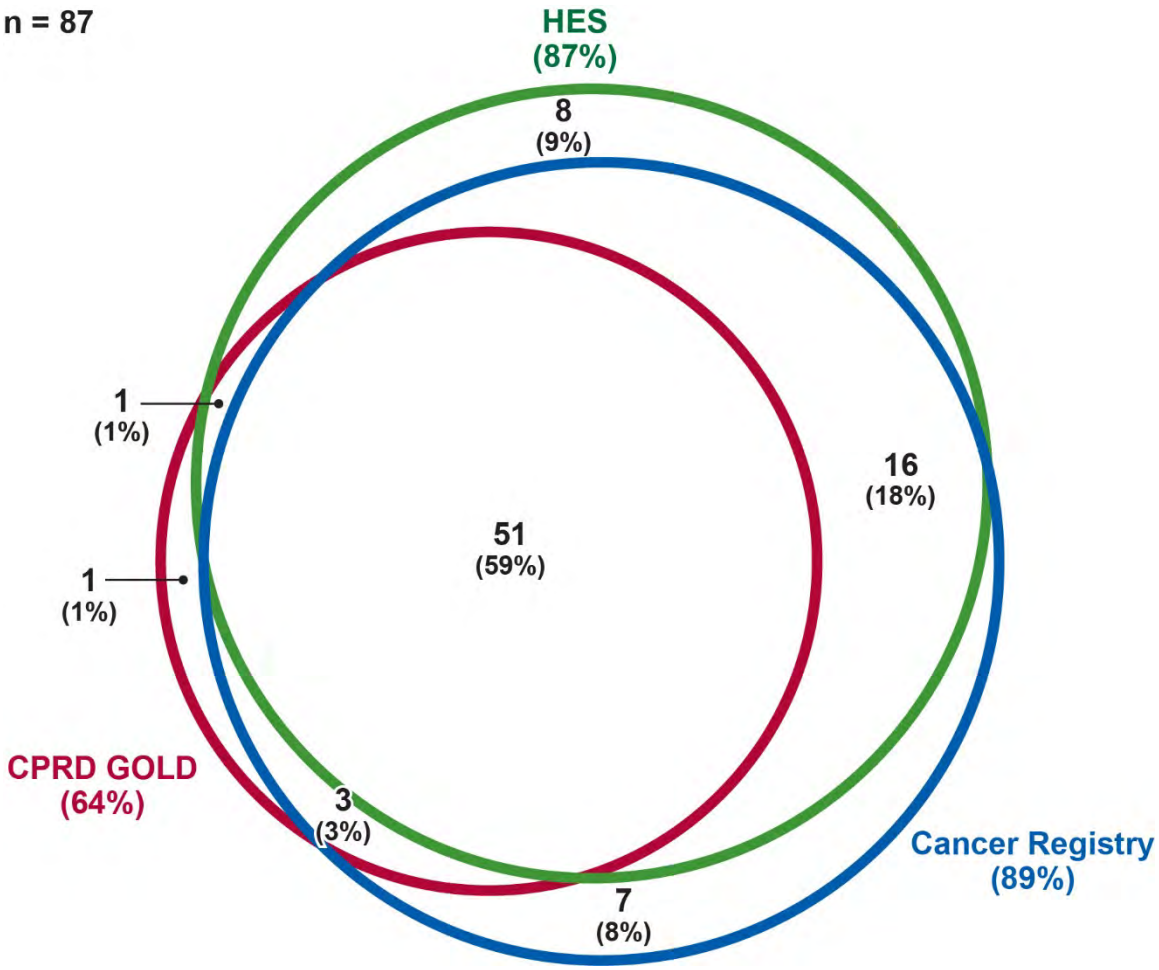
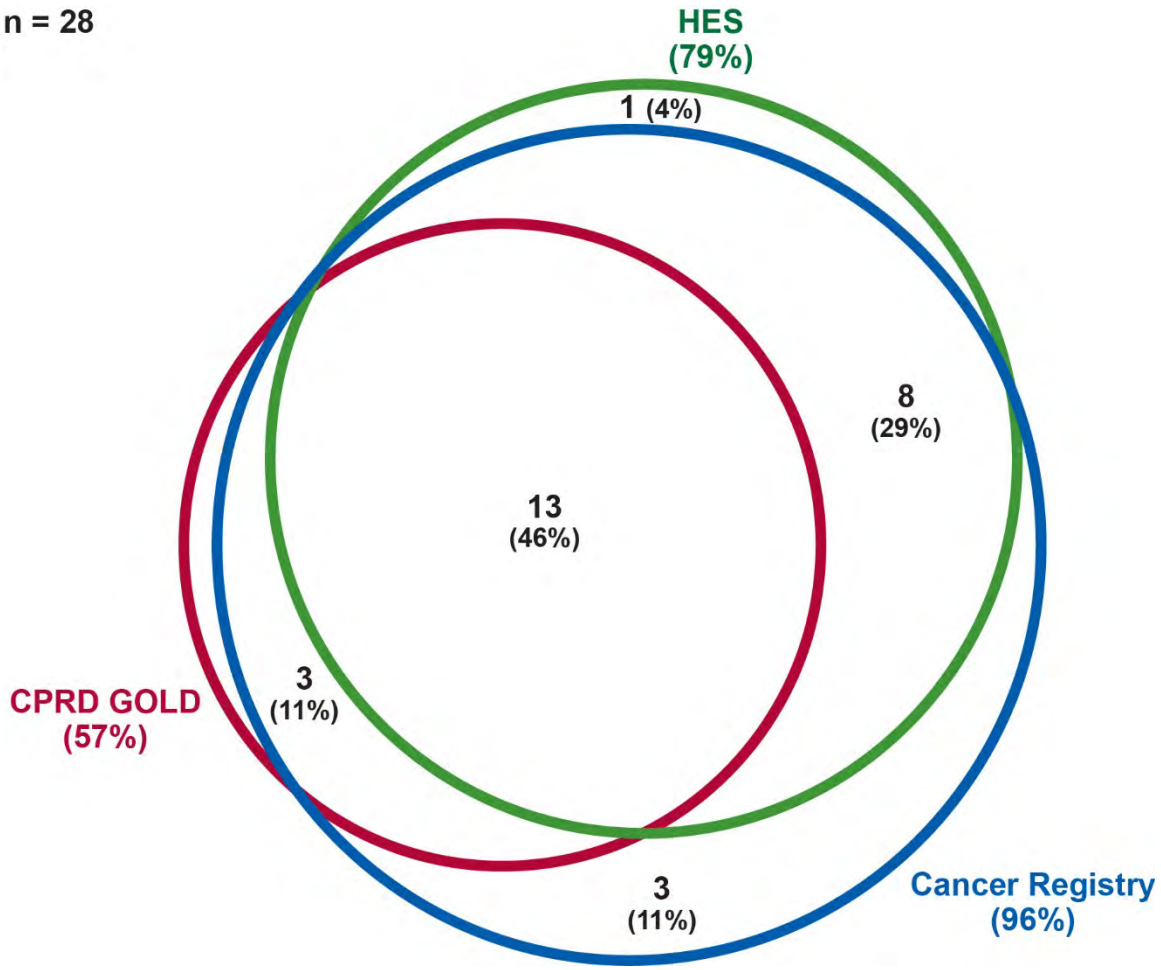
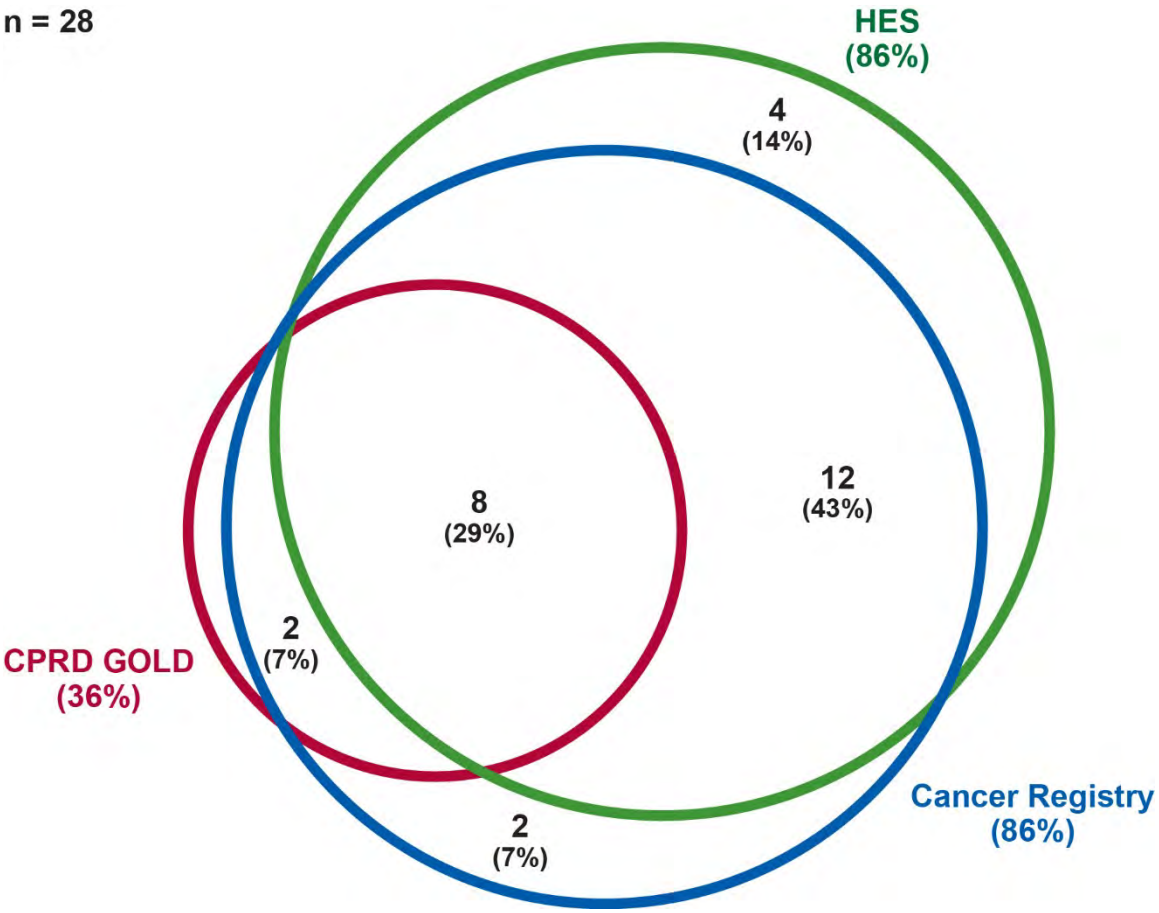


Figure 6-4. Corpus Uteri Proportional Venn Diagram



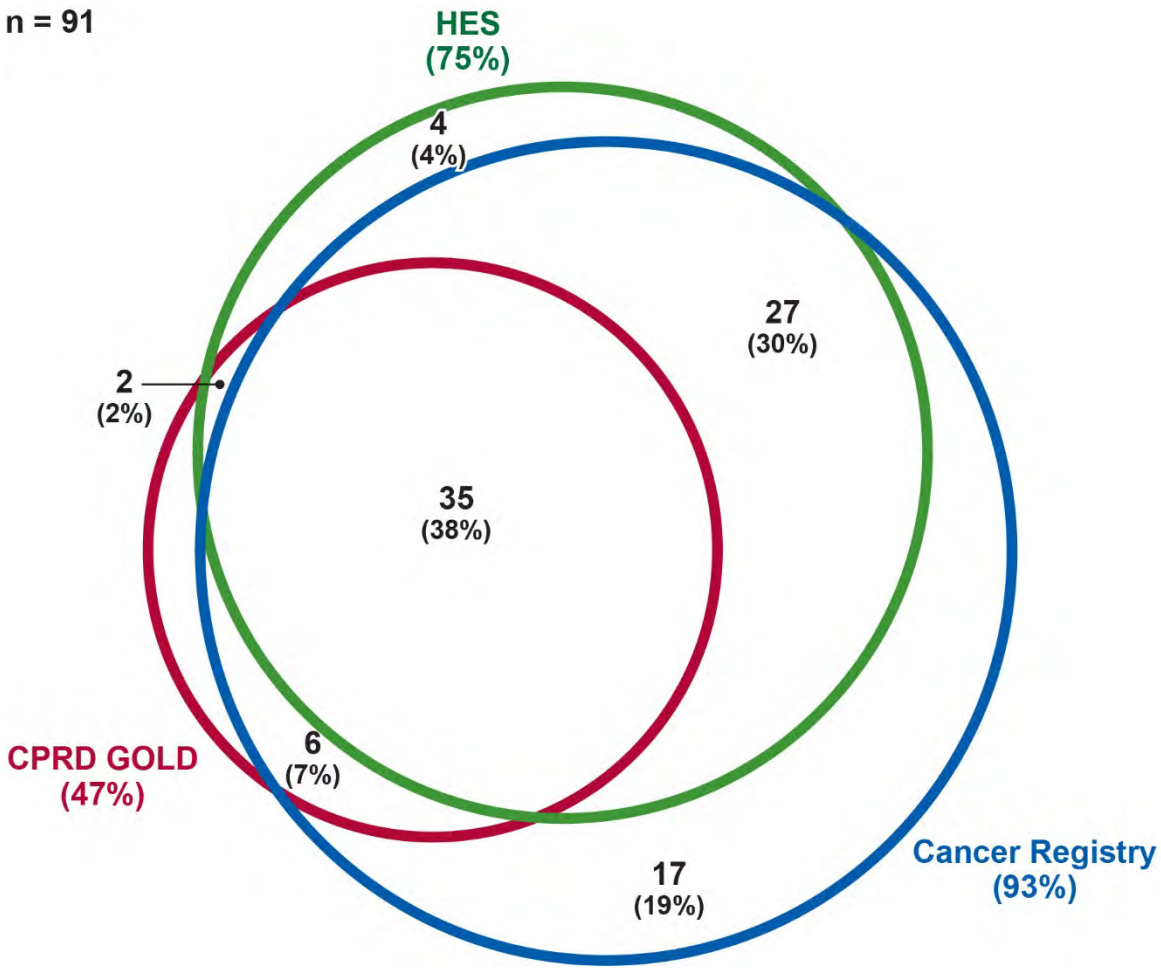
Note: The blank region is an artifact of the graphing software; no cases fall within that region.

Figure 6-5. Kidney and Renal Pelvis Proportional Venn Diagram



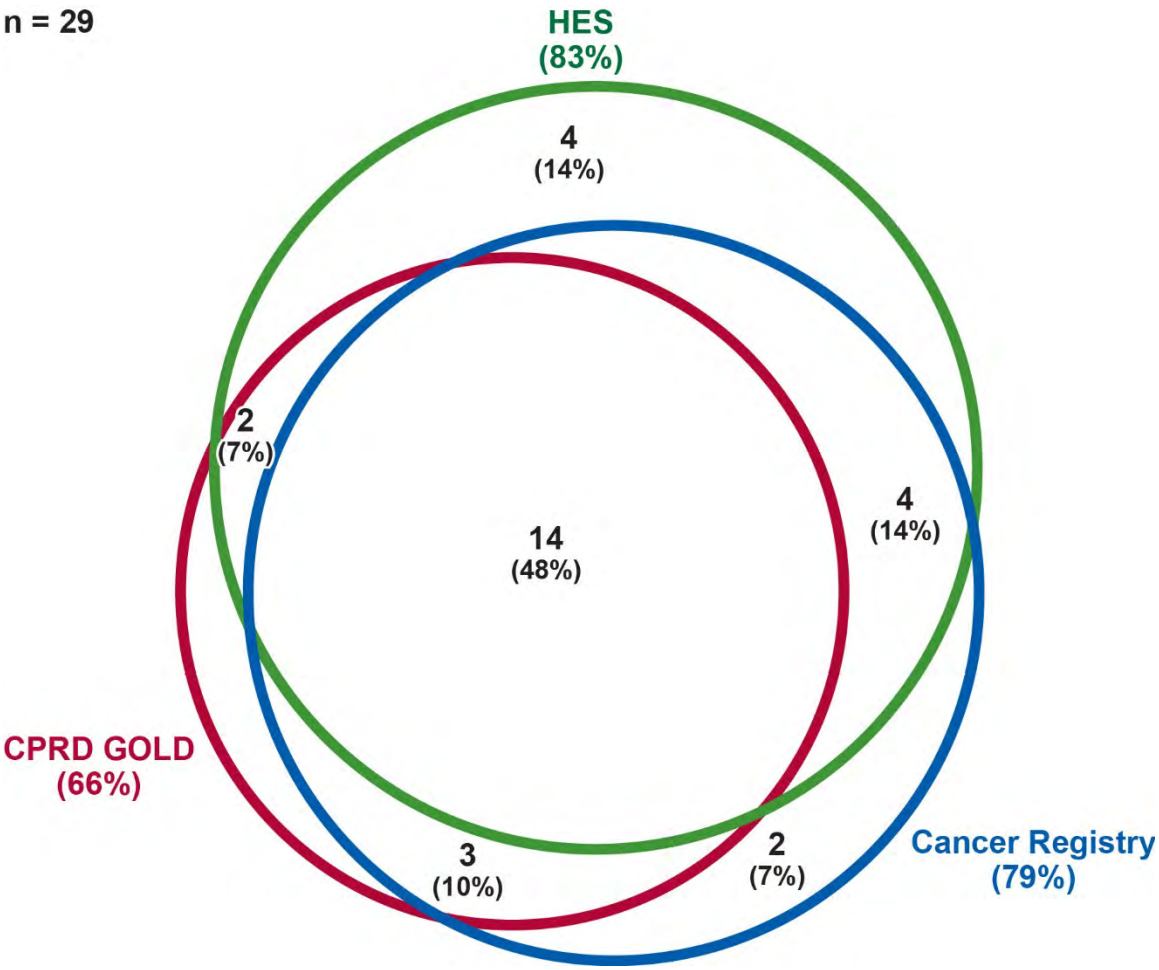
Note: The blank region is an artifact of the graphing software; no cases fall within that region.

Figure 6-6. Lung and Bronchus Proportional Venn Diagram



Note: The blank region is an artifact of the graphing software; no cases fall within that region.

Figure 6-7. Non-Hodgkin Lymphoma Proportional Venn Diagram



Note: The blank region is an artifact of the graphing software; no cases fall within that region.

Figure 6-8. Pancreas Proportional Venn Diagram

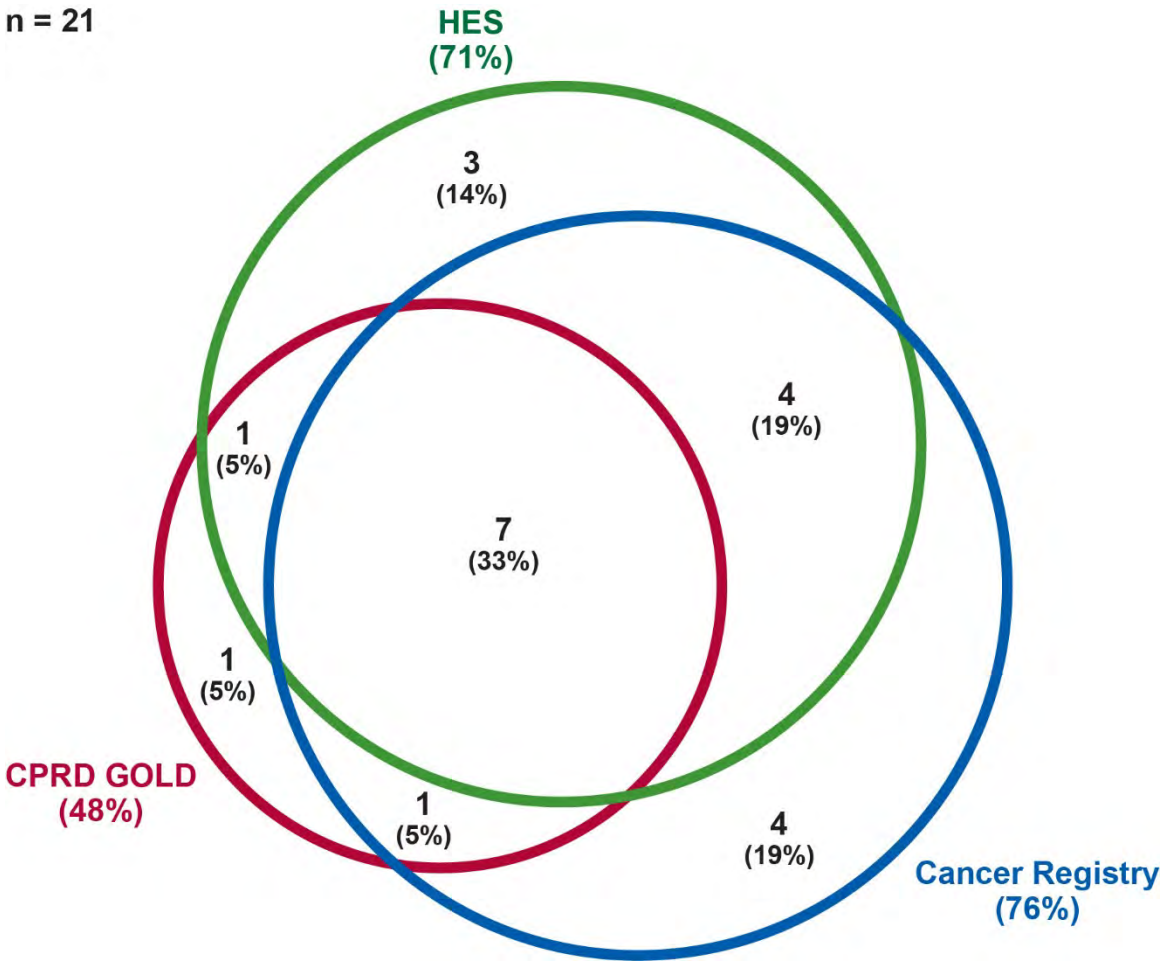


Figure 6-9. Prostate Proportional Venn Diagram

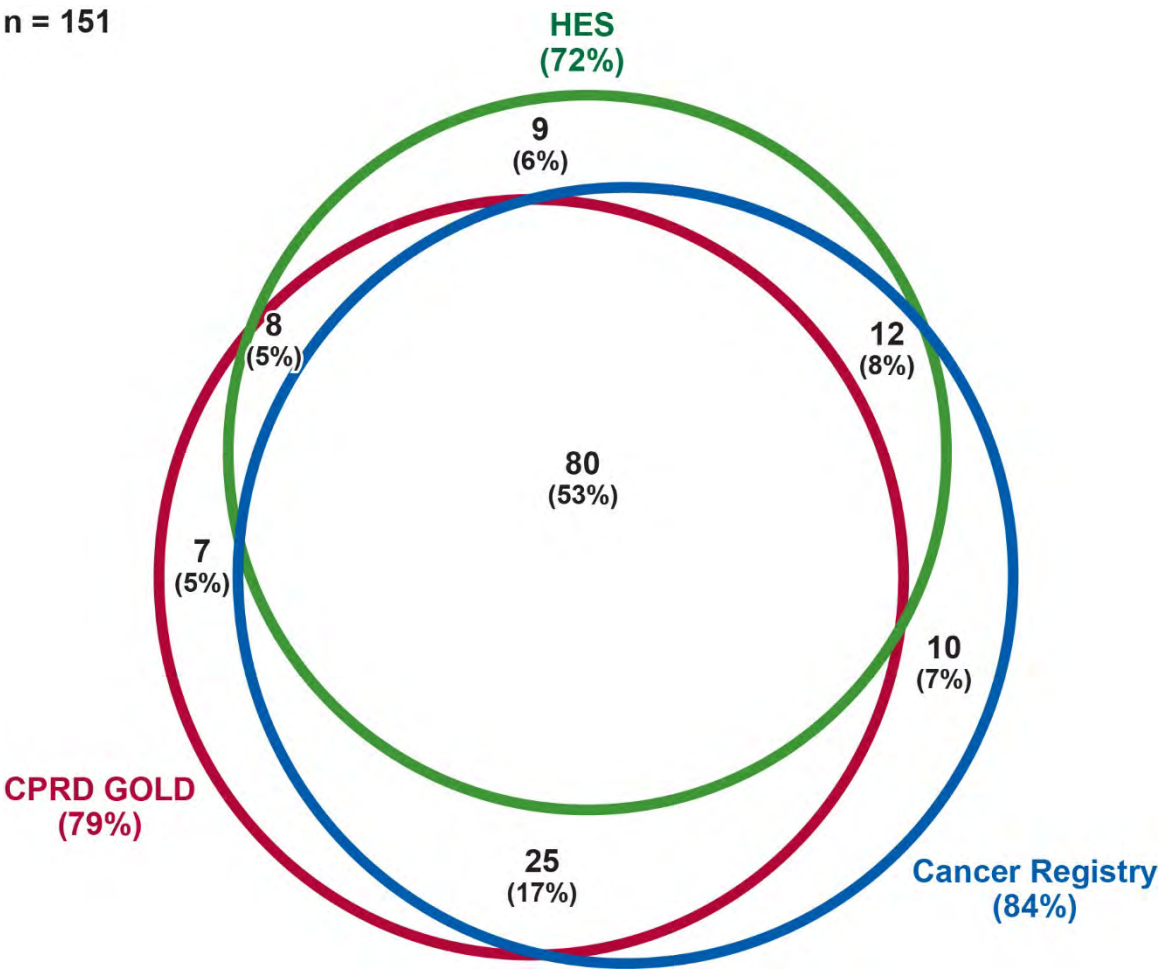
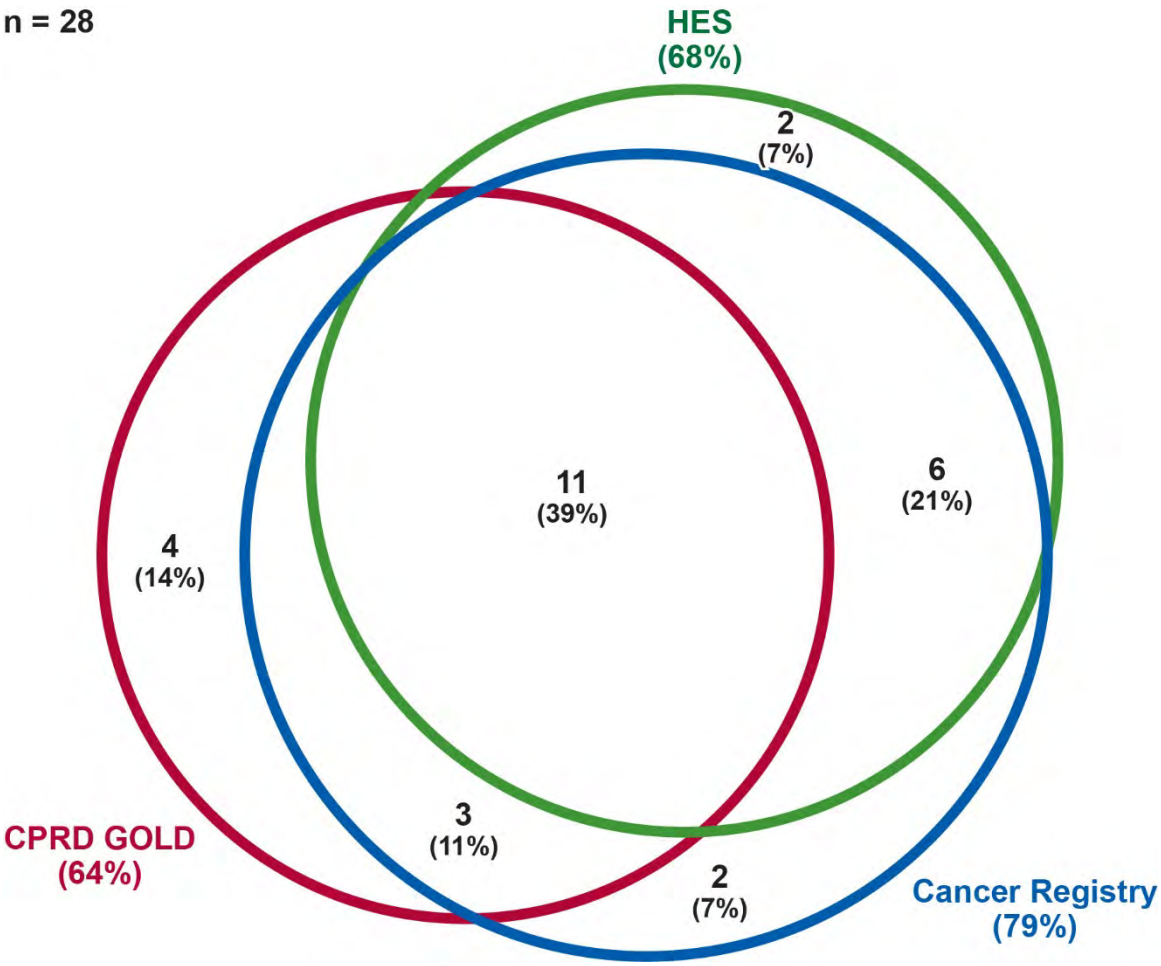


Figure 6-10. Melanoma of the Skin Proportional Venn Diagram

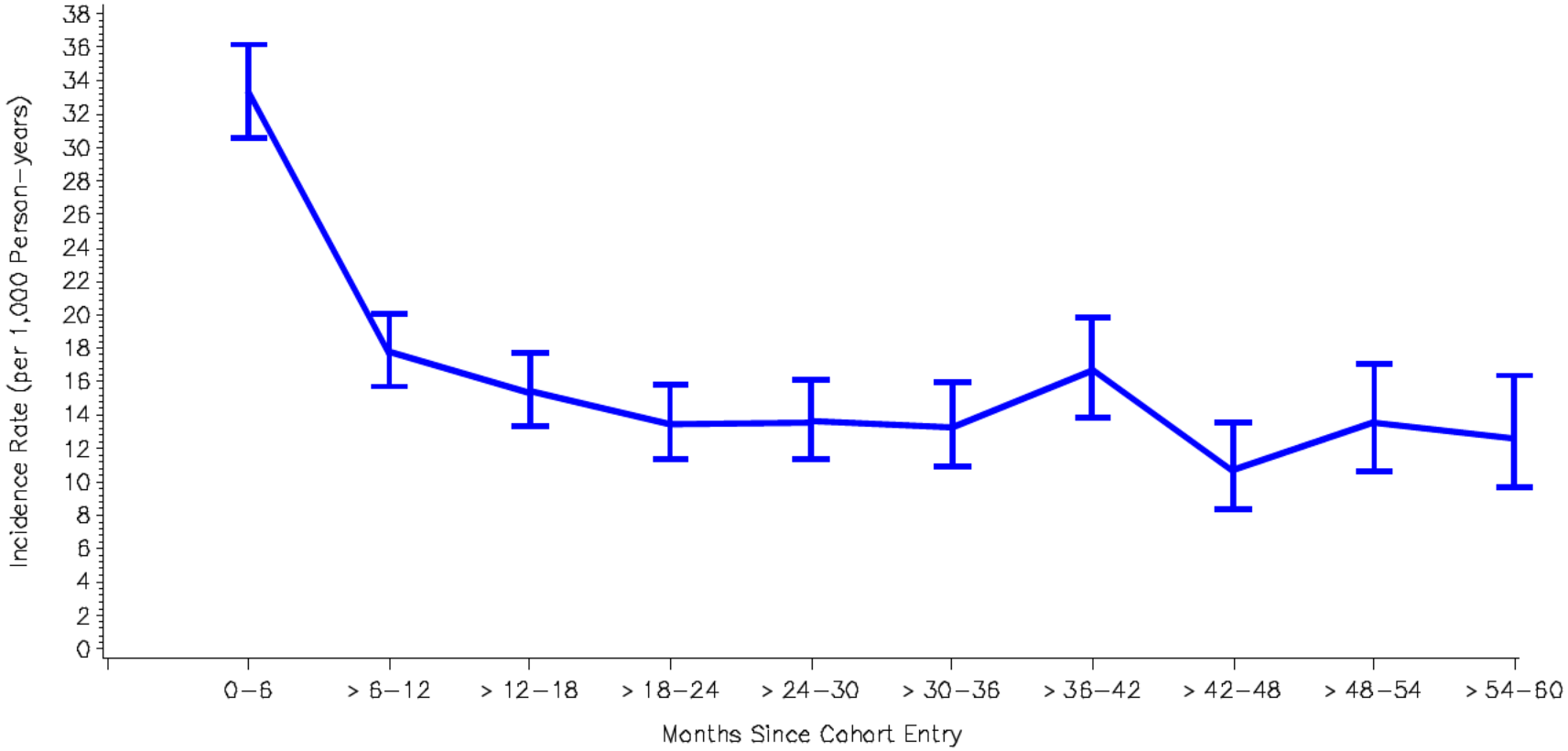


Note: The blank region is an artifact of the graphing software; no cases fall within that region.

Annex 7.
Figures Depicting Incidence Rates of Cancer Endpoints by Time Since Cohort Entry

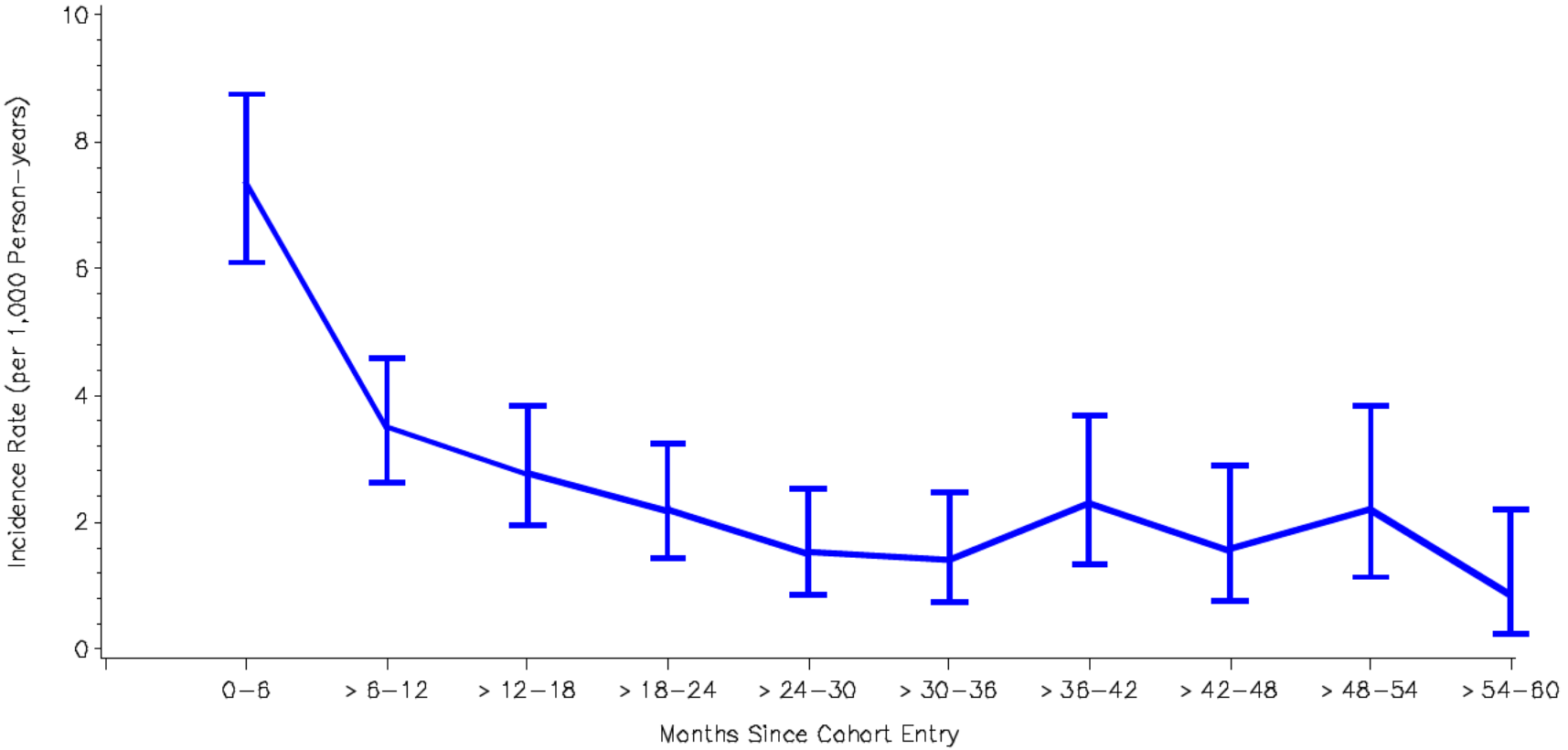
List of Figures

Figure 12.5.1.1.1. Incidence Rates for Composite Cancer Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



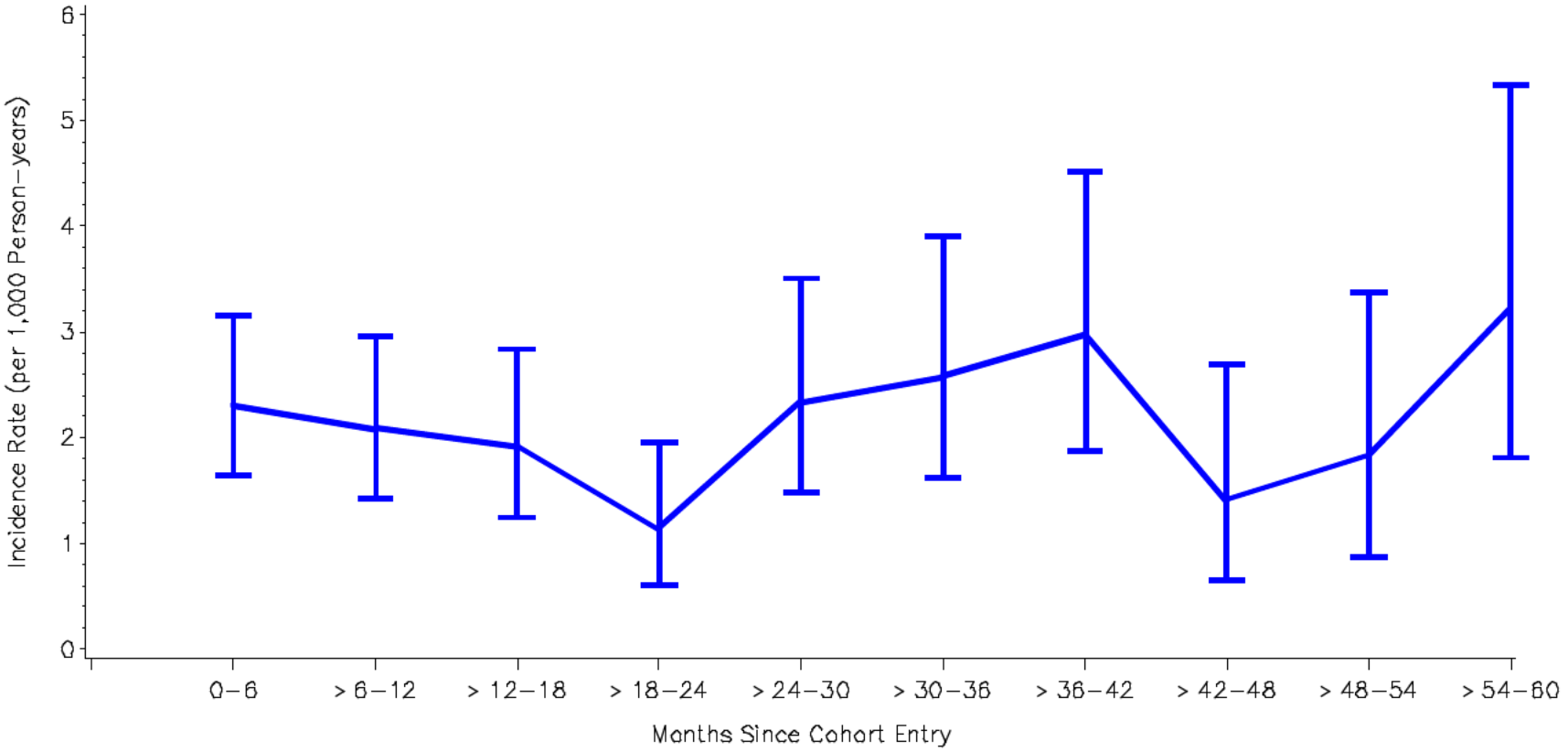
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.1.2. Incidence Rates for Urinary Bladder Cancer Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



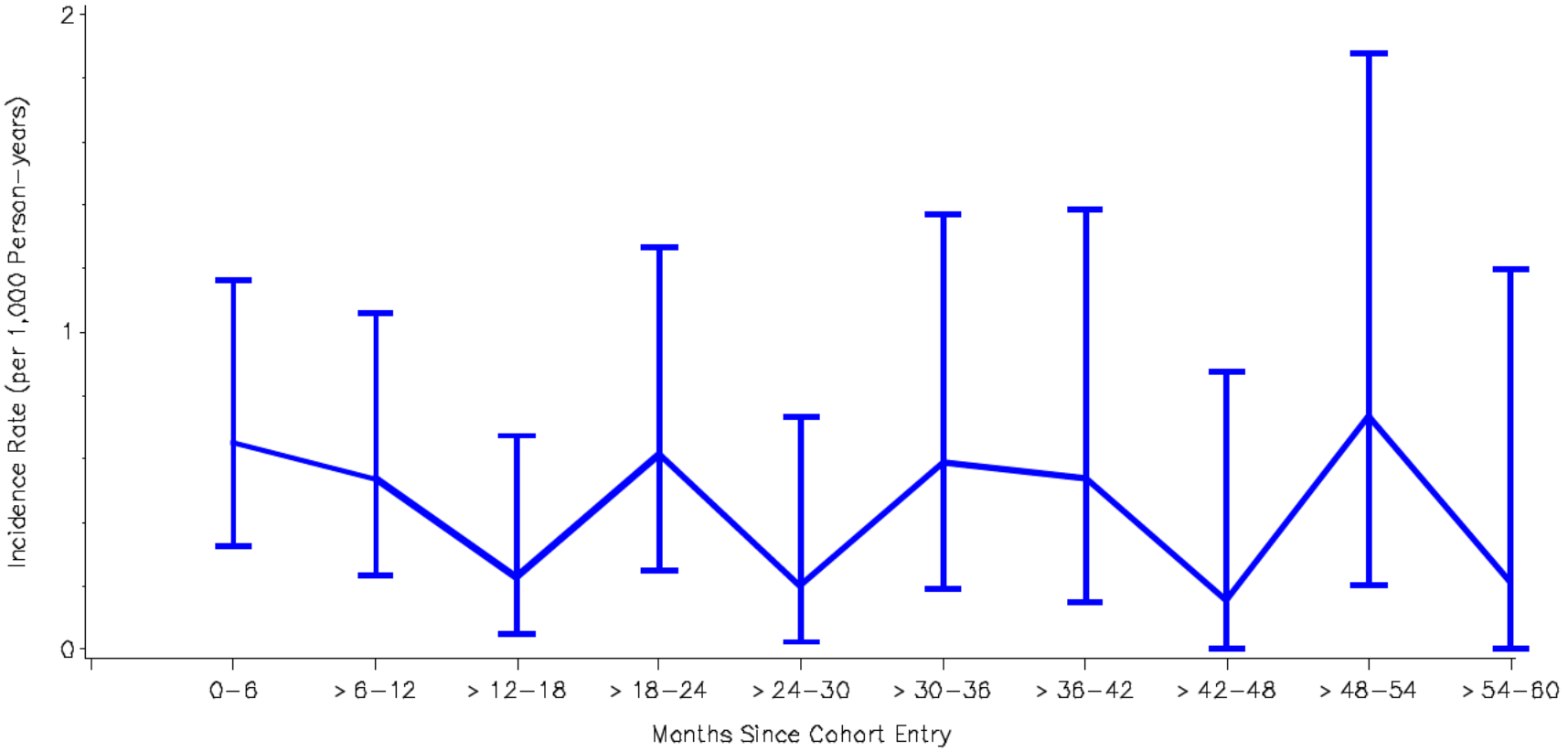
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.1.4. Incidence Rates for Colorectal Cancer Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



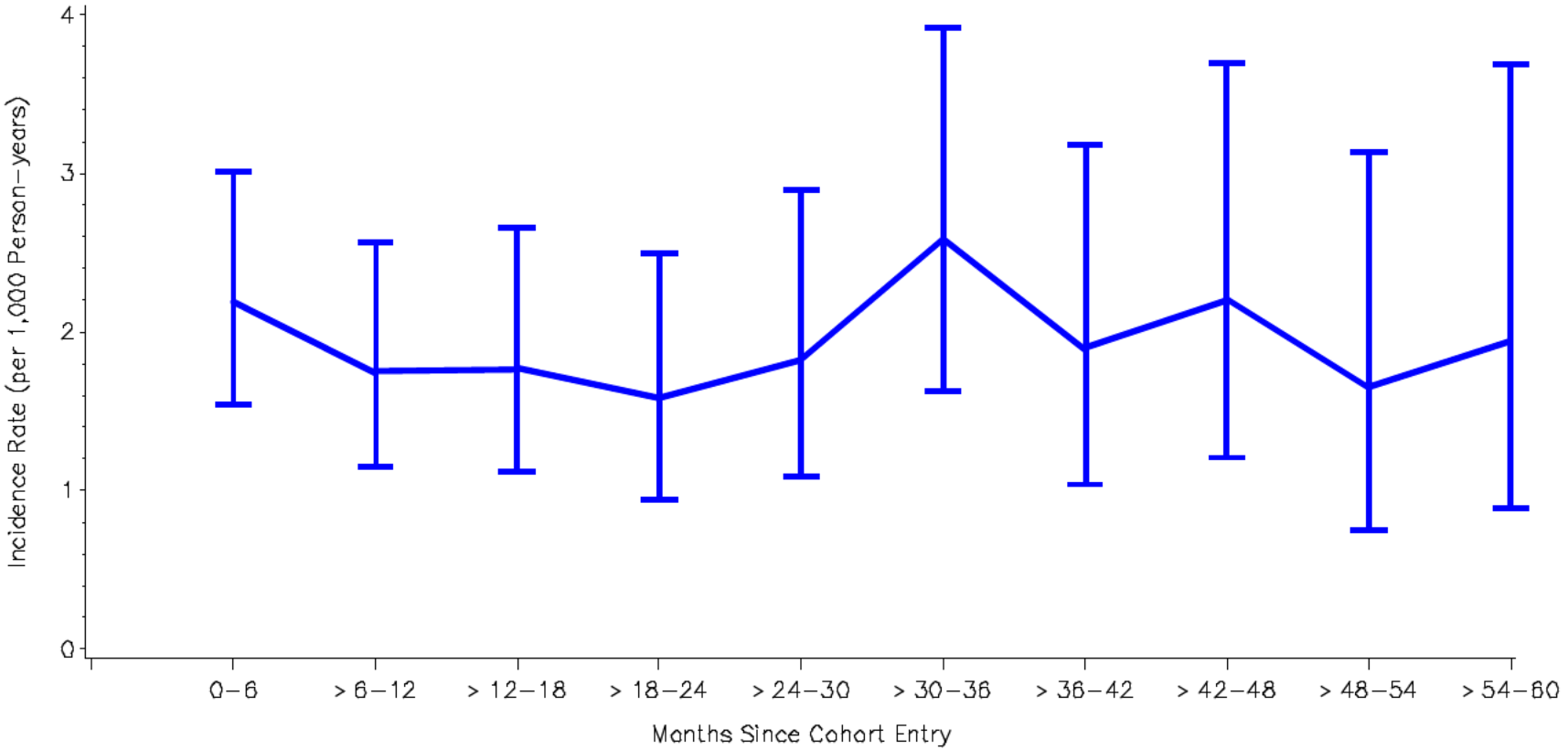
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.1.6. Incidence Rates for Cancer of Kidney and Renal System Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



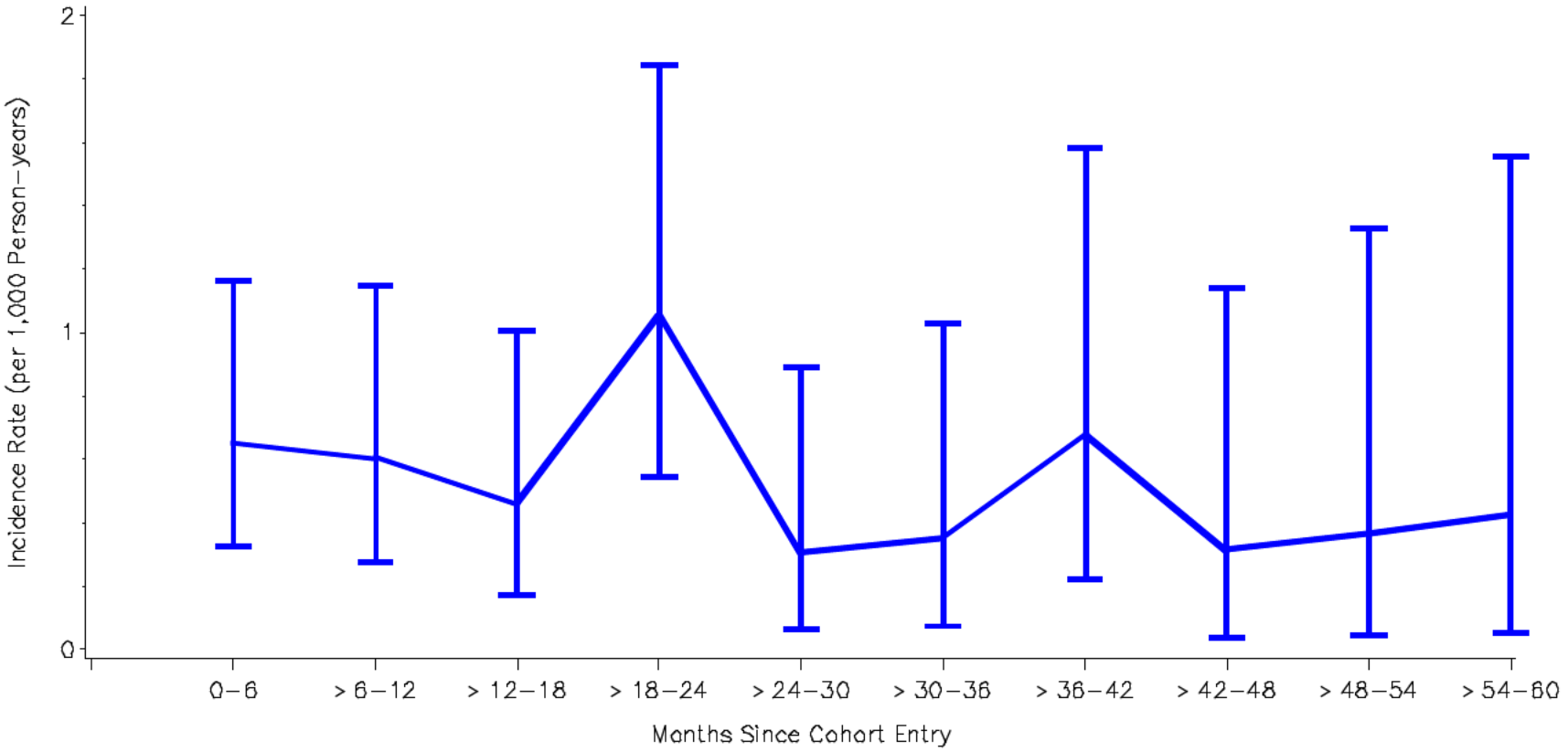
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.1.7. Incidence Rates for Cancer of the Lung and Bronchus Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



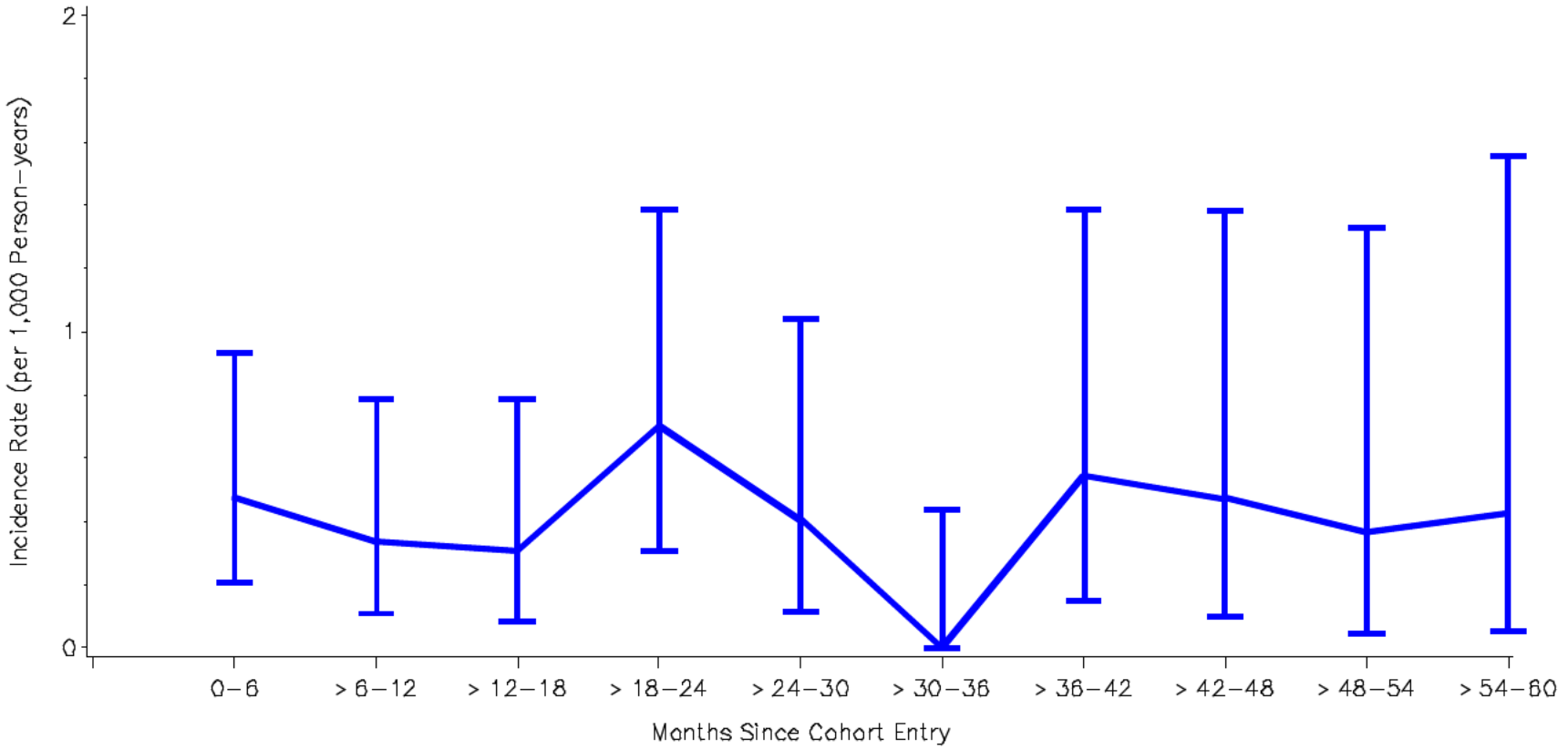
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.1.8. Incidence Rates for Non-Hodgkin Lymphoma Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



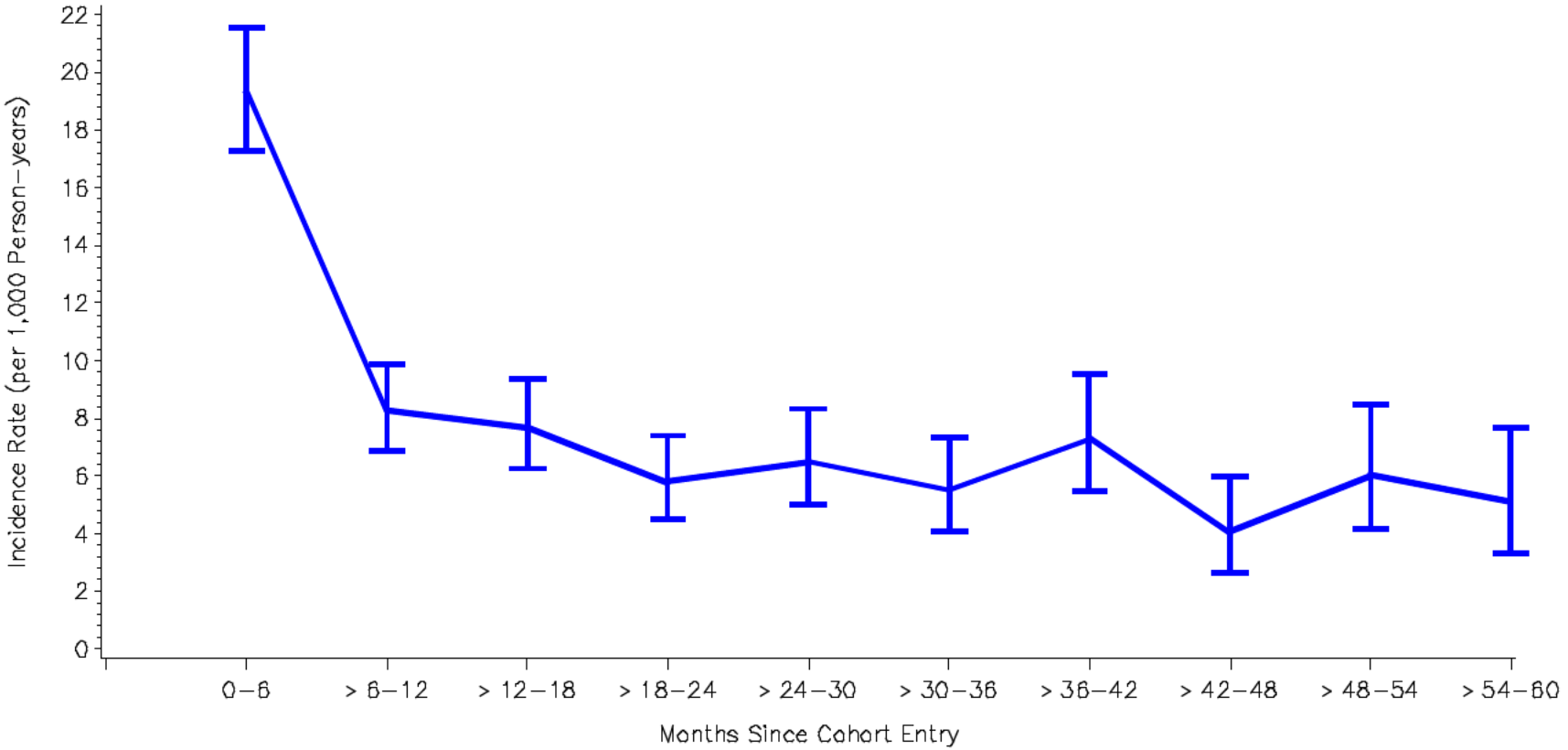
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.1.9. Incidence Rates for Pancreatic Cancer Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



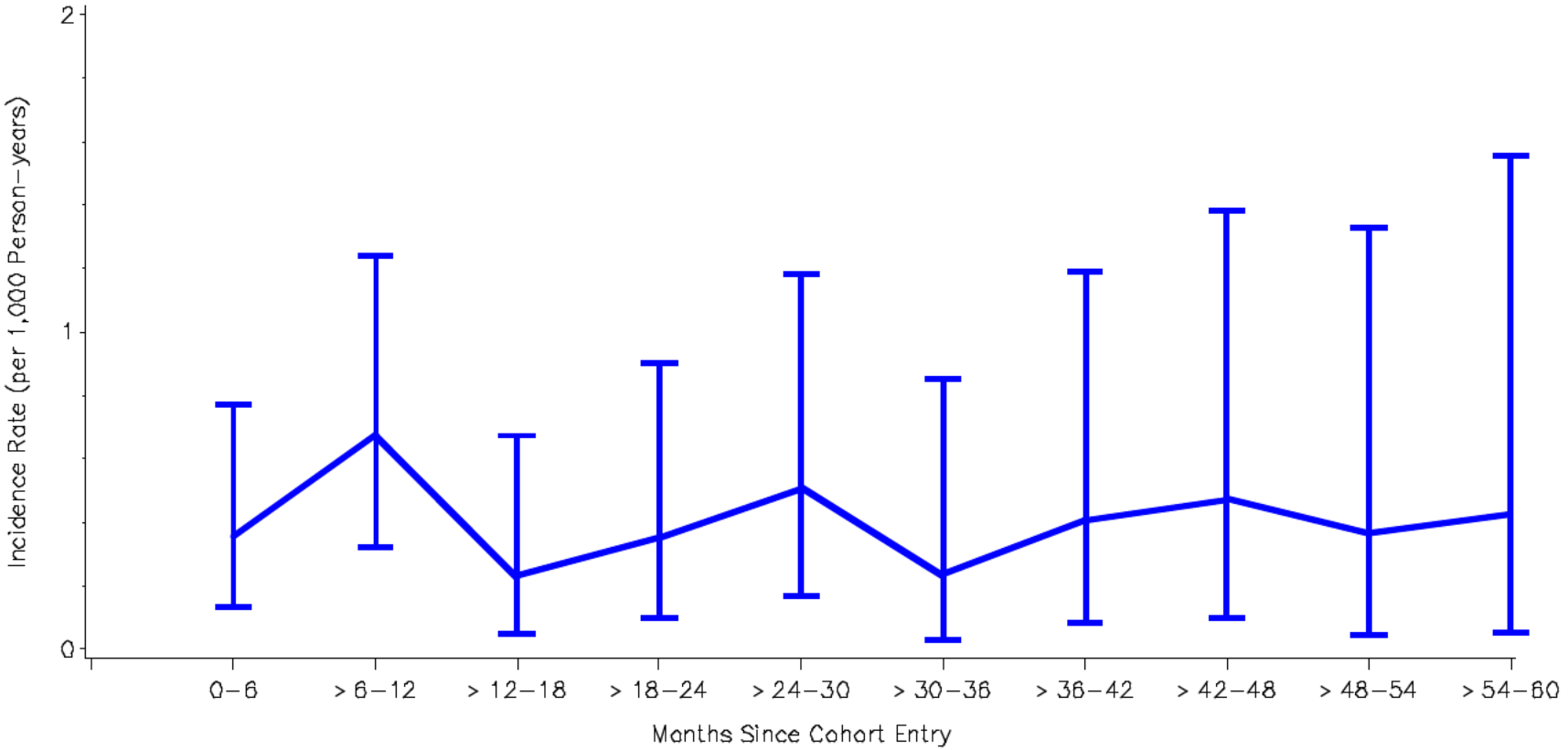
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.1.10. Incidence Rates for Prostate Cancer Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



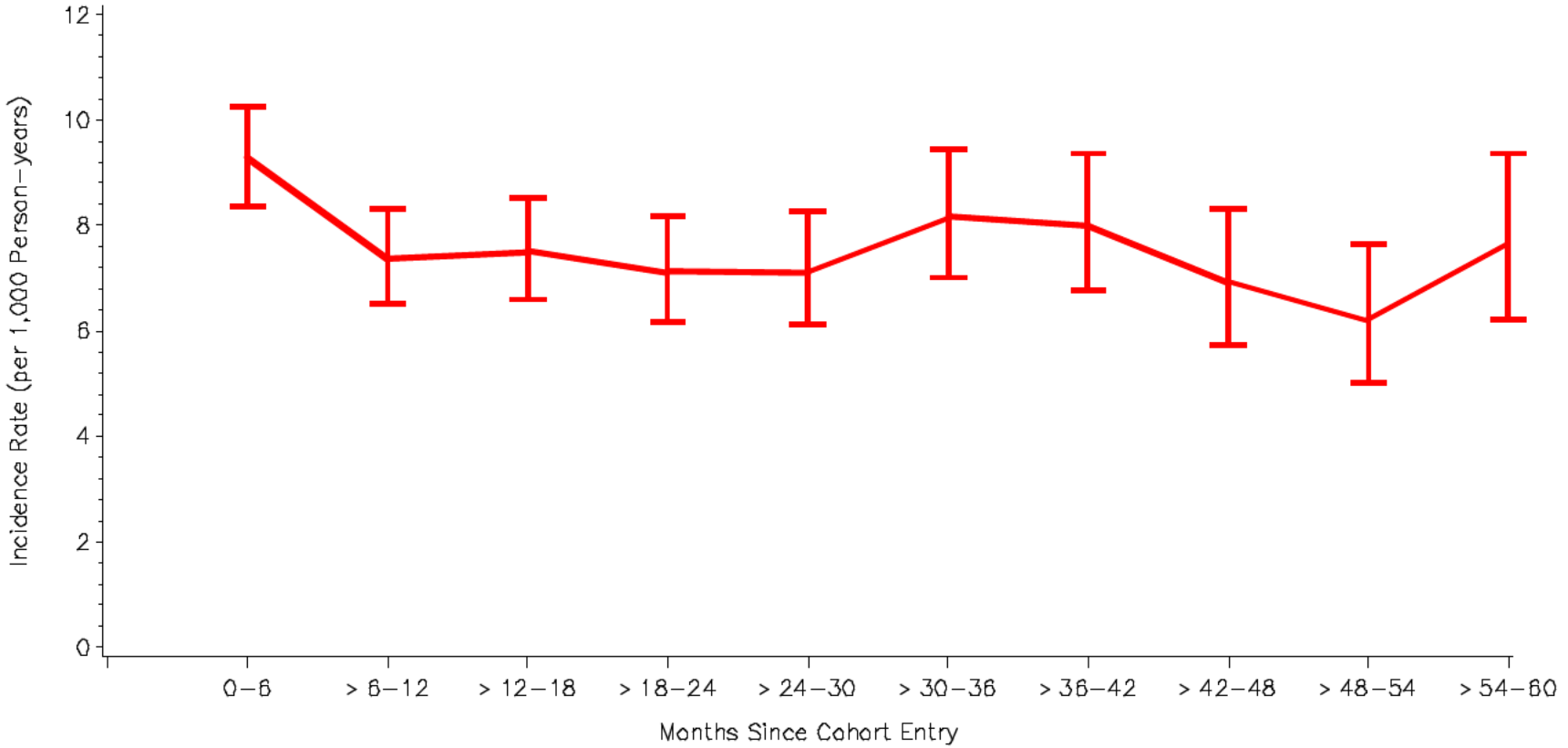
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.1.11. Incidence Rates for Melanoma of the Skin Endpoint Definition 5, by Months Since Cohort Entry, Male Patients



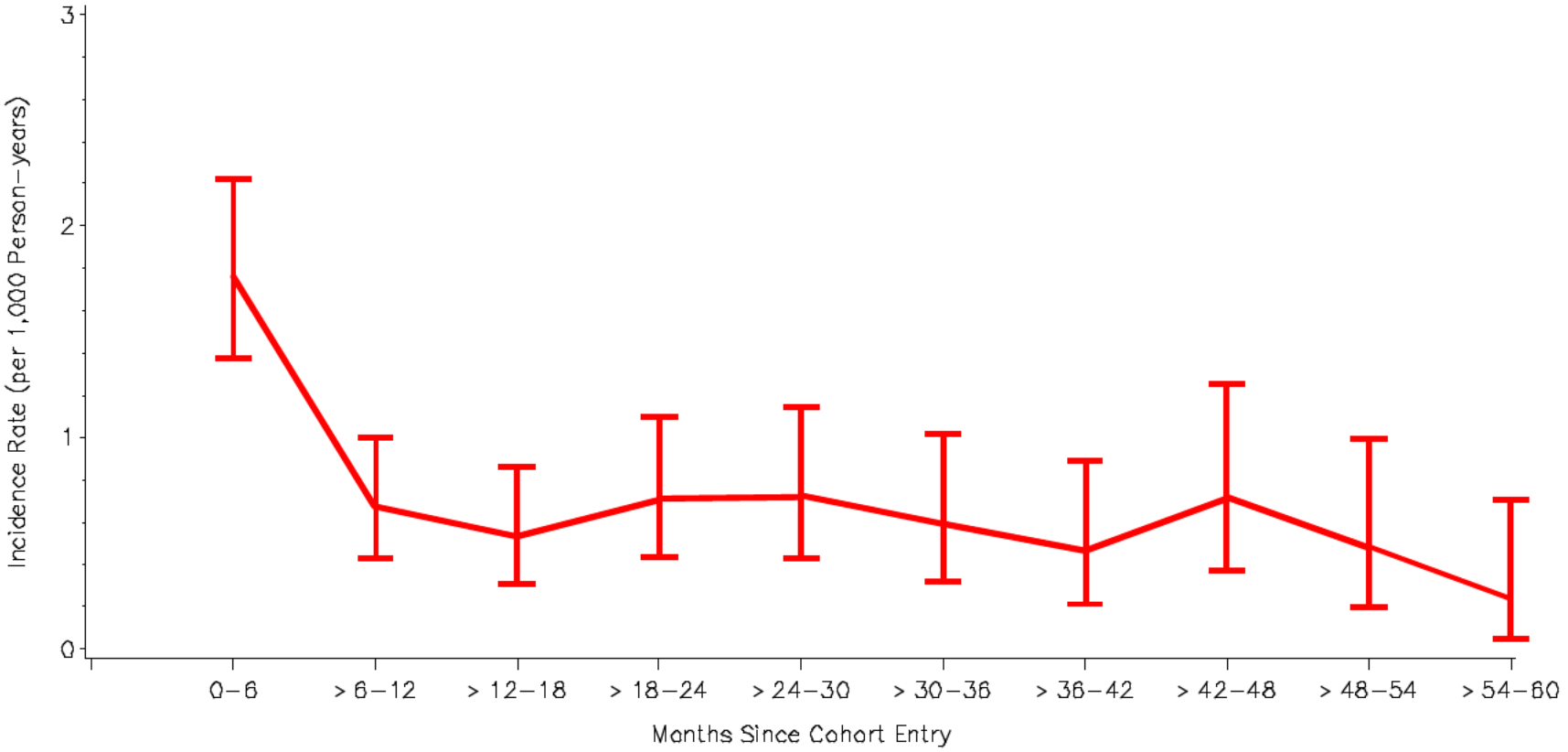
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.1. Incidence Rates for Composite Cancer Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



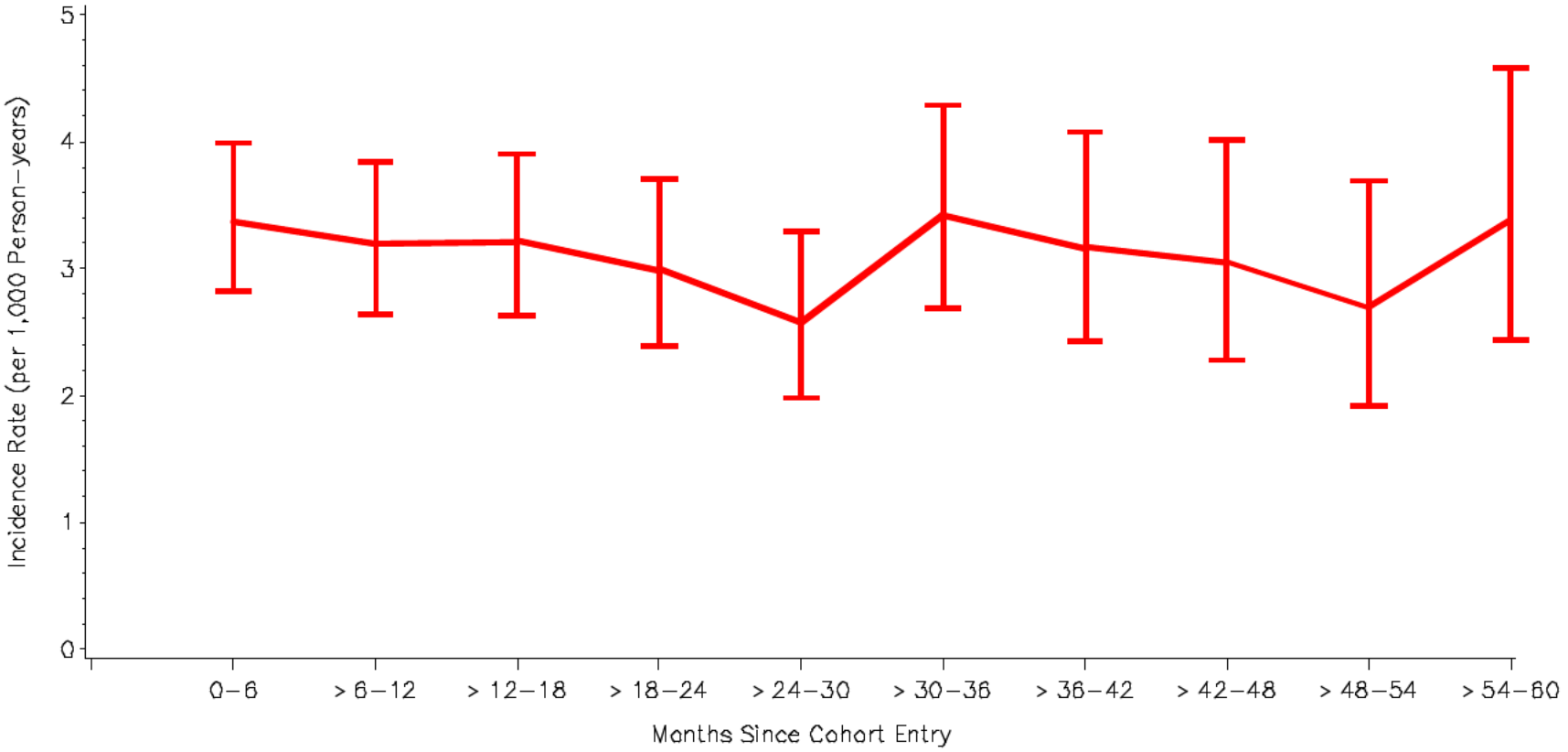
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.2. Incidence Rates for Urinary Bladder Cancer Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



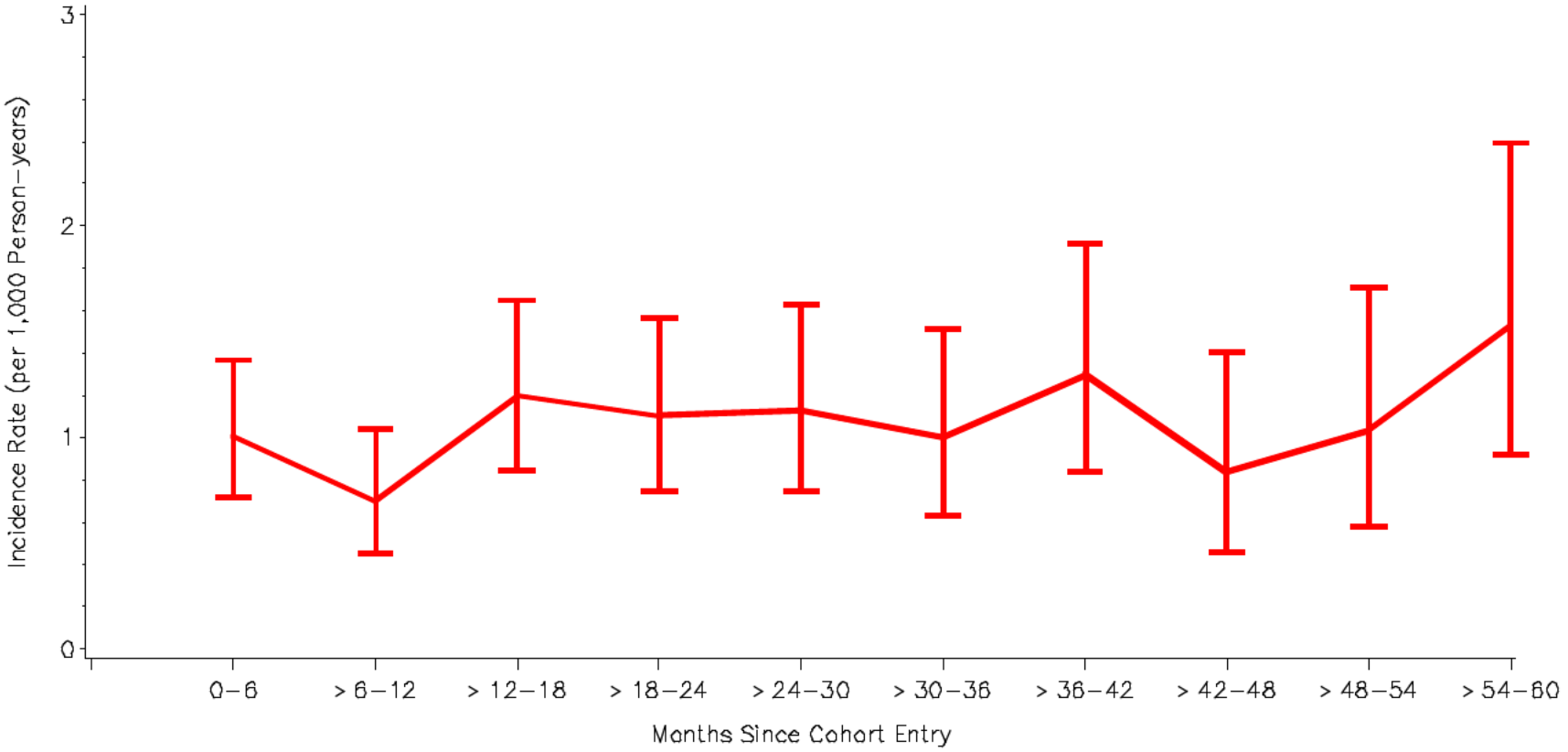
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.3. Incidence Rates for Breast Cancer Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



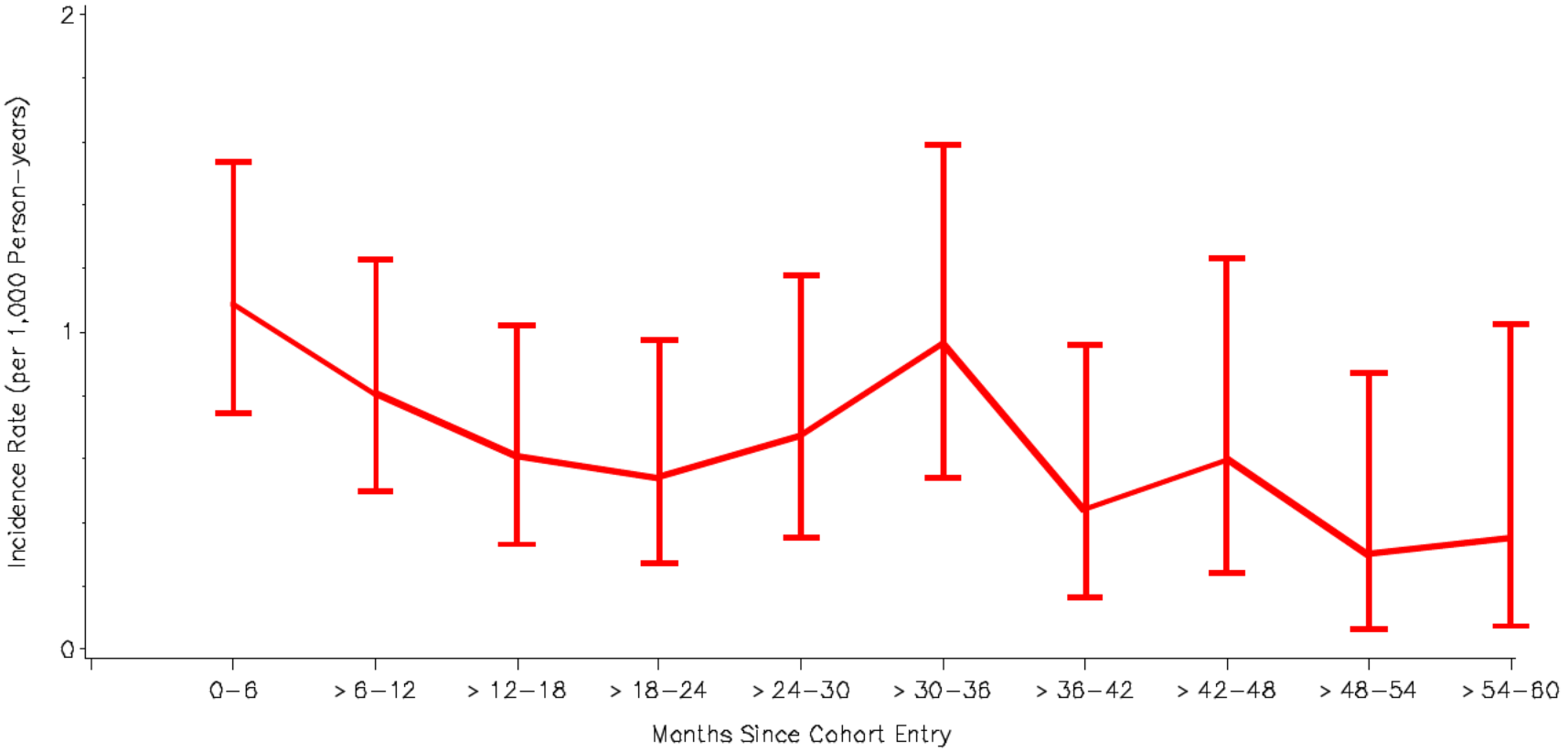
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.4. Incidence Rates for Colorectal Cancer Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



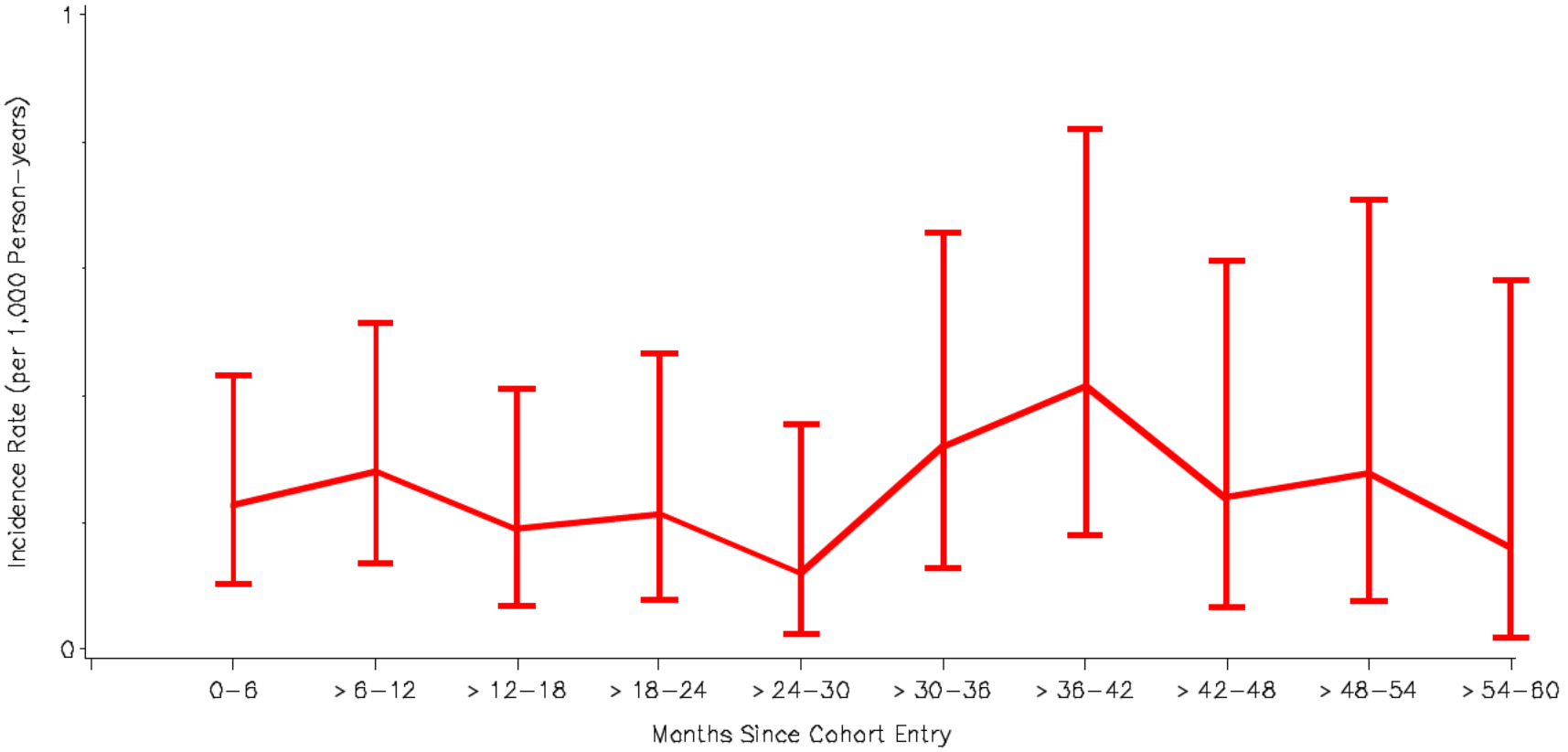
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.5. Incidence Rates for Corpus Uteri Cancer Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



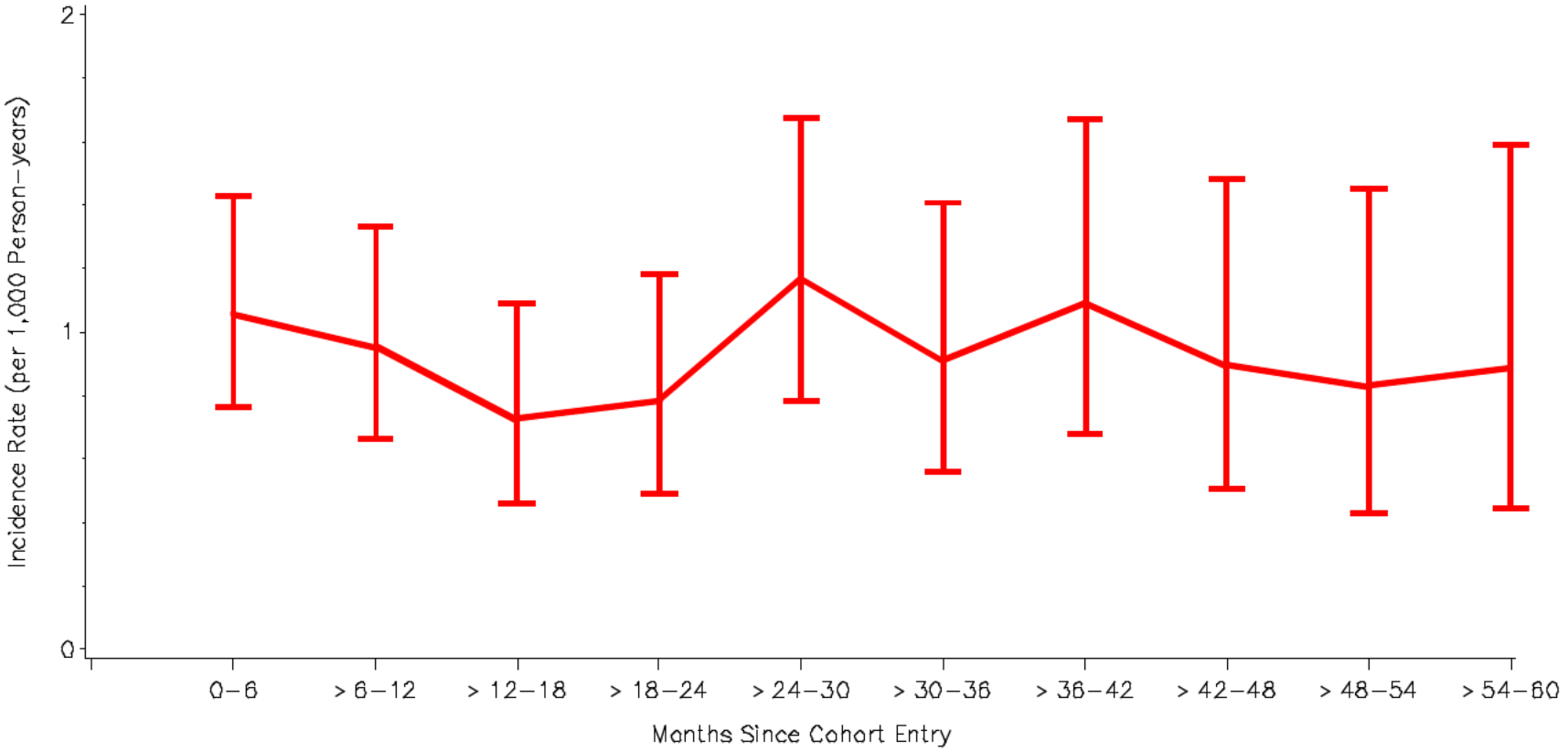
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.6. Incidence Rates for Cancer of Kidney and Renal System Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



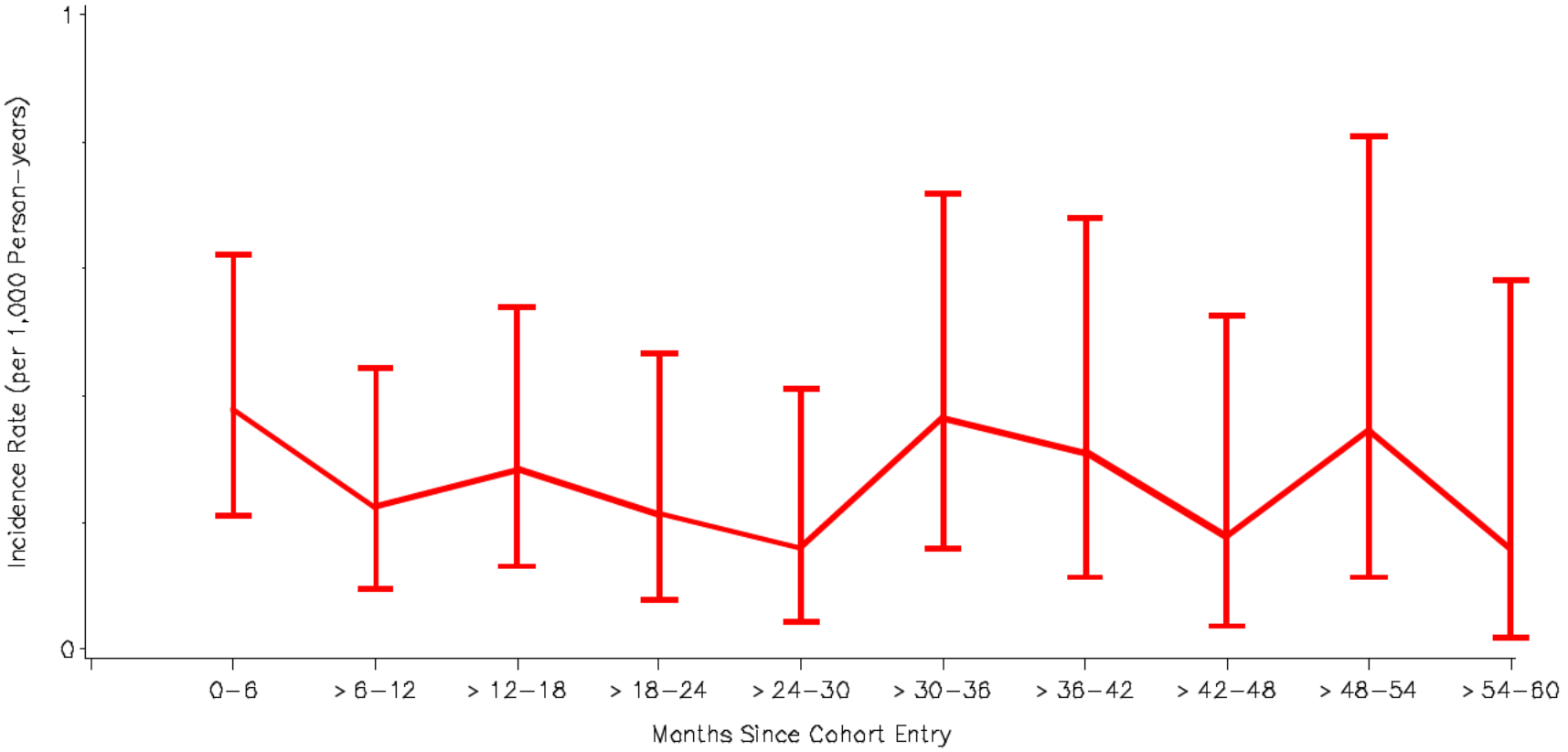
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.7. Incidence Rates for Cancer of the Lung and Bronchus Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



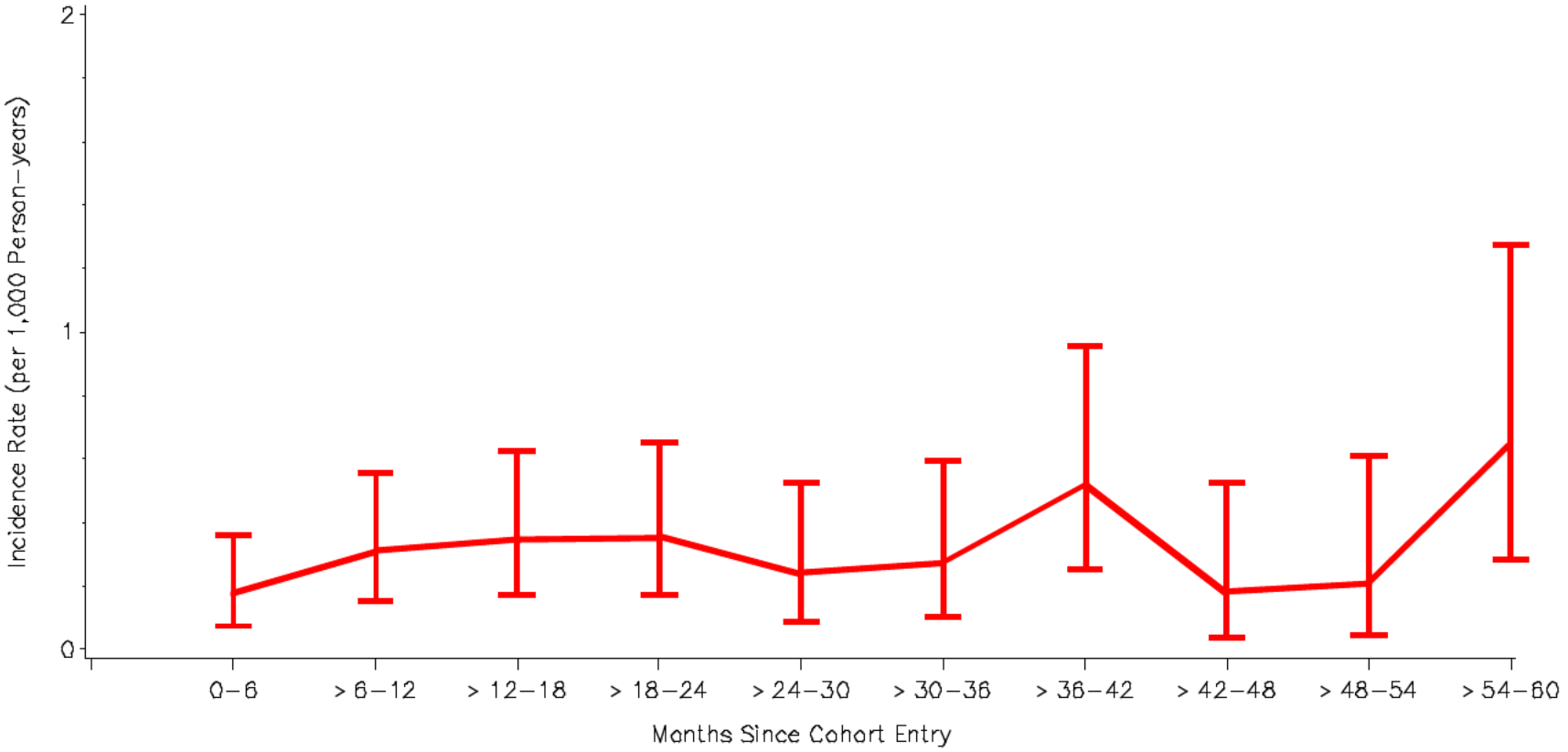
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.8. Incidence Rates for Non-Hodgkin Lymphoma Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



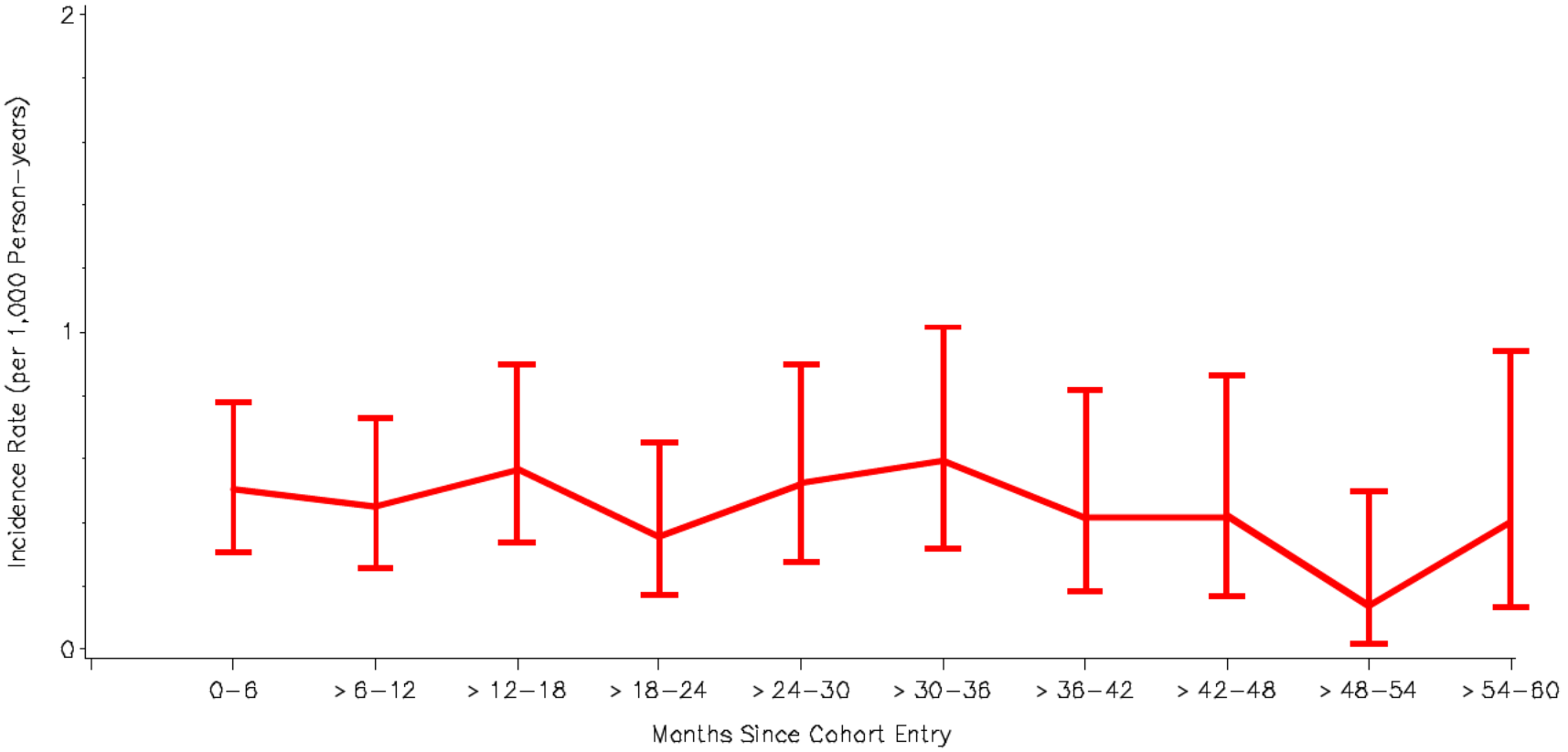
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.9. Incidence Rates for Pancreatic Cancer Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



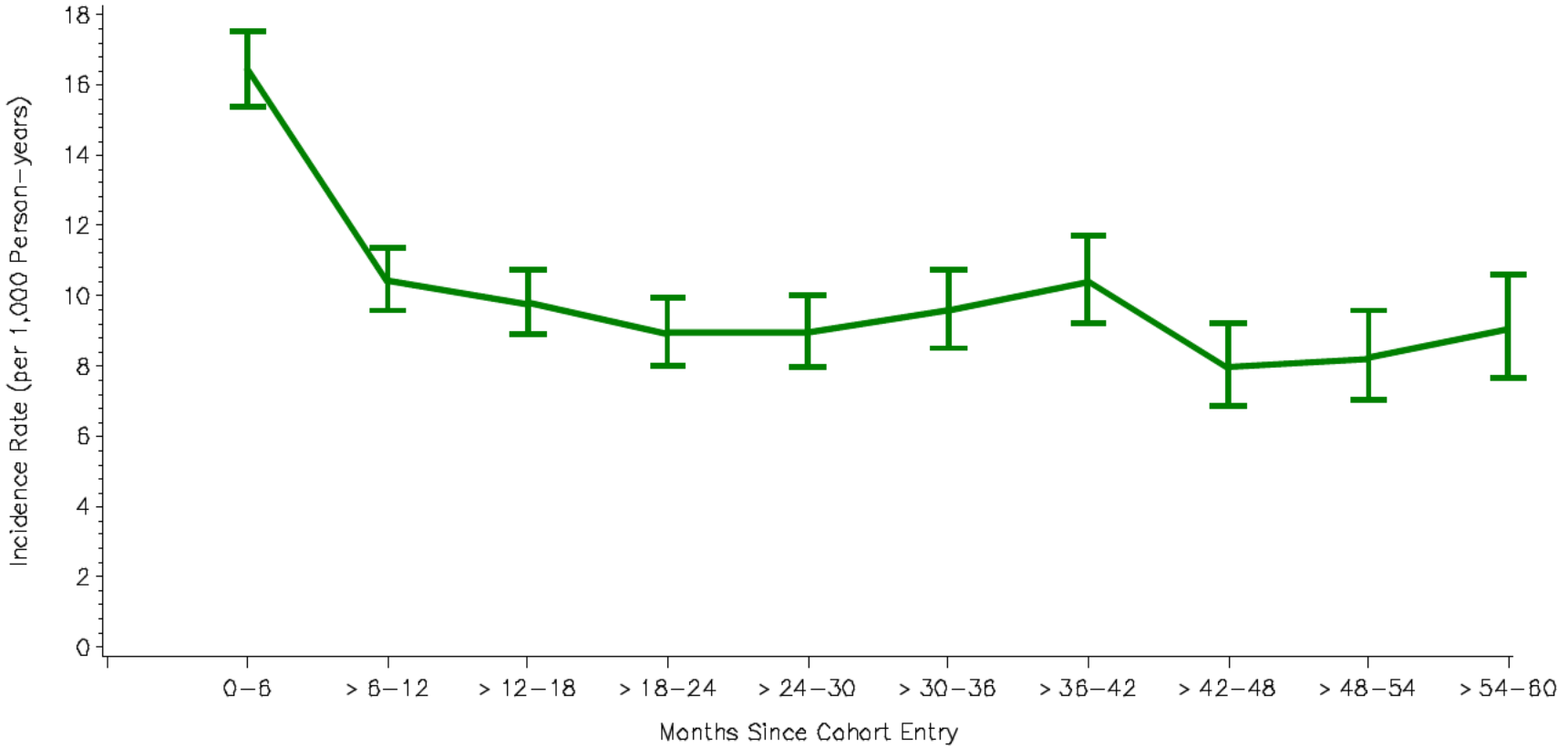
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.2.11. Incidence Rates for Melanoma of the Skin Endpoint Definition 5, by Months Since Cohort Entry, Female Patients



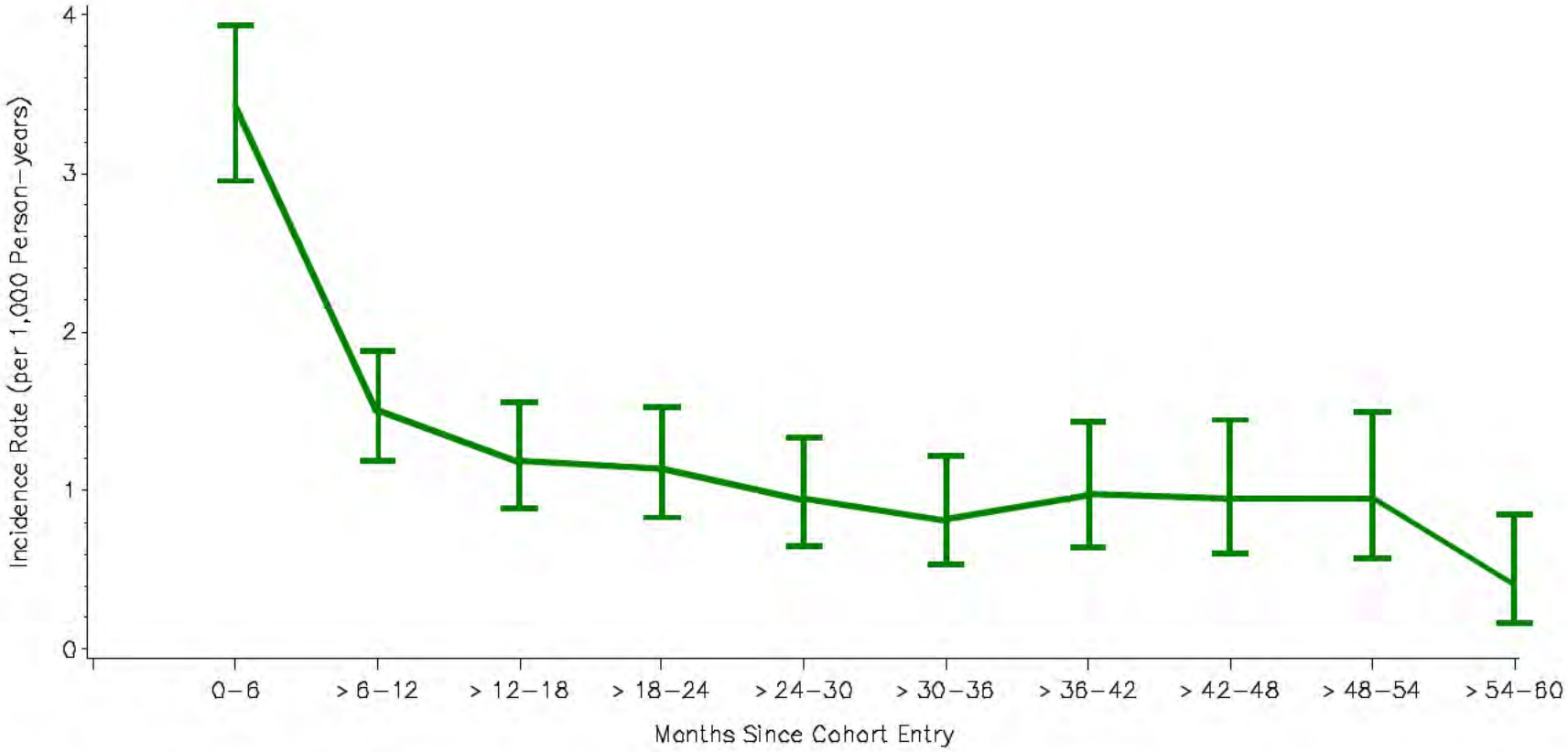
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.3.1. Incidence Rates for Composite Cancer Endpoint Definition 5, by Months Since Cohort Entry, All Patients



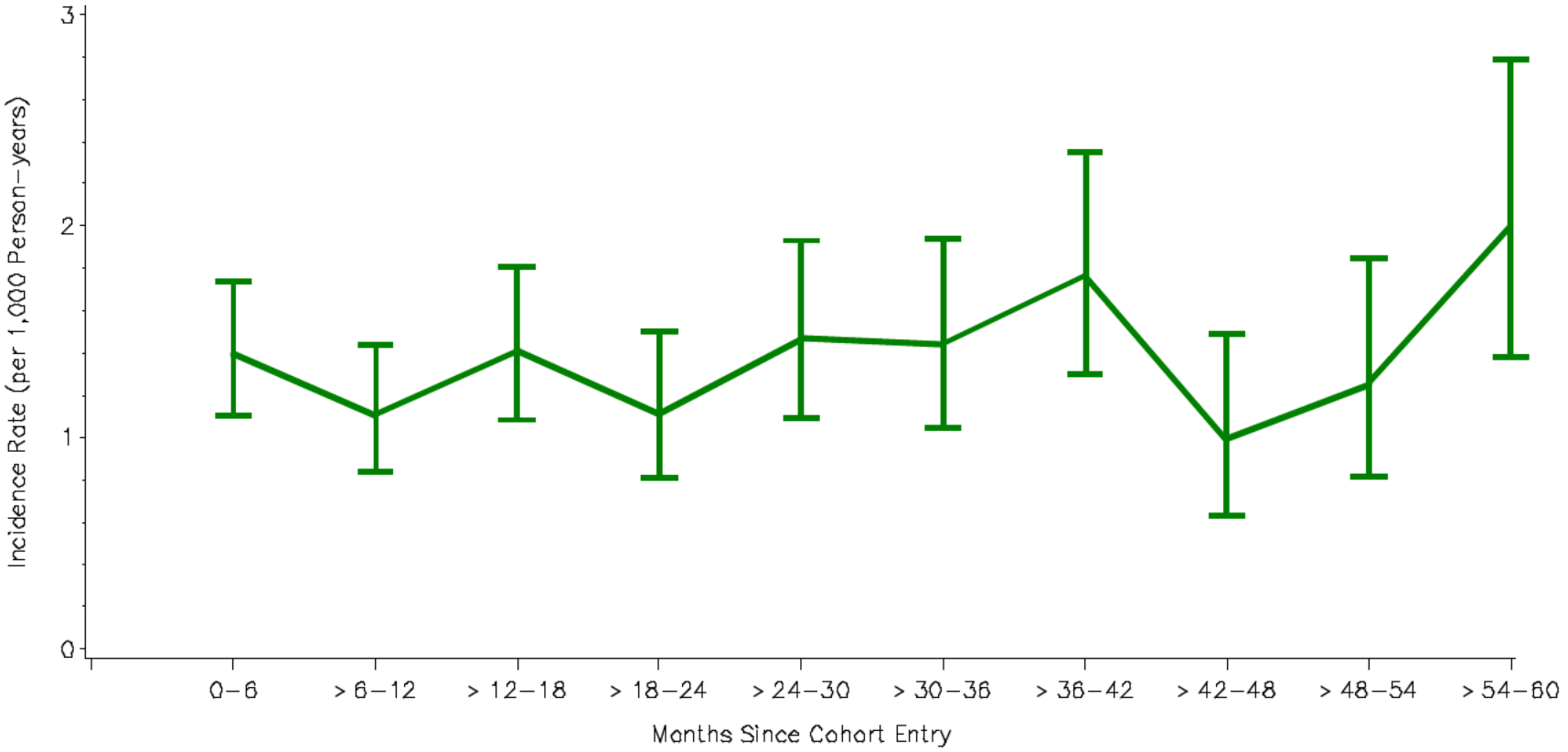
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.3.2. Incidence Rates for Urinary Bladder Cancer Endpoint Definition 5, by Months Since Cohort Entry, All Patients



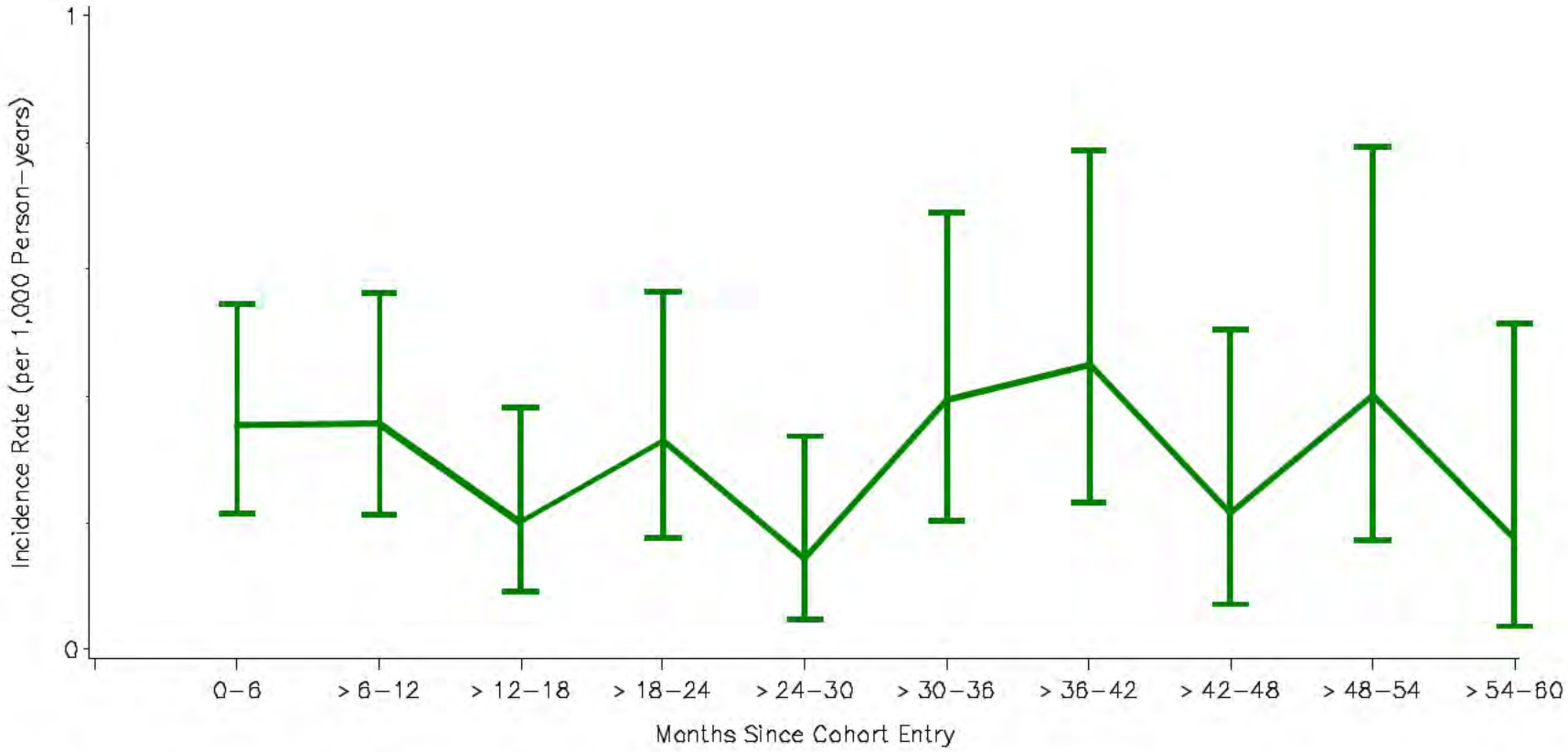
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.3.4. Incidence Rates for Colorectal Cancer Endpoint Definition 5, by Months Since Cohort Entry, All Patients



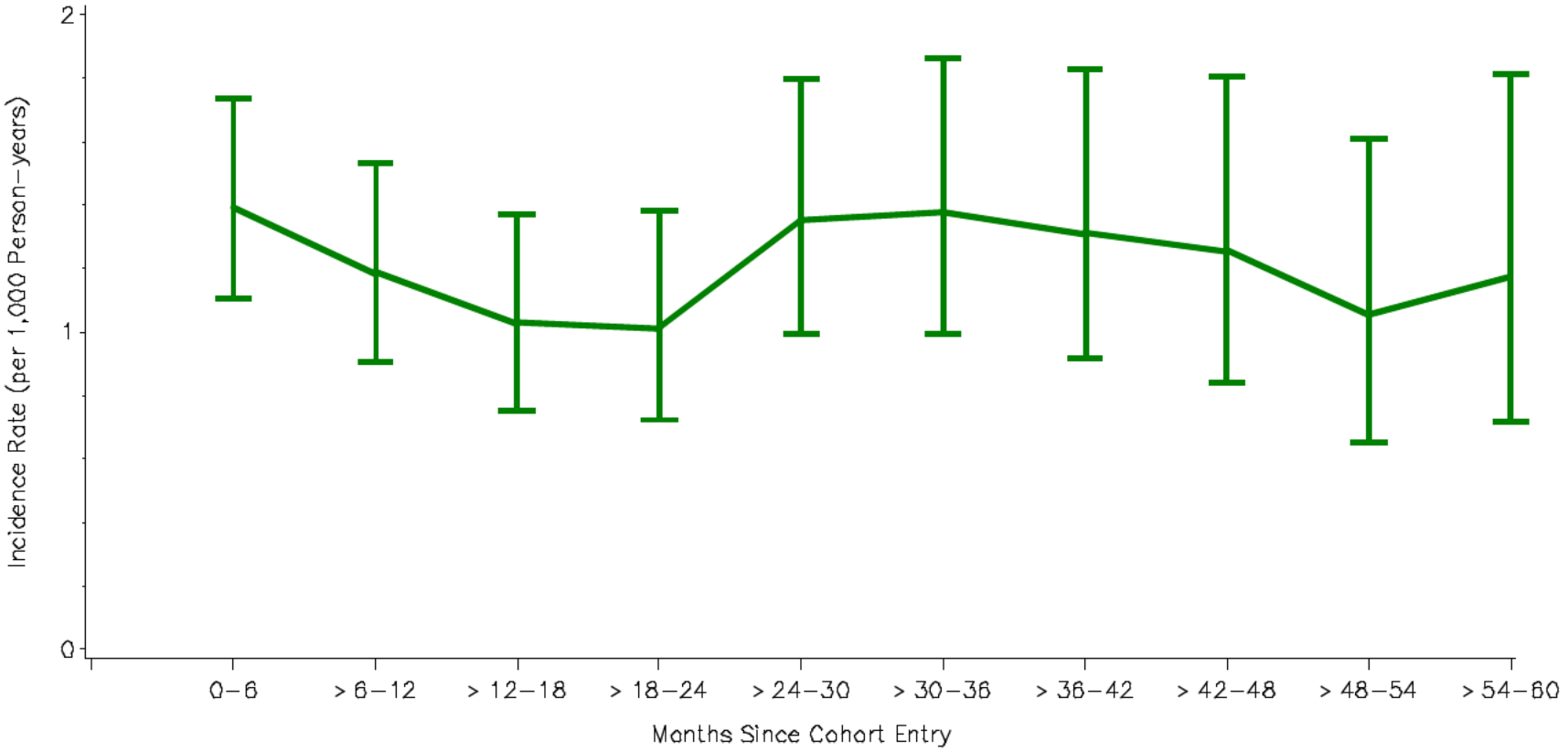
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.3.6. Incidence Rates for Cancer of Kidney and Renal System Endpoint Definition 5, by Months Since Cohort Entry, All Patients



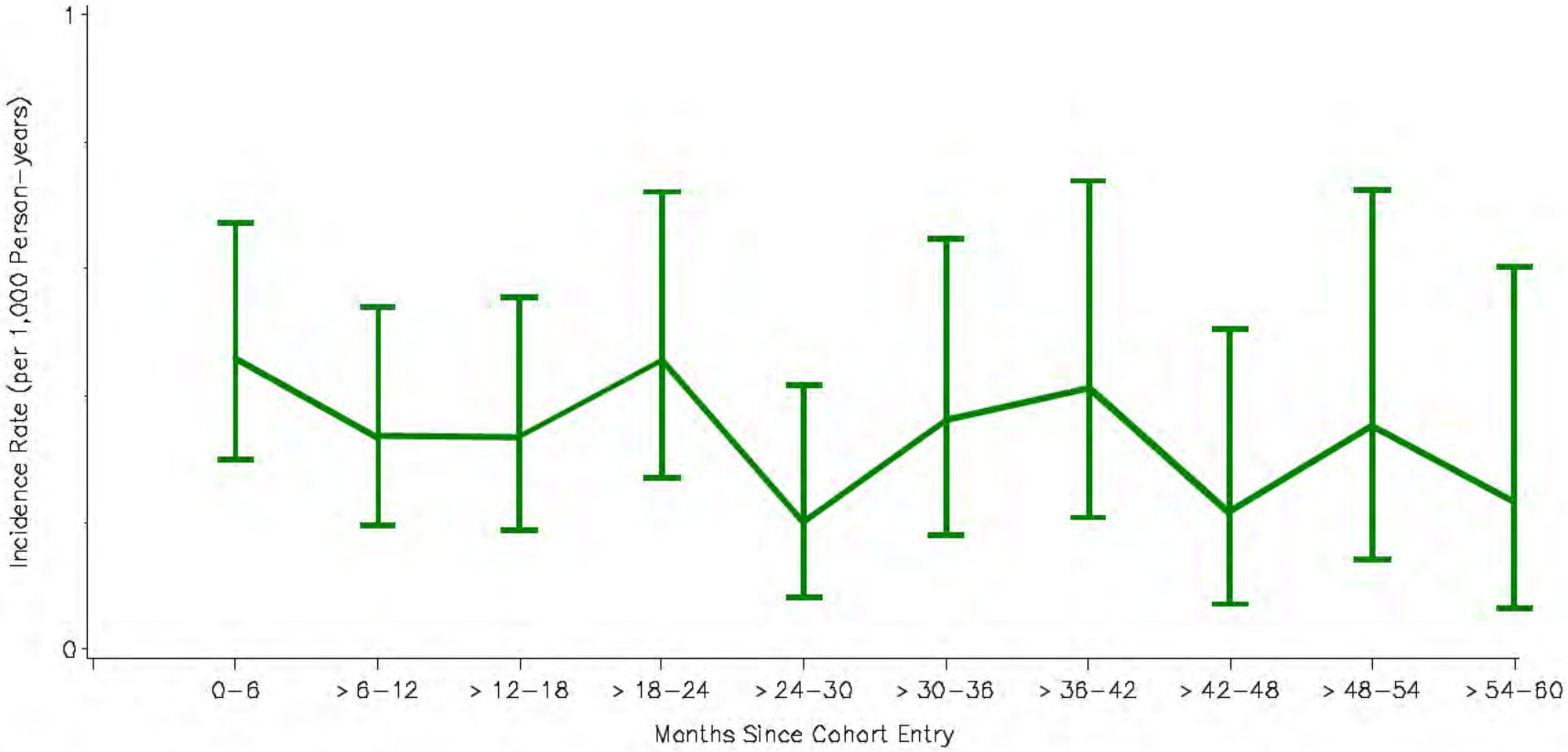
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.3.7. Incidence Rates for Cancer of the Lung and Bronchus Endpoint Definition 5, by Months Since Cohort Entry, All Patients



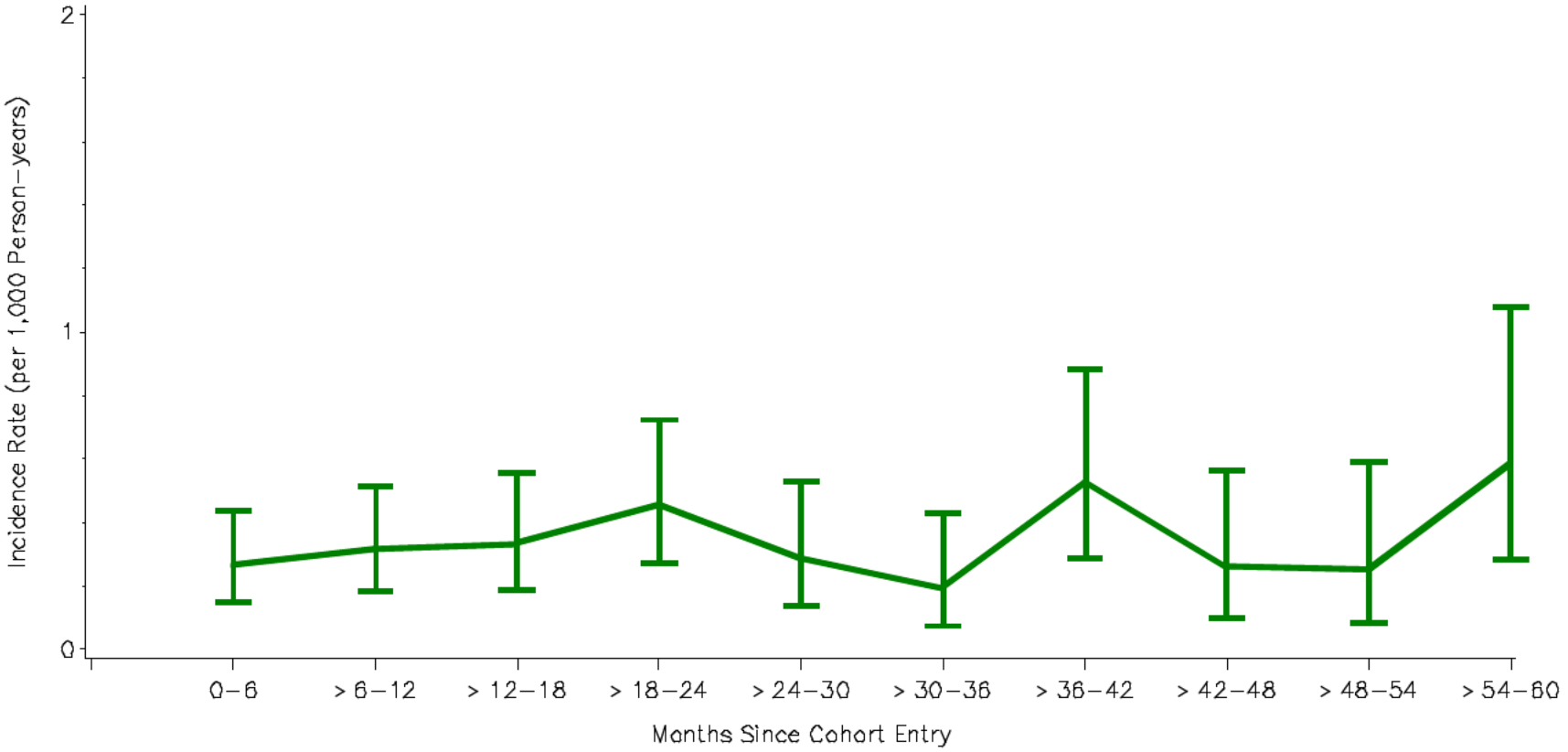
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.3.8. Incidence Rates for Non-Hodgkin Lymphoma Endpoint Definition 5, by Months Since Cohort Entry, All Patients



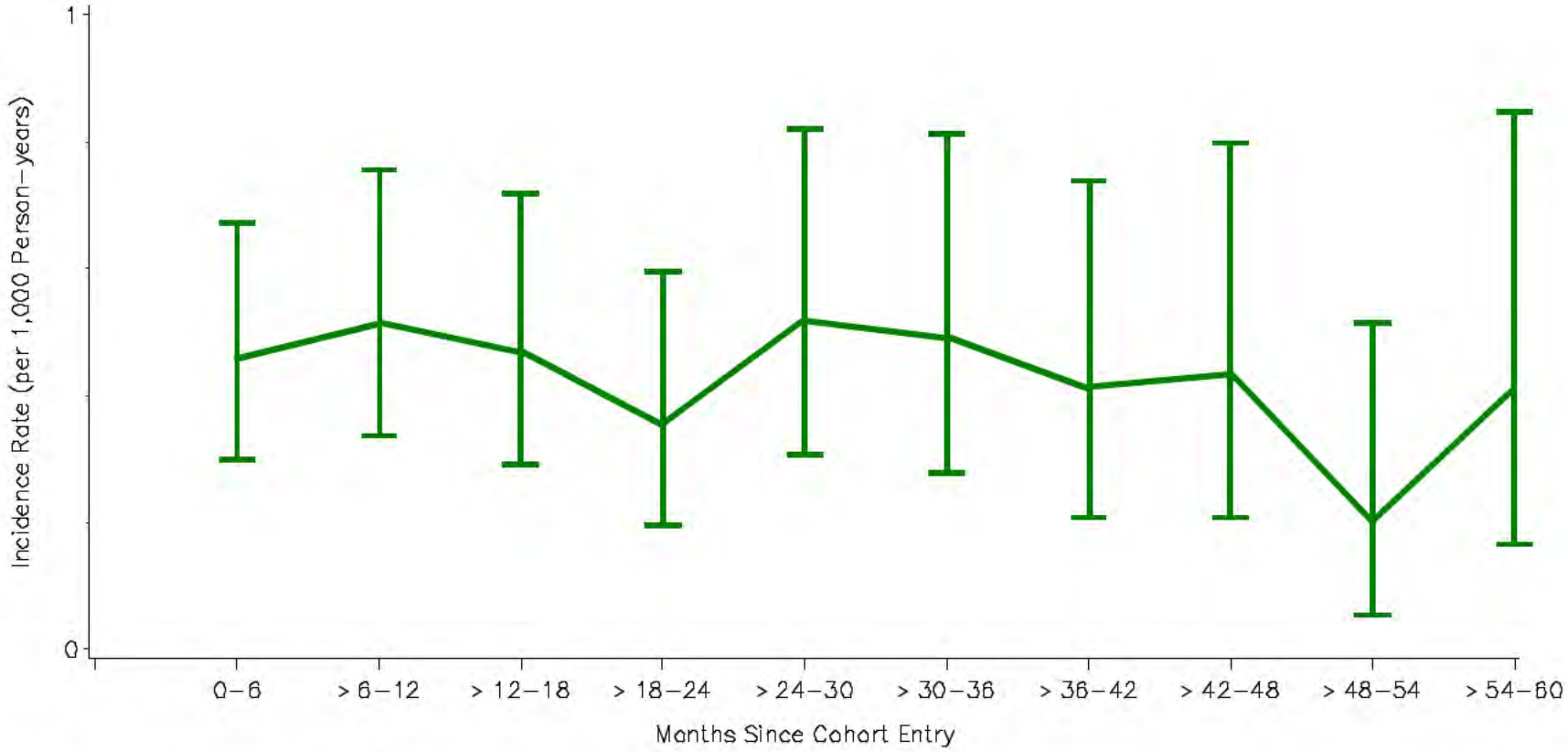
Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.3.9. Incidence Rates for Pancreatic Cancer Endpoint Definition 5, by Months Since Cohort Entry, All Patients



Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Figure 12.5.1.3.11. Incidence Rates for Melanoma of the Skin Endpoint Definition 5, by Months Since Cohort Entry, All Patients



Note: This analysis was limited to the first 5 years of follow-up. Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for ones from linked practices in the validation cohort. Vertical bars represent 95% confidence intervals.

Annex 8. Analysis Tables

As a guide to the tables with results of the validation of cancer endpoints, Tables N3 show analyses according to ever-exposure to the OAB study medications based on the five cancer endpoint definitions ("Analyses") discussed in Section 9.9.2.6. The set of Tables N3.a report results for the sex-specific composite cancer endpoints, as well as overall results (in which information is combined across sexes); results are presented for users of any OAB drug and for users of the individual study OAB drugs. In the set of Tables N3.a, each numbered table (N3.a1, N3.a2, etc.) gives results for the analysis using the case definition that is specified in the last digit of the table number (e.g., N3.a4 gives results for definition 4). In each table, in addition to the overall and sex-specific results, age-stratified results (< 65 years and ≥ 65 years) are presented (with the same sex-specific and overall [sexes combined] results shown within each age group). Results for individual study cancers are presented in tables numbered N3.b-N3.k, which follow the same pattern of organization as for Tables N3.a regarding sex-specific and age-specific results and analysis groups (case definitions), but only results for analysis 5 are presented for individual study cancers.

Analysis 5 (definition 5) is the main analysis (Table N3.a5). This analysis included all provisional (PROV-1) cases from non-linked practices, PROV-1 cases from linked practices not in the validation cohort but that were confirmed by linkage to NCDR or HES data (CONF-2 and CONF-4), and CONF-1 cases in linked practices in the validation cohort (Figure 9).

List of Analysis Results Tables

Drug Utilization Study

Validation of Cardiovascular Endpoints

Validation of Covariates

Cardiovascular Endpoints

Cancer Endpoints

Table A1. Characteristics of Patients Exposed to Any Overactive Bladder Drug (N = 119,912) at Study Cohort Entry, Overall and Stratified by Age at Cohort Entry

	Age at Cohort Entry (Years)					
	< 65		≥ 65		Overall	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Age at cohort entry (years)						
Mean (SD)	49.1	(11.2)	76.5	(7.5)	62.4	(16.7)
18-24	2,217	(3.6)			2,217	(1.8)
25-34	5,011	(8.1)			5,011	(4.2)
35-44	12,005	(19.5)			12,005	(10.0)
45-54	18,411	(29.9)			18,411	(15.4)
55-64	23,951	(38.9)			23,951	(20.0)
65-74			25,429	(43.6)	25,429	(21.2)
75-84			23,612	(40.5)	23,612	(19.7)
85+			9,276	(15.9)	9,276	(7.7)
Sex						
Male	16,160	(26.2)	20,019	(34.3)	36,179	(30.2)
Female	45,435	(73.8)	38,298	(65.7)	83,733	(69.8)
Calendar year at cohort entry						
2004	6,304	(10.2)	6,294	(10.8)	12,598	(10.5)
2005	6,311	(10.2)	6,375	(10.9)	12,686	(10.6)
2006	5,980	(9.7)	6,231	(10.7)	12,211	(10.2)
2007	6,356	(10.3)	6,078	(10.4)	12,434	(10.4)
2008	6,363	(10.3)	5,918	(10.1)	12,281	(10.2)
2009	6,988	(11.3)	6,405	(11.0)	13,393	(11.2)
2010	7,235	(11.7)	6,635	(11.4)	13,870	(11.6)
2011	7,858	(12.8)	7,140	(12.2)	14,998	(12.5)
2012	8,200	(13.3)	7,241	(12.4)	15,441	(12.9)
Index of Multiple Deprivation						
1	12,661	(20.6)	14,092	(24.2)	26,753	(22.3)
2	11,737	(19.1)	12,839	(22.0)	24,576	(20.5)
3	12,152	(19.7)	11,970	(20.5)	24,122	(20.1)
4	13,294	(21.6)	11,017	(18.9)	24,311	(20.3)
5	11,751	(19.1)	8,399	(14.4)	20,150	(16.8)

Table A1. Characteristics of Patients Exposed to Any Overactive Bladder Drug (N = 119,912) at Study Cohort Entry, Overall and Stratified by Age at Cohort Entry

	Age at Cohort Entry (Years)					
	< 65		≥ 65		Overall	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Overactive bladder	32,604	(52.9)	26,898	(46.1)	59,502	(49.6)
Hypertension						
Diagnosis codes only	18,762	(30.5)	16,183	(27.8)	34,945	(29.1)
Medications only	4,214	(6.8)	819	(1.4)	5,033	(4.2)
Diagnosis codes and medications	18,186	(29.5)	38,574	(66.1)	56,760	(47.3)
Diabetes						
Diagnosis codes only	741	(1.2)	2,044	(3.5)	2,785	(2.3)
Medications only	279	(0.5)	63	(0.1)	342	(0.3)
Diagnosis codes and medications	3,349	(5.4)	7,019	(12.0)	10,368	(8.6)
Smoking						
Never	29,328	(47.6)	27,460	(47.1)	56,788	(47.4)
Former	17,137	(27.8)	25,092	(43.0)	42,229	(35.2)
Current	14,386	(23.4)	5,065	(8.7)	19,451	(16.2)
Unknown history	744	(1.2)	700	(1.2)	1,444	(1.2)
Alcohol use						
Non-drinker	7,983	(13.0)	8,306	(14.2)	16,289	(13.6)
Low-moderate intake	31,530	(51.2)	30,909	(53.0)	62,439	(52.1)
High-very high intake	11,493	(18.7)	10,515	(18.0)	22,008	(18.4)
Drinker unknown quantity	3,579	(5.8)	3,537	(6.1)	7,116	(5.9)
Unknown history	7,010	(11.4)	5,050	(8.7)	12,060	(10.1)
Alcohol-related conditions						
Alcoholism or alcohol-related diseases	2,357	(3.8)	1,149	(2.0)	3,506	(2.9)
No alcoholism or alcohol-related diseases	59,238	(96.2)	57,168	(98.0)	116,406	(97.1)

Table A1. Characteristics of Patients Exposed to Any Overactive Bladder Drug (N = 119,912) at Study Cohort Entry, Overall and Stratified by Age at Cohort Entry

	Age at Cohort Entry (Years)					
	< 65		≥ 65		Overall	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
History of AMI	782	(1.3)	4,028	(6.9)	4,810	(4.0)
History of stroke	1,618	(2.6)	6,691	(11.5)	8,309	(6.9)
History of transient ischemic attack	627	(1.0)	4,241	(7.3)	4,868	(4.1)
History of coronary heart disease	2,712	(4.4)	12,829	(22.0)	15,541	(13.0)
History of heart failure	301	(0.5)	3,568	(6.1)	3,869	(3.2)
History of peripheral artery disease/peripheral vascular disease	2,359	(3.8)	6,033	(10.3)	8,392	(7.0)
Menopause (females only)	12,307	(27.1)	7,532	(19.7)	19,839	(23.7)
Health services utilization [mean (SD)]						
Outpatient visits	9.5	(8.6)	12.2	(10.0)	10.8	(9.4)
Hospitalizations	0.5	(1.3)	0.6	(1.2)	0.5	(1.3)

AMI = acute myocardial infarction; SD = standard deviation.
Note: Study cohort entry is date of index prescription.

Table A2. Descriptive Summary of Overactive Bladder Exposure at Study Cohort Entry (N = 119,912)

Variable	n	(%)
Index prescription(s)[a]		
Oxybutynin	40,651	(33.9)
Tolterodine	37,506	(31.3)
Darifenacin	151	(0.1)
Solifenacin	33,120	(27.6)
Trospium	6,071	(5.1)
Fesoterodine	2,344	(2.0)
More than one study OAB drug at cohort entry	69	(0.1)
De novo single exposure[b]		
Oxybutynin	40,627	(33.9)
Tolterodine	37,466	(31.2)
Darifenacin	151	(0.1)
Solifenacin	33,055	(27.6)
Trospium	6,050	(5.0)
Fesoterodine	2,343	(2.0)

OAB = overactive bladder.

Note: Anyone in the de novo single exposure group will also have a qualifying index prescription for that drug.

[a] Exposure to index prescription means no exposure to this drug (or these drugs) within the prior 12 months; however, patient may have had prior exposure to other OAB drugs. Prescriptions for OAB drugs that start prior to cohort entry and overlap with the cohort entry date are not included in the definition of index prescription.

[b] De novo single exposure means taking this drug at cohort entry, with no prior exposure to any other OAB drug during the previous 12 months; however, patient could have had exposure to this OAB drug if the prescription was more than 12 months ago.

Table A3. Characteristics of Exposed Patients, by Index Overactive Bladder Drug(s)[a] at Study Cohort Entry

	Oxybutynin (n = 40,651)		Tolterodine (n = 37,506)		Darifenacin (n = 151)		Solifenacin (n = 33,120)		Trospium (n = 6,071)		Fesoterodine (n = 2,344)		More Than One Study OAB Drug at Cohort Entry (n = 69)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Age at cohort entry (years)														
Mean (SD)	62.8	(17.4)	62.8	(16.3)	65.3	(14.4)	61.3	(16.3)	64.1	(16.1)	60.1	(16.5)	59.9	(13.6)
18-24	965	(2.4)	541	(1.4)	1	(0.7)	585	(1.8)	76	(1.3)	49	(2.1)		
25-34	1,902	(4.7)	1,446	(3.9)	2	(1.3)	1,337	(4.0)	204	(3.4)	117	(5.0)	3	(4.3)
35-44	3,918	(9.6)	3,629	(9.7)	13	(8.6)	3,638	(11.0)	534	(8.8)	265	(11.3)	8	(11.6)
45-54	5,804	(14.3)	5,622	(15.0)	21	(13.9)	5,693	(17.2)	819	(13.5)	439	(18.7)	13	(18.8)
55-64	7,610	(18.7)	7,766	(20.7)	30	(19.9)	6,839	(20.6)	1,230	(20.3)	458	(19.5)	18	(26.1)
65-74	8,355	(20.6)	8,118	(21.6)	43	(28.5)	6,989	(21.1)	1,395	(23.0)	512	(21.8)	17	(24.6)
75-84	8,429	(20.7)	7,583	(20.2)	32	(21.2)	5,880	(17.8)	1,303	(21.5)	378	(16.1)	7	(10.1)
85+	3,668	(9.0)	2,801	(7.5)	9	(6.0)	2,159	(6.5)	510	(8.4)	126	(5.4)	3	(4.3)
Sex														
Male	13,137	(32.3)	11,766	(31.4)	45	(29.8)	8,644	(26.1)	1,868	(30.8)	702	(29.9)	17	(24.6)
Female	27,514	(67.7)	25,740	(68.6)	106	(70.2)	24,476	(73.9)	4,203	(69.2)	1,642	(70.1)	52	(75.4)
Calendar year at cohort entry														
2004	4,097	(10.1)	6,914	(18.4)			152	(0.5)	1,431	(23.6)			4	(5.8)
2005	3,768	(9.3)	6,488	(17.3)			1,292	(3.9)	1,126	(18.5)			12	(17.4)
2006	3,855	(9.5)	5,626	(15.0)			1,911	(5.8)	814	(13.4)			5	(7.2)
2007	4,179	(10.3)	4,938	(13.2)	33	(21.9)	2,731	(8.2)	545	(9.0)			8	(11.6)
2008	4,023	(9.9)	3,961	(10.6)	44	(29.1)	3,784	(11.4)	407	(6.7)	57	(2.4)	5	(7.2)
2009	4,351	(10.7)	3,240	(8.6)	21	(13.9)	5,045	(15.2)	334	(5.5)	395	(16.9)	7	(10.1)
2010	4,675	(11.5)	2,636	(7.0)	4	(2.6)	5,596	(16.9)	380	(6.3)	566	(24.1)	13	(18.8)
2011	5,628	(13.8)	2,066	(5.5)	19	(12.6)	6,138	(18.5)	461	(7.6)	677	(28.9)	9	(13.0)
2012	6,075	(14.9)	1,637	(4.4)	30	(19.9)	6,471	(19.5)	573	(9.4)	649	(27.7)	6	(8.7)

Table A3. Characteristics of Exposed Patients, by Index Overactive Bladder Drug(s)[a] at Study Cohort Entry

	Oxybutynin (n = 40,651)		Tolterodine (n = 37,506)		Darifenacin (n = 151)		Solifenacin (n = 33,120)		Trospium (n = 6,071)		Fesoterodine (n = 2,344)		More Than One Study OAB Drug at Cohort Entry (n = 69)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Index of Multiple Deprivation														
1	8,543	(21.0)	9,083	(24.2)	41	(27.2)	7,288	(22.0)	1,295	(21.3)	482	(20.6)	21	(30.4)
2	8,238	(20.3)	7,468	(19.9)	29	(19.2)	6,995	(21.1)	1,307	(21.5)	521	(22.2)	18	(26.1)
3	8,345	(20.5)	7,549	(20.1)	27	(17.9)	6,456	(19.5)	1,323	(21.8)	413	(17.6)	9	(13.0)
4	8,783	(21.6)	7,259	(19.4)	33	(21.9)	6,640	(20.0)	1,050	(17.3)	534	(22.8)	12	(17.4)
5	6,742	(16.6)	6,147	(16.4)	21	(13.9)	5,741	(17.3)	1,096	(18.1)	394	(16.8)	9	(13.0)
Overactive bladder	18,937	(46.6)	18,666	(49.8)	87	(57.6)	17,273	(52.2)	3,232	(53.2)	1,267	(54.1)	40	(58.0)
Hypertension														
Diagnosis codes only	11,812	(29.1)	11,412	(30.4)	45	(29.8)	9,242	(27.9)	1,780	(29.3)	634	(27.0)	20	(29.0)
Medications only	1,687	(4.1)	1,523	(4.1)	7	(4.6)	1,432	(4.3)	247	(4.1)	132	(5.6)	5	(7.2)
Diagnosis codes and medications	19,374	(47.7)	17,235	(46.0)	74	(49.0)	15,971	(48.2)	2,963	(48.8)	1,106	(47.2)	37	(53.6)
Diabetes														
Diagnosis codes only	971	(2.4)	842	(2.2)	4	(2.6)	761	(2.3)	153	(2.5)	53	(2.3)	1	(1.4)
Medications only	117	(0.3)	84	(0.2)	1	(0.7)	113	(0.3)	15	(0.2)	12	(0.5)		
Diagnosis codes and medications	3,623	(8.9)	2,936	(7.8)	11	(7.3)	2,990	(9.0)	566	(9.3)	235	(10.0)	7	(10.1)
Smoking														
Never	19,050	(46.9)	18,018	(48.0)	72	(47.7)	15,622	(47.2)	2,896	(47.7)	1,098	(46.8)	32	(46.4)
Former	14,448	(35.5)	12,702	(33.9)	52	(34.4)	12,043	(36.4)	2,093	(34.5)	871	(37.2)	20	(29.0)
Current	6,597	(16.2)	6,164	(16.4)	25	(16.6)	5,313	(16.0)	963	(15.9)	372	(15.9)	17	(24.6)
Unknown history	556	(1.4)	622	(1.7)	2	(1.3)	142	(0.4)	119	(2.0)	3	(0.1)		
Alcohol use														
Non-drinker	5,607	(13.8)	4,973	(13.3)	33	(21.9)	4,455	(13.5)	839	(13.8)	372	(15.9)	10	(14.5)
Low-moderate intake	20,817	(51.2)	19,242	(51.3)	74	(49.0)	17,901	(54.0)	3,138	(51.7)	1,233	(52.6)	34	(49.3)
High-very high intake	7,496	(18.4)	6,881	(18.3)	29	(19.2)	6,128	(18.5)	1,069	(17.6)	389	(16.6)	16	(23.2)
Drinker unknown quantity	2,405	(5.9)	2,360	(6.3)	3	(2.0)	1,815	(5.5)	381	(6.3)	147	(6.3)	5	(7.2)
Unknown history	4,326	(10.6)	4,050	(10.8)	12	(7.9)	2,821	(8.5)	644	(10.6)	203	(8.7)	4	(5.8)
Alcohol-related conditions														
Alcoholism or alcohol-related diseases	1,261	(3.1)	1,010	(2.7)	6	(4.0)	967	(2.9)	172	(2.8)	87	(3.7)	3	(4.3)
No alcoholism or alcohol-related diseases	39,390	(96.9)	36,496	(97.3)	145	(96.0)	32,153	(97.1)	5,899	(97.2)	2,257	(96.3)	66	(95.7)

Table A3. Characteristics of Exposed Patients, by Index Overactive Bladder Drug(s)[a] at Study Cohort Entry

	Oxybutynin (n = 40,651)		Tolterodine (n = 37,506)		Darifenacin (n = 151)		Solifenacin (n = 33,120)		Trospium (n = 6,071)		Fesoterodine (n = 2,344)		More Than One Study OAB Drug at Cohort Entry (n = 69)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
History of AMI	1,723	(4.2)	1,539	(4.1)	9	(6.0)	1,179	(3.6)	270	(4.4)	87	(3.7)	3	(4.3)
History of stroke	2,984	(7.3)	2,594	(6.9)	15	(9.9)	2,044	(6.2)	497	(8.2)	172	(7.3)	3	(4.3)
History of transient ischemic attack	1,682	(4.1)	1,563	(4.2)	9	(6.0)	1,207	(3.6)	306	(5.0)	99	(4.2)	2	(2.9)
History of coronary heart disease	5,309	(13.1)	4,964	(13.2)	25	(16.6)	4,034	(12.2)	915	(15.1)	285	(12.2)	9	(13.0)
History of heart failure	1,438	(3.5)	1,259	(3.4)	9	(6.0)	863	(2.6)	234	(3.9)	64	(2.7)	2	(2.9)
History of peripheral artery disease/peripheral vascular disease	2,951	(7.3)	2,567	(6.8)	11	(7.3)	2,228	(6.7)	480	(7.9)	149	(6.4)	6	(8.7)
Menopause (females only)	6,050	(22.0)	6,175	(24.0)	26	(24.5)	6,079	(24.8)	1,080	(25.7)	410	(25.0)	19	(36.5)
Health services utilization [mean (SD)]														
Outpatient visits	10.8	(9.6)	10.7	(9.5)	12.3	(11.0)	10.6	(8.9)	11.5	(9.8)	10.8	(8.5)	10.9	(9.2)
Hospitalizations	0.5	(1.4)	0.5	(1.2)	1.0	(1.7)	0.6	(1.2)	0.6	(1.2)	0.7	(1.3)	0.8	(1.4)

AMI = acute myocardial infarction; OAB = overactive bladder; SD = standard deviation.

[a] This table includes all patients with a qualifying index prescription. Patients who entered the cohort on more than one medication are only included in the rightmost column.

Table A4. Characteristics of Exposed Patients,[a] by Each Index Overactive Bladder Drug at Study Cohort Entry

	Oxybutynin (n = 40,755)		Tolterodine (n = 37,625)		Darifenacin (n = 153)		Solifenacin (n = 33,159)		Trospium (n = 6,092)		Fesoterodine (n = 2,348)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Age at cohort entry (years)												
Mean (SD)	62.8	(17.4)	62.9	(16.3)	65.4	(14.3)	61.3	(16.3)	64.1	(16.1)	60.1	(16.5)
18-24	965	(2.4)	542	(1.4)	1	(0.7)	585	(1.8)	76	(1.2)	49	(2.1)
25-34	1,906	(4.7)	1,448	(3.8)	2	(1.3)	1,340	(4.0)	204	(3.3)	117	(5.0)
35-44	3,927	(9.6)	3,637	(9.7)	13	(8.5)	3,642	(11.0)	537	(8.8)	266	(11.3)
45-54	5,814	(14.3)	5,639	(15.0)	21	(13.7)	5,700	(17.2)	824	(13.5)	440	(18.7)
55-64	7,635	(18.7)	7,796	(20.7)	31	(20.3)	6,848	(20.7)	1,234	(20.3)	459	(19.5)
65-74	8,382	(20.6)	8,148	(21.7)	44	(28.8)	7,000	(21.1)	1,397	(22.9)	512	(21.8)
75-84	8,444	(20.7)	7,607	(20.2)	32	(20.9)	5,883	(17.7)	1,308	(21.5)	378	(16.1)
85+	3,682	(9.0)	2,808	(7.5)	9	(5.9)	2,161	(6.5)	512	(8.4)	127	(5.4)
Sex												
Male	13,168	(32.3)	11,796	(31.4)	47	(30.7)	8,652	(26.1)	1,871	(30.7)	703	(29.9)
Female	27,587	(67.7)	25,829	(68.6)	106	(69.3)	24,507	(73.9)	4,221	(69.3)	1,645	(70.1)
Calendar year at cohort entry												
2004	4,116	(10.1)	6,931	(18.4)			152	(0.5)	1,438	(23.6)		
2005	3,785	(9.3)	6,512	(17.3)			1,297	(3.9)	1,129	(18.5)		
2006	3,866	(9.5)	5,639	(15.0)			1,912	(5.8)	818	(13.4)		
2007	4,187	(10.3)	4,955	(13.2)	33	(21.6)	2,734	(8.2)	548	(9.0)		
2008	4,033	(9.9)	3,970	(10.6)	44	(28.8)	3,789	(11.4)	407	(6.7)	57	(2.4)
2009	4,360	(10.7)	3,245	(8.6)	21	(13.7)	5,050	(15.2)	335	(5.5)	395	(16.8)
2010	4,689	(11.5)	2,652	(7.0)	4	(2.6)	5,604	(16.9)	380	(6.2)	ô (2	(24.1)
2011	5,635	(13.8)	2,075	(5.5)	20	(13.1)	6,146	(18.5)	464	(7.6)	679	(28.9)
2012	6,084	(14.9)	1,646	(4.4)	31	(20.3)	6,475	(19.5)	573	(9.4)	650	(27.7)

Table A4. Characteristics of Exposed Patients,[a] by Each Index Overactive Bladder Drug at Study Cohort Entry

	Oxybutynin (n = 40,755)		Tolterodine (n = 37,625)		Darifenacin (n = 153)		Solifenacin (n = 33,159)		Trospium (n = 6,092)		Fesoterodine (n = 2,348)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Index of Multiple Deprivation												
1	8,565	(21.0)	9,111	(24.2)	43	(28.1)	7,301	(22.0)	1,302	(21.4)	483	(20.6)
2	8,263	(20.3)	7,495	(19.9)	29	(19.0)	7,003	(21.1)	1,312	(21.5)	521	(22.2)
3	8,369	(20.5)	7,573	(20.1)	27	(17.6)	6,461	(19.5)	1,327	(21.8)	414	(17.6)
4	8,802	(21.6)	7,285	(19.4)	33	(21.6)	6,647	(20.0)	1,055	(17.3)	534	(22.7)
5	6,756	(16.6)	6,161	(16.4)	21	(13.7)	5,747	(17.3)	1,096	(18.0)	396	(16.9)
Overactive bladder	19,003	(46.6)	18,741	(49.8)	87	(56.9)	17,296	(52.2)	3,246	(53.3)	1,270	(54.1)
Hypertension												
Diagnosis codes only	11,840	(29.1)	11,447	(30.4)	46	(30.1)	9,252	(27.9)	1,787	(29.3)	634	(27.0)
Medications only	1,694	(4.2)	1,528	(4.1)	7	(4.6)	1,435	(4.3)	248	(4.1)	133	(5.7)
Diagnosis codes and medications	19,433	(47.7)	17,297	(46.0)	75	(49.0)	15,991	(48.2)	2,973	(48.8)	1,109	(47.2)
Diabetes												
Diagnosis codes only	976	(2.4)	845	(2.2)	4	(2.6)	762	(2.3)	153	(2.5)	53	(2.3)
Medications only	118	(0.3)	85	(0.2)	1	(0.7)	113	(0.3)	15	(0.2)	12	(0.5)
Diagnosis codes and medications	3,632	(8.9)	2,947	(7.8)	11	(7.2)	2,992	(9.0)	569	(9.3)	237	(10.1)
Smoking												
Never	19,099	(46.9)	18,072	(48.0)	72	(47.1)	15,643	(47.2)	2,909	(47.8)	1,101	(46.9)
Former	14,477	(35.5)	12,744	(33.9)	54	(35.3)	12,053	(36.3)	2,097	(34.4)	872	(37.1)
Current	6,620	(16.2)	6,185	(16.4)	25	(16.3)	5,320	(16.0)	967	(15.9)	372	(15.8)
Unknown history	559	(1.4)	624	(1.7)	2	(1.3)	143	(0.4)	119	(2.0)	3	(0.1)
Alcohol use												
Non-drinker	5,629	(13.8)	4,991	(13.3)	33	(21.6)	4,462	(13.5)	843	(13.8)	373	(15.9)
Low-moderate intake	20,860	(51.2)	19,308	(51.3)	75	(49.0)	17,923	(54.1)	3,148	(51.7)	1,234	(52.6)
High-very high intake	7,520	(18.5)	6,898	(18.3)	30	(19.6)	6,134	(18.5)	1,072	(17.6)	391	(16.7)
Drinker unknown quantity	2,411	(5.9)	2,366	(6.3)	3	(2.0)	1,816	(5.5)	383	(6.3)	147	(6.3)
Unknown history	4,335	(10.6)	4,062	(10.8)	12	(7.8)	2,824	(8.5)	646	(10.6)	203	(8.6)
Alcohol-related conditions												
Alcoholism or alcohol-related diseases	1,266	(3.1)	1,015	(2.7)	6	(3.9)	967	(2.9)	172	(2.8)	87	(3.7)
No alcoholism or alcohol-related diseases	39,489	(96.9)	36,610	(97.3)	147	(96.1)	32,192	(97.1)	5,920	(97.2)	2,261	(96.3)

Table A4. Characteristics of Exposed Patients,[a] by Each Index Overactive Bladder Drug at Study Cohort Entry

	Oxybutynin (n = 40,755)		Tolterodine (n = 37,625)		Darifenacin (n = 153)		Solifenacin (n = 33,159)		Trospium (n = 6,092)		Fesoterodine (n = 2,348)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
History of AMI	1,728	(4.2)	1,542	(4.1)	9	(5.9)	1,180	(3.6)	271	(4.4)	87	(3.7)
History of stroke	2,991	(7.3)	2,605	(6.9)	15	(9.8)	2,046	(6.2)	497	(8.2)	172	(7.3)
History of transient ischemic attack	1,689	(4.1)	1,567	(4.2)	9	(5.9)	1,208	(3.6)	307	(5.0)	99	(4.2)
History of coronary heart disease	5,324	(13.1)	4,978	(13.2)	25	(16.3)	4,038	(12.2)	919	(15.1)	285	(12.1)
History of heart failure	1,443	(3.5)	1,264	(3.4)	9	(5.9)	863	(2.6)	235	(3.9)	64	(2.7)
History of peripheral artery disease/peripheral vascular disease	2,957	(7.3)	2,579	(6.9)	11	(7.2)	2,230	(6.7)	482	(7.9)	150	(6.4)
Menopause (females only)	6,067	(22.0)	6,196	(24.0)	26	(24.5)	6,091	(24.9)	1,087	(25.8)	411	(25.0)
Health services utilization [mean (SD)]												
Outpatient visits	10.8	(9.6)	10.7	(9.5)	12.5	(11.5)	10.6	(8.9)	11.5	(9.7)	10.8	(8.5)
Hospitalizations	0.5	(1.4)	0.5	(1.2)	1.0	(1.7)	0.6	(1.2)	0.6	(1.2)	0.7	(1.3)

AMI = acute myocardial infarction; SD = standard deviation.

[a] This table includes all patients with a qualifying index prescription. Patients who entered the cohort on more than one medication are represented for each qualifying medication, therefore the sum of patient counts across medications exceeds the number of patients in the study cohort.

Table A5. Characteristics of Patients Exposed to Overactive Bladder Drug(s) at Index Prescription, Stratified by Patient's Eligibility for Linkage to Hospital Episode Statistics and/or Office for National Statistics Mortality Data

	Patients Eligible for Linkage to Both HES and ONS Mortality Data (n = 65,691)		Patients Eligible for Linkage to HES Data but Not ONS Mortality Data (n = 2,679)		Patients Eligible for Linkage to ONS Mortality Data but Not HES Data (n = 1)		Patients Not Eligible for Linkage to HES or ONS Mortality Data (n = 51,541)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Age at cohort entry (years)								
Mean (SD)	62.8	(16.7)	61.8	(17.1)	75.0		62.0	(16.7)
18-24	1,182	(1.8)	48	(1.8)			987	(1.9)
25-34	2,696	(4.1)	155	(5.8)			2,160	(4.2)
35-44	6,370	(9.7)	283	(10.6)			5,352	(10.4)
45-54	9,865	(15.0)	403	(15.0)			8,143	(15.8)
55-64	13,075	(19.9)	507	(18.9)			10,369	(20.1)
65-74	13,943	(21.2)	548	(20.5)			10,938	(21.2)
75-84	13,247	(20.2)	541	(20.2)	1	(100.0)	9,823	(19.1)
85+	5,313	(8.1)	194	(7.2)			3,769	(7.3)
Sex								
Male	19,707	(30.0)	872	(32.5)	1	(100.0)	15,599	(30.3)
Female	45,984	(70.0)	1,807	(67.5)			35,942	(69.7)
Calendar year at cohort entry								
2004	6,927	(10.5)	253	(9.4)			5,418	(10.5)
2005	6,827	(10.4)	265	(9.9)			5,594	(10.9)
2006	6,612	(10.1)	258	(9.6)			5,341	(10.4)
2007	6,910	(10.5)	249	(9.3)			5,275	(10.2)
2008	6,740	(10.3)	282	(10.5)			5,259	(10.2)
2009	7,463	(11.4)	290	(10.8)	1	(100.0)	5,639	(10.9)
2010	7,663	(11.7)	309	(11.5)			5,898	(11.4)
2011	8,280	(12.6)	382	(14.3)			6,336	(12.3)
2012	8,269	(12.6)	391	(14.6)			6,781	(13.2)

Table A5. Characteristics of Patients Exposed to Overactive Bladder Drug(s) at Index Prescription, Stratified by Patient's Eligibility for Linkage to Hospital Episode Statistics and/or Office for National Statistics Mortality Data

	Patients Eligible for Linkage to Both HES and ONS Mortality Data (n = 65,691)		Patients Eligible for Linkage to HES Data but Not ONS Mortality Data (n = 2,679)		Patients Eligible for Linkage to ONS Mortality Data but Not HES Data (n = 1)		Patients Not Eligible for Linkage to HES or ONS Mortality Data (n = 51,541)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Index OAB drug prescription(s) at cohort entry								
Oxybutynin	23,988	(36.5)	969	(36.2)			15,670	(30.4)
Tolterodine	20,285	(30.9)	888	(33.1)	1	(100.0)	16,292	(31.6)
Darifenacin	88	(0.1)	5	(0.2)			58	(0.1)
Solifenacin	16,856	(25.7)	712	(26.6)			15,487	(30.0)
Trospium	3,122	(4.8)	80	(3.0)			2,848	(5.5)
Fesoterodine	1,211	(1.8)	21	(0.8)			1,111	(2.2)
More than one study OAB drug	141	(0.2)	4	(0.1)			75	(0.1)
Index of Multiple Deprivation								
1	15,147	(23.1)	533	(19.9)			11,073	(21.5)
2	15,875	(24.2)	528	(19.7)			8,173	(15.9)
3	12,758	(19.4)	603	(22.5)			10,761	(20.9)
4	11,910	(18.1)	577	(21.5)	1	(100.0)	11,823	(22.9)
5	10,001	(15.2)	438	(16.3)			9,711	(18.8)
Overactive bladder	33,973	(51.7)	1,277	(47.7)			24,252	(47.1)
Hypertension								
Diagnosis codes only	19,358	(29.5)	812	(30.3)			14,775	(28.7)
Medications only	2,488	(3.8)	102	(3.8)			2,443	(4.7)
Diagnosis codes and medications	31,206	(47.5)	1,159	(43.3)	1	(100.0)	24,394	(47.3)
Diabetes								
Diagnosis codes only	1,586	(2.4)	59	(2.2)			1,140	(2.2)
Medications only	199	(0.3)	11	(0.4)			132	(0.3)
Diagnosis codes and medications	5,842	(8.9)	233	(8.7)			4,293	(8.3)

Table A5. Characteristics of Patients Exposed to Overactive Bladder Drug(s) at Index Prescription, Stratified by Patient's Eligibility for Linkage to Hospital Episode Statistics and/or Office for National Statistics Mortality Data

	Patients Eligible for Linkage to Both HES and ONS Mortality Data (n = 65,691)		Patients Eligible for Linkage to HES Data but Not ONS Mortality Data (n = 2,679)		Patients Eligible for Linkage to ONS Mortality Data but Not HES Data (n = 1)		Patients Not Eligible for Linkage to HES or ONS Mortality Data (n = 51,541)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Smoking								
Never	31,311	(47.7)	1,311	(48.9)	1	(100.0)	24,165	(46.9)
Former	23,595	(35.9)	933	(34.8)			17,701	(34.3)
Current	10,026	(15.3)	398	(14.9)			9,027	(17.5)
Unknown history	759	(1.2)	37	(1.4)			648	(1.3)
Alcohol use								
Non-drinker	8,297	(12.6)	519	(19.4)	1	(100.0)	7,472	(14.5)
Low-moderate intake	34,221	(52.1)	1,228	(45.8)			26,990	(52.4)
High-very high intake	13,148	(20.0)	495	(18.5)			8,365	(16.2)
Drinker unknown quantity	3,493	(5.3)	135	(5.0)			3,488	(6.8)
Unknown history	6,532	(9.9)	302	(11.3)			5,226	(10.1)
Alcohol-related conditions								
Alcoholism or alcohol-related diseases	1,838	(2.8)	81	(3.0)			1,587	(3.1)
No alcoholism or alcohol-related diseases	63,853	(97.2)	2,598	(97.0)	1	(100.0)	49,954	(96.9)
History of AMI	2,619	(4.0)	103	(3.8)			2,088	(4.1)
History of stroke	4,547	(6.9)	161	(6.0)			3,601	(7.0)
History of transient ischemic attack	2,610	(4.0)	91	(3.4)			2,167	(4.2)
History of coronary heart disease	8,742	(13.3)	323	(12.1)			6,476	(12.6)
History of heart failure	2,410	(3.7)	79	(2.9)			1,380	(2.7)
History of peripheral artery disease/peripheral vascular disease	4,650	(7.1)	177	(6.6)			3,565	(6.9)
Menopause (females only)	11,740	(25.5)	403	(22.3)			7,696	(21.4)
Health services utilization [mean (SD)]								
Outpatient visits	10.8	(9.2)	10.7	(9.8)	14.0		10.8	(9.7)
Hospitalizations	0.6	(1.4)	0.6	(1.2)	0.0		0.4	(1.1)

AMI = acute myocardial infarction; HES = hospital episode statistics; OAB = overactive bladder; ONS = Office for National Statistics; SD = standard deviation.

Table A6. Characterization of Index Therapy Episode,[a] by Overactive Bladder Drug

	Oxybutynin (n = 39,994)		Tolterodine (n = 36,777)		Darifenacin (n = 140)		Solifenacin (n = 31,856)		Trospium (n = 5,543)		Fesoterodine (n = 2,238)		More Than One Study OAB Drug (n = 3,364)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Duration of therapy episode														
Mean (SD) months	5.5	(10.9)	8.4	(16.0)	8.9	(14.4)	7.5	(12.4)	6.7	(13.2)	5.7	(8.4)	1.4	(3.9)
< 1 month	3,779	(9.4)	1,769	(4.8)	18	(12.9)	1,412	(4.4)	404	(7.3)	126	(5.6)	1,782	(53.0)
≥ 1 month and ≤ 3 months	24,052	(60.1)	20,731	(56.4)	56	(40.0)	16,894	(53.0)	3,133	(56.5)	1,260	(56.3)	1,378	(41.0)
> 3 months and ≤ 6 months	4,401	(11.0)	4,488	(12.2)	19	(13.6)	4,421	(13.9)	694	(12.5)	311	(13.9)	130	(3.9)
> 6 months and ≤ 9 months	1,943	(4.9)	2,107	(5.7)	12	(8.6)	2,073	(6.5)	349	(6.3)	130	(5.8)	27	(0.8)
> 9 months	5,819	(14.5)	7,682	(20.9)	35	(25.0)	7,056	(22.1)	963	(17.4)	411	(18.4)	47	(1.4)
Number of prescriptions during episode														
1	22,570	(56.4)	18,340	(49.9)	57	(40.7)	14,547	(45.7)	2,880	(52.0)	1,028	(45.9)	1,723	(51.2)
2	5,122	(12.8)	4,426	(12.0)	13	(9.3)	4,100	(12.9)	655	(11.8)	347	(15.5)	1,019	(30.3)
3	2,378	(5.9)	2,377	(6.5)	15	(10.7)	2,215	(7.0)	390	(7.0)	157	(7.0)	287	(8.5)
4	1,515	(3.8)	1,521	(4.1)	5	(3.6)	1,466	(4.6)	228	(4.1)	107	(4.8)	113	(3.4)
5+	8,409	(21.0)	10,113	(27.5)	50	(35.7)	9,528	(29.9)	1,390	(25.1)	599	(26.8)	222	(6.6)
Initial daily dose[b]														
Low	30,381	(76.0)	36,688	(99.8)	128	(91.4)	29,901	(93.9)	4,902	(88.4)	2,107	(94.1)	2,052	(61.0)
High	9,613	(24.0)	89	(0.2)	12	(8.6)	1,955	(6.1)	641	(11.6)	131	(5.9)	1,312	(39.0)
Daily dose changed during therapy episode														
No change	34,814	(87.0)	35,294	(96.0)	123	(87.9)	27,088	(85.0)	5,395	(97.3)	1,928	(86.1)	3,101	(92.2)
Increased	4,056	(10.1)	947	(2.6)	17	(12.1)	4,586	(14.4)	74	(1.3)	291	(13.0)	194	(5.8)
Decreased	1,124	(2.8)	536	(1.5)			182	(0.6)	74	(1.3)	19	(0.8)	69	(2.1)
Prior exposure to study drugs[c]														
Any OAB drug	517	(1.3)	708	(1.9)	11	(7.9)	707	(2.2)	402	(7.3)	85	(3.8)	3,300	(98.1)
Oxybutynin			578	(1.6)	3	(2.1)	292	(0.9)	139	(2.5)	24	(1.1)	1,260	(37.5)
Tolterodine	405	(1.0)			3	(2.1)	365	(1.1)	283	(5.1)	23	(1.0)	1,696	(50.4)
Darifenacin	1	(0.0)	1	(0.0)					1	(0.0)			7	(0.2)
Solifenacin	72	(0.2)	51	(0.1)	3	(2.1)			29	(0.5)	46	(2.1)	183	(5.4)
Trospium	55	(0.1)	89	(0.2)	1	(0.7)	60	(0.2)			7	(0.3)	242	(7.2)
Fesoterodine	4	(0.0)	4	(0.0)	1	(0.7)	8	(0.0)	3	(0.1)			13	(0.4)
More than one study OAB drug	20	(0.1)	15	(0.0)			17	(0.1)	52	(0.9)	12	(0.5)	93	(2.8)

Table A6. Characterization of Index Therapy Episode,[a] by Overactive Bladder Drug

	Oxybutynin (n = 39,994)		Tolterodine (n = 36,777)		Darifenacin (n = 140)		Solifenacin (n = 31,856)		Trospium (n = 5,543)		Fesoterodine (n = 2,238)		More Than One Study OAB Drug (n = 3,364)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Reason therapy episode ended														
Discontinued OAB therapy	31,361	(78.4)	29,111	(79.2)	82	(58.6)	23,081	(72.5)	4,372	(78.9)	1,537	(68.7)	19	(0.6)
Added another OAB drug	3,536	(8.8)	3,513	(9.6)	37	(26.4)	2,165	(6.8)	534	(9.6)	194	(8.7)	65	(1.9)
Switched to another OAB drug	94	(0.2)	119	(0.3)			28	(0.1)	8	(0.1)	5	(0.2)	3,222	(95.8)
Did not end[d]	5,003	(12.5)	4,034	(11.0)	21	(15.0)	6,582	(20.7)	629	(11.3)	502	(22.4)	58	(1.7)

CPRD = Clinical Practice Research Datalink; NA = not applicable; OAB = overactive bladder; SD = standard deviation.

Note: Each study participant had only one initial therapy episode.

[a] Drug episodes were created by concatenating consecutive prescriptions for the same drug into a single continuous episode as long as the gap between consecutive prescriptions was no more than 60 days. A drug episode refers to the period of continuous treatment with a given drug, plus 7 days added to the end of the last prescription in the episode. Therapy episodes were created by examining single-drug and multiple-drug use over time, by overlapping and interleaving drug episodes. The end of a therapy episode was defined by the end of a drug episode, or a switch to or add-on of another OAB medication.

[b] The value of initial daily dose was classified as "low" if it was less than or equal to the mode daily dose value for that OAB drug and as "high" if it was greater than the mode. If the patient was taking multiple OAB drugs during the index therapy episode, initial daily dose was classified as "high" if any of the OAB drugs were classified as "high" initial daily dose.

[c] If multiple exposures preceded the index therapy episode, then each exposure was counted for each individual drug and for "more than one study OAB drug."

[d] Therapy episode continued through either the end of study period, the end of patient/practice enrollment in the CPRD, or patient death.

Table A7. Characteristics of Therapy Episodes,[a] by Overactive Bladder Drug

	Therapy Episode													
	Oxybutynin		Tolterodine		Darifenacin		Solifenacin		Trospium		Fesoterodine		More Than One Study OAB Drug	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total therapy episodes	69,581	(100.0)	63,407	(100.0)	741	(100.0)	65,466	(100.0)	14,308	(100.0)	6,782	(100.0)	25,515	(100.0)
Total therapy episodes that ended because of a switch to another OAB drug or an add-on of another OAB drug	6,348	(9.1)	6,916	(10.9)	190	(25.6)	5,471	(8.4)	1,643	(11.5)	765	(11.3)	24,816	(97.3)
Add-on OAB drug														
Oxybutynin	NA		2,093	(3.3)	44	(5.9)	1,881	(2.9)	422	(2.9)	187	(2.8)	125	(0.5)
Tolterodine	2,337	(3.4)	NA		24	(3.2)	1,615	(2.5)	423	(3.0)	107	(1.6)	102	(0.4)
Darifenacin	50	(0.1)	55	(0.1)	NA		89	(0.1)	18	(0.1)	13	(0.2)	14	(0.1)
Solifenacin	2,961	(4.3)	3,265	(5.1)	69	(9.3)	NA		631	(4.4)	302	(4.5)	159	(0.6)
Trospium	563	(0.8)	950	(1.5)	29	(3.9)	894	(1.4)	NA		136	(2.0)	96	(0.4)
Fesoterodine	282	(0.4)	344	(0.5)	21	(2.8)	913	(1.4)	111	(0.8)	NA		45	(0.2)
More than one study OAB drug	7	(0.0)	7	(0.0)	1	(0.1)	4	(0.0)	2	(0.0)	4	(0.1)	0	(0.0)
Switch to another OAB drug														
Oxybutynin	NA		60	(0.1)	1	(0.1)	30	(0.0)	12	(0.1)	1	(0.0)	5,108	(20.0)
Tolterodine	59	(0.1)	NA		0	(0.0)	19	(0.0)	8	(0.1)	0	(0.0)	5,564	(21.8)
Darifenacin	2	(0.0)	2	(0.0)	NA		2	(0.0)	0	(0.0)	0	(0.0)	238	(0.9)
Solifenacin	65	(0.1)	110	(0.2)	0	(0.0)	NA		15	(0.1)	11	(0.2)	8,410	(33.0)
Trospium	14	(0.0)	23	(0.0)	1	(0.1)	15	(0.0)	NA		4	(0.1)	2,753	(10.8)
Fesoterodine	8	(0.0)	7	(0.0)	0	(0.0)	9	(0.0)	1	(0.0)	NA		1,623	(6.4)
More than one study OAB drug	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	579	(2.3)
Drug was not renewed or refilled	63,233	(90.9)	56,491	(89.1)	551	(74.4)	59,995	(91.6)	12,665	(88.5)	6,017	(88.7)	699	(2.7)
Initial dose increased	7,966	(11.4)	1,927	(3.0)	162	(21.9)	11,413	(17.4)	342	(2.4)	1,217	(17.9)	1,584	(6.2)
Initial dose decreased	3,037	(4.4)	1,085	(1.7)	11	(1.5)	688	(1.1)	249	(1.7)	86	(1.3)	450	(1.8)
Episode not preceded by exposure to any OAB drug in prior 12 months	64,531	(92.7)	59,009	(93.1)	670	(90.4)	59,512	(90.9)	13,148	(91.9)	6,096	(89.9)	22,210	(87.0)

NA = not applicable; OAB = overactive bladder.

Note: For all therapy episodes, each patient can contribute to more than one therapy episode.

[a] Drug episodes were created by concatenating consecutive prescriptions for the same drug into a single continuous episode as long as the gap between consecutive prescriptions was no more than 60 days. A drug episode refers to the period of continuous treatment with a given drug, plus 7 days added to the end of the last prescription in the episode. Therapy episodes were created by examining single-drug and multiple-drug use over time, by overlapping and interleaving drug episodes. The end of a therapy episode was defined by the end of a drug episode, or a switch to or add-on of another OAB medication.

Table A8. Prescribed Strengths of Overactive Bladder Drugs

Formulation	Number Exposed[a] n	Prescriptions n	Prescriptions per Exposed Patient Mean	Prescriptions per Exposed Patient SD
Oxybutynin				
2.5 mg	25,845	157,992	6.1	16.3
2.5 mg + 3 mg	6	55	9.2	18.6
2.5 mg + 5 mg	152	871	5.7	15.3
2.5 mg + 5 mg + 10 mg	2	2	1.0	0.0
2.5 mg + 10 mg	17	90	5.3	10.8
2.5 mg + 3.9 mg/24 h (patch)	18	27	1.5	1.7
2.5 mg + 500 mcg/1 ml (solution)	3	3	1.0	0.0
3 mg	1,648	9,544	5.8	18.4
3 mg + 5 mg	8	26	3.3	2.4
3 mg + 10 mg	1	1	1.0	
3 mg + 3.9 mg/24 h (patch)	1	1	1.0	
5 mg	23,198	160,209	6.9	16.6
5 mg + 10 mg	475	4,341	9.1	22.3
5 mg + 3.9 mg/24 h (patch)	22	72	3.3	6.6
5 mg + 1 mg/1 ml (solution) or 5 mg/5 ml (solution)	4	4	1.0	0.0
5 mg + 500 mcg/1 ml (solution)	4	4	1.0	0.0
10 mg	4,332	45,895	10.6	18.6
10 mg + 3.9 mg/24 h (patch)	5	26	5.2	4.3
3.9 mg/24 h (patch)	3,559	20,792	5.8	11.4
1 mg/1 ml (solution) or 5 mg/5 ml (solution)	96	613	6.4	9.4
1 mg/1 ml (solution) or 5 mg/5 ml (solution) + 500 mcg/1 ml (solution)	4	5	1.3	0.5
500 mcg/1 ml (solution)	299	2,942	9.8	17.4
Tolterodine				
1 mg	5,572	36,627	6.6	15.8
1 mg + 2 mg	44	185	4.2	6.2
1 mg + 4 mg	42	75	1.8	2.4
2 mg	6,593	55,084	8.4	18.5
2 mg + 4 mg	80	202	2.5	3.3
4 mg	37,483	381,470	10.2	19.7

Table A8. Prescribed Strengths of Overactive Bladder Drugs

Formulation	Number Exposed[a] n	Prescriptions n	Prescriptions per Exposed Patient Mean	Prescriptions per Exposed Patient SD
Darifenacin				
7.5 mg	594	4,020	6.8	16.3
7.5 mg + 15 mg	9	19	2.1	3.0
15 mg	199	1,705	8.6	13.8
Solifenacin				
5 mg	45,740	338,304	7.4	14.1
5 mg + 10 mg	394	680	1.7	5.4
10 mg	12,947	142,912	11.0	17.4
Trospium				
20 mg	9,224	87,944	9.5	20.0
20 mg + 60 mg	3	8	2.7	2.9
60 mg	2,075	10,956	5.3	8.2
Fesoterodine				
4 mg	5,297	27,010	5.1	8.7
4 mg + 8 mg	64	68	1.1	0.3
8 mg	1,733	13,243	7.6	10.0

SD = standard deviation.

[a] Patients could contribute information to more than one formulation and more than one drug.

Table ValCV1. Results of Validation of Cardiovascular Endpoints

	Questionnaires Sent	Questionnaires Returned (Response Rate %)	Case Status Confirmed by Questionnaire	PPV (95% CI)	NPV (95% CI)
Decision from original algorithm					
Acute myocardial infarction					
Definite	137	114 (83.2%)	112	98.2 (93.8, 99.8)	
Probable	162	134 (82.7%)	123	91.8 (85.8, 95.8)	
Possible (definition 1)	32	24 (75.0%)	22	91.7 (73.0, 99.0)	
Possible (definition 2)	1,097	864 (78.8%)	22	2.5 (1.6, 3.8)	
Stroke - original definition					
Definite	157	131 (83.4%)	101	77.1 (68.9, 84.0)	
Probable	249	207 (83.1%)	97	46.9 (39.9, 53.9)	
Possible	135	114 (84.4%)	48	42.1 (32.9, 51.7)	
Non-cases alive	185	149 (80.5%)	147		98.7 (95.2, 99.8)
Non-cases dead	185	146 (78.9%)	123		84.2 (77.3, 89.7)
Decision from revised algorithm for stroke					
Stroke - updated definition					
Definite	120	98 (81.7%)	90	91.8 (84.5, 96.4)	
Probable	107	90 (84.1%)	71	78.9 (69.0, 86.8)	
Possible	48	44 (91.7%)	37	84.1 (69.9, 93.4)	
Decision from patient profile review					
Acute myocardial infarction					
Definite	213	179 (84.0%)	173	96.6 (92.8, 98.8)	
Probable	94	76 (80.9%)	71	93.4 (85.3, 97.8)	
Possible	97	77 (79.4%)	22	28.6 (18.8, 40.0)	
Non-case	1,024	804 (78.5%)	791		98.4 (97.3, 99.1)
Stroke					
Definite	164	137 (83.5%)	120	87.6 (80.9, 92.6)	
Probable	97	83 (85.6%)	66	79.5 (69.2, 87.6)	
Possible	42	36 (85.7%)	25	69.4 (51.9, 83.7)	
Non-case	238	196 (82.4%)	161		82.1 (76.1, 87.2)

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.
Note: Exact binomial confidence intervals are reported for PPV and NPV.

Table ValCV2a. Results of Profile Review of Cardiovascular Endpoints - AMI and Stroke

	Decision From Patient Profile Review				
Decision From Algorithm	**Definite**	**Probable**	**Possible**	**Non-case**	**PPV (95% CI)**
Acute myocardial infarction					
Definite	160 (98.2%)	3 (1.8%)	0	0	100.0 (97.8, 100.0)
Probable	85 (42.3%)	106 (52.7%)	5 (2.5%)	5 (2.5%)	97.5 (94.3, 99.2)
Possible (definition 1)	2 (6.1%)	5 (15.2%)	25 (75.8%)	1 (3.0%)	97.0 (84.2, 99.9)
Possible (definition 2)	6 (0.3%)	11 (0.5%)	138 (6.2%)	2,078 (93.1%)	6.9 (5.9, 8.1)
Stroke - original definition					
Definite	123 (66.1%)	24 (12.9%)	0	39 (21.0%)	79.0 (72.5, 84.6)
Probable	72 (18.8%)	73 (19.1%)	19 (5.0%)	218 (57.1%)	42.9 (37.9, 48.1)
Possible	7 (4.5%)	26 (16.7%)	38 (24.4%)	85 (54.5%)	45.5 (37.5, 53.7)
Stroke - updated definition					
Definite	116 (83.5%)	16 (11.5%)	0	7 (5.0%)	95.0 (89.9, 98.0)
Probable	70 (46.1%)	55 (36.2%)	8 (5.3%)	19 (12.5%)	87.5 (81.2, 92.3)
Possible	4 (7.5%)	23 (43.4%)	25 (47.2%)	1 (1.9%)	98.1 (89.9, 100.0)

CI = confidence interval; PPV = positive predictive value.

Note: Exact binomial confidence intervals are reported for PPV and NPV.

Table ValCV2b. Results of Profile Review of Cardiovascular Endpoints - Out-of-Hospital CHD Deaths

	Decision From Patient Profile Review		
Decision From Algorithm	**Fatal AMI**	**Out-of-Hospital CHD Death**	**Other Cause of Death**
AMI	40 (100.0%)	0	0
CHD (other than AMI)	1 (1.1%)	90 (97.8%)	1 (1.1%)
Unknown cause of death with recent history of CHD	10 (32.3%)	6 (19.4%)	15 (48.4%)

AMI = acute myocardial infarction; CHD = coronary heart disease.

Table ValCov1a. Results of Covariate Validation, Smoking (Smoking Status From the CPRD Based on the Closest Data Before the *Index* Date)

	Questionnaires			
CPRD Data	**Never Smoker**	**Current Smoker**	**Former Smoker**	**Unknown**
Overall				
Never smoker	718 (93.5%)	6 (0.8%)	37 (4.8%)	7 (0.9%)
Current smoker	11 (3.7%)	232 (77.1%)	52 (17.3%)	6 (2.0%)
Former smoker	111 (17.1%)	32 (4.9%)	492 (75.6%)	16 (2.5%)
Unknown	7 (63.6%)	0	4 (36.4%)	0
AMI questionnaire				
Never smoker	409 (94.5%)	6 (1.4%)	15 (3.5%)	3 (0.7%)
Current smoker	8 (4.0%)	155 (77.5%)	37 (18.5%)	0
Former smoker	59 (16.0%)	26 (7.0%)	275 (74.5%)	9 (2.4%)
Unknown	2 (33.3%)	0	4 (66.7%)	0
Stroke questionnaire				
Never smoker	192 (92.3%)	0	13 (6.3%)	3 (1.4%)
Current smoker	2 (3.6%)	41 (73.2%)	10 (17.9%)	3 (5.4%)
Former smoker	29 (17.1%)	4 (2.4%)	130 (76.5%)	7 (4.1%)
Unknown	2 (100.0%)	0	0	0
Non-case questionnaires				
Never smoker	117 (92.1%)	0	9 (7.1%)	1 (0.8%)
Current smoker	1 (2.2%)	36 (80.0%)	5 (11.1%)	3 (6.7%)
Former smoker	23 (20.5%)	2 (1.8%)	87 (77.7%)	0
Unknown	3 (100.0%)	0	0	0

AMI = acute myocardial infarction; CPRD = Clinical Practice Research Datalink.

Table ValCov1b. Results of Covariate Validation, Smoking (Smoking Status From the CPRD Based on the Closest Data Before the *Endpoint* Date)

	Questionnaires			
CPRD Data	Never Smoker	Current Smoker	Former Smoker	Unknown
Overall				
Never smoker	708 (96.7%)	3 (0.4%)	15 (2.0%)	6 (0.8%)
Current smoker	13 (4.5%)	241 (84.0%)	27 (9.4%)	6 (2.1%)
Former smoker	123 (17.3%)	26 (3.7%)	543 (76.6%)	17 (2.4%)
Unknown	3 (100.0%)	0	0	0
AMI questionnaire				
Never smoker	406 (96.9%)	3 (0.7%)	7 (1.7%)	3 (0.7%)
Current smoker	8 (4.2%)	164 (85.4%)	20 (10.4%)	0
Former smoker	63 (15.9%)	20 (5.1%)	304 (76.8%)	9 (2.3%)
Unknown	1 (100.0%)	0	0	0
Stroke questionnaire				
Never smoker	187 (95.4%)	0	7 (3.6%)	2 (1.0%)
Current smoker	4 (8.0%)	39 (78.0%)	4 (8.0%)	3 (6.0%)
Former smoker	33 (17.5%)	6 (3.2%)	142 (75.1%)	8 (4.2%)
Unknown	1 (100.0%)	0	0	0
Non-case questionnaires				
Never smoker	115 (98.3%)	0	1 (0.9%)	1 (0.9%)
Current smoker	1 (2.2%)	38 (84.4%)	3 (6.7%)	3 (6.7%)
Former smoker	27 (21.8%)	0	97 (78.2%)	0
Unknown	1 (100.0%)	0	0	0

AMI = acute myocardial infarction; CPRD = Clinical Practice Research Datalink.

Table ValCov1c. Results of Covariate Validation, Smoking (Smoking Status From the CPRD Based on the Closest Data *to* the Endpoint Date)

	Questionnaires			
CPRD Data	Never Smoker	Current Smoker	Former Smoker	Unknown
Overall				
Never smoker	702 (97.2%)	3 (0.4%)	11 (1.5%)	6 (0.8%)
Current smoker	15 (5.8%)	212 (81.9%)	26 (10.0%)	6 (2.3%)
Former smoker	129 (17.2%)	55 (7.3%)	548 (73.2%)	17 (2.3%)
Unknown	1 (100.0%)	0	0	0
AMI questionnaire				
Never smoker	403 (97.6%)	3 (0.7%)	4 (1.0%)	3 (0.7%)
Current smoker	9 (5.3%)	144 (84.7%)	17 (10.0%)	0
Former smoker	66 (15.5%)	40 (9.4%)	310 (72.9%)	9 (2.1%)
Unknown	0	0	0	0
Stroke questionnaire				
Never smoker	184 (95.8%)	0	6 (3.1%)	2 (1.0%)
Current smoker	5 (11.4%)	30 (68.2%)	6 (13.6%)	3 (6.8%)
Former smoker	36 (18.0%)	15 (7.5%)	141 (70.5%)	8 (4.0%)
Unknown	0	0	0	0
Non-case questionnaires				
Never smoker	115 (98.3%)	0	1 (0.9%)	1 (0.9%)
Current smoker	1 (2.2%)	38 (84.4%)	3 (6.7%)	3 (6.7%)
Former smoker	27 (21.8%)	0	97 (78.2%)	0
Unknown	1 (100.0%)	0	0	0

AMI = acute myocardial infarction; CPRD = Clinical Practice Research Datalink.

Table ValCov2a. Results of Covariate Validation - Body Mass Index, Menopause, History of AMI and Stroke, Covariate Status From the CPRD Based on the Closest Data Before the *Index* Date

	Questionnaires				
CPRD Data	**Yes**	**No**	**Unknown**	**PPV (95% CI)**	**NPV (95% CI)**
Overall					
Body mass index ≥ 30					
Yes	325 (76.1%)	76 (17.8%)	26 (6.1%)	76.1 (71.8, 80.1)	
No	33 (4.0%)	734 (90.0%)	49 (6.0%)		90.0 (87.7, 91.9)
Unknown	76 (16.2%)	290 (61.7%)	104 (22.1%)		
Menopause					
Yes	204 (85.7%)	7 (2.9%)	27 (11.3%)	85.7 (80.6, 89.9)	
No	653 (76.6%)	100 (11.7%)	100 (11.7%)		11.7 (9.6, 14.1)
AMI questionnaire					
Body mass index ≥ 30					
Yes	214 (78.7%)	48 (17.6%)	10 (3.7%)	78.7 (73.3, 83.4)	
No	19 (4.2%)	417 (91.4%)	20 (4.4%)		91.4 (88.5, 93.8)
Unknown	54 (20.5%)	159 (60.2%)	51 (19.3%)		
Menopause					
Yes	149 (83.2%)	6 (3.4%)	24 (13.4%)	83.2 (76.9, 88.4)	
No	333 (71.8%)	69 (14.9%)	62 (13.4%)		14.9 (11.8, 18.4)
History of AMI					
Yes	82 (78.8%)	22 (21.2%)	0	78.8 (69.7, 86.2)	
No	43 (4.5%)	910 (94.5%)	10 (1.0%)		94.5 (92.9, 95.9)
Stroke questionnaire					
Body mass index ≥ 30					
Yes	74 (70.5%)	17 (16.2%)	14 (13.3%)	70.5 (60.8, 79.0)	
No	8 (3.7%)	186 (86.5%)	21 (9.8%)		86.5 (81.2, 90.8)
Unknown	13 (11.4%)	74 (64.9%)	27 (23.7%)		
Menopause					
Yes	34 (97.1%)	1 (2.9%)	0	97.1 (85.1, 99.9)	
No	197 (85.3%)	13 (5.6%)	21 (9.1%)		5.6 (3.0, 9.4)
History of stroke					
Yes	69 (48.6%)	68 (47.9%)	5 (3.5%)	48.6 (40.1, 57.1)	
No	40 (13.5%)	254 (85.8%)	2 (0.7%)		85.8 (81.3, 89.6)

CPRD Data	Questionnaires			PPV (95% CI)	NPV (95% CI)
	Yes	No	Unknown		
Non-case alive questionnaire					
Body mass index ≥ 30					
Yes	27 (93.1%)	2 (6.9%)	0	93.1 (77.2, 99.2)	
No	3 (4.2%)	65 (90.3%)	4 (5.6%)		90.3 (81.0, 96.0)
Unknown	8 (18.2%)	29 (65.9%)	7 (15.9%)		
Menopause					
Yes	15 (88.2%)	0	2 (11.8%)	88.2 (63.6, 98.5)	
No	52 (61.2%)	18 (21.2%)	15 (17.6%)		21.2 (13.1, 31.4)
History of AMI					
Yes	2 (66.7%)	1 (33.3%)	0	66.7 (9.4, 99.2)	
No	2 (1.4%)	138 (98.6%)	0		98.6 (94.9, 99.8)
History of stroke					
Yes	6 (60.0%)	3 (30.0%)	1 (10.0%)	60.0 (26.2, 87.8)	
No	2 (1.5%)	131 (98.5%)	0		98.5 (94.7, 99.8)
Non-case dead questionnaire					
Body mass index ≥ 30					
Yes	10 (47.6%)	9 (42.9%)	2 (9.5%)	47.6 (25.7, 70.2)	
No	3 (4.1%)	66 (90.4%)	4 (5.5%)		90.4 (81.2, 96.1)
Unknown	1 (2.1%)	28 (58.3%)	19 (39.6%)		
Menopause					
Yes	6 (85.7%)	0	1 (14.3%)	85.7 (42.1, 99.6)	
No	71 (97.3%)	0	2 (2.7%)		n/a
History of AMI or coronary heart disease					
Yes	3 (7.7%)	36 (92.3%)	n/a	7.7 (1.6, 20.9)	
No	1 (1.0%)	104 (99.0%)	n/a		99.0 (94.8, 100.0)
History of stroke or cerebrovascular disease					
Yes	3 (10.7%)	25 (89.3%)	n/a	10.7 (2.3, 28.2)	
No	2 (1.7%)	114 (98.3%)	n/a		98.3 (93.9, 99.8)

AMI = acute myocardial infarction; CI = confidence interval; CPRD = Clinical Practice Research Datalink; NPV = negative predictive value; PPV = positive predictive value.

Note: Exact binomial confidence intervals are reported for PPV and NPV.

Table ValCov2b. Results of Covariate Validation - Body Mass Index, Menopause, History of AMI and Stroke, Covariate Status From the CPRD Based on the Closest Data Before the *Endpoint* Date

	Questionnaires				
CPRD Data	**Yes**	**No**	**Unknown**	**PPV (95% CI)**	**NPV (95% CI)**
Overall					
Body mass index ≥ 30					
Yes	350 (82.0%)	57 (13.3%)	20 (4.7%)	82.0 (78.0, 85.5)	
No	27 (3.2%)	777 (91.7%)	43 (5.1%)		91.7 (89.7, 93.5)
Unknown	57 (13.0%)	266 (60.6%)	116 (26.4%)		
Menopause					
Yes	210 (83.3%)	9 (3.6%)	33 (13.1%)	83.3 (78.1, 87.7)	
No	647 (77.1%)	98 (11.7%)	94 (11.2%)		11.7 (9.6, 14.0)
AMI questionnaire					
Body mass index ≥ 30					
Yes	230 (81.9%)	39 (13.9%)	12 (4.3%)	81.9 (76.8, 86.2)	
No	20 (4.1%)	452 (92.4%)	17 (3.5%)		92.4 (89.7, 94.6)
Unknown	37 (16.7%)	133 (59.9%)	52 (23.4%)		
Menopause					
Yes	153 (81.8%)	7 (3.7%)	27 (14.4%)	81.8 (75.5, 87.1)	
No	329 (72.1%)	68 (14.9%)	59 (12.9%)		14.9 (11.8, 18.5)
History of AMI					
Yes	94 (70.1%)	39 (29.1%)	1 (0.7%)	70.1 (61.6, 77.7)	
No	31 (3.3%)	893 (95.7%)	9 (1.0%)		95.7 (94.2, 96.9)
Stroke questionnaire					
Body mass index ≥ 30					
Yes	79 (79.0%)	14 (14.0%)	7 (7.0%)	79.0 (69.7, 86.5)	
No	7 (3.2%)	192 (86.9%)	22 (10.0%)		86.9 (81.7, 91.0)
Unknown	9 (8.0%)	71 (62.8%)	33 (29.2%)		
Menopause					
Yes	34 (97.1%)	1 (2.9%)	0	97.1 (85.1, 99.9)	
No	197 (85.3%)	13 (5.6%)	21 (9.1%)		5.6 (3.0, 9.4)
History of stroke					
Yes	81 (43.5%)	100 (53.8%)	5 (2.7%)	43.5 (36.3, 51.0)	
No	28 (11.1%)	222 (88.1%)	2 (0.8%)		88.1 (83.4, 91.8)

CPRD Data	Questionnaires			PPV (95% CI)	NPV (95% CI)
	Yes	No	Unknown		
Non-case alive questionnaire					
Body mass index ≥ 30					
Yes	31 (93.9%)	2 (6.1%)	0	93.9 (79.8, 99.3)	
No	0	66 (98.5%)	1 (1.5%)		98.5 (92.0, 100.0)
Unknown	7 (15.6%)	28 (62.2%)	10 (22.2%)		
Menopause					
Yes	17 (73.9%)	1 (4.3%)	5 (21.7%)	73.9 (51.6, 89.8)	
No	50 (63.3%)	17 (21.5%)	12 (15.2%)		21.5 (13.1, 32.2)
History of AMI					
Yes	2 (66.7%)	1 (33.3%)	0	66.7 (9.4, 99.2)	
No	2 (1.4%)	138 (98.6%)	0		98.6 (94.9, 99.8)
History of stroke					
Yes	6 (46.2%)	6 (46.2%)	1 (7.7%)	46.2 (19.2, 74.9)	
No	2 (1.5%)	128 (98.5%)	0		98.5 (94.6, 99.8)
Non-case dead questionnaire					
Body mass index ≥ 30					
Yes	10 (76.9%)	2 (15.4%)	1 (7.7%)	76.9 (46.2, 95.0)	
No	0	67 (95.7%)	3 (4.3%)		95.7 (88.0, 99.1)
Unknown	4 (6.8%)	34 (57.6%)	21 (35.6%)		
Menopause					
Yes	6 (85.7%)	0	1 (14.3%)	85.7 (42.1, 99.6)	
No	71 (97.3%)	0	2 (2.7%)		n/a
History of AMI or coronary heart disease					
Yes	3 (7.3%)	38 (92.7%)	n/a	7.3 (1.5, 19.9)	
No	1 (1.0%)	102 (99.0%)	n/a		99.0 (94.7, 100.0)
History of stroke or cerebrovascular disease					
Yes	4 (11.8%)	30 (88.2%)	n/a	11.8 (3.3, 27.5)	
No	1 (0.9%)	109 (99.1%)	n/a		99.1 (95.0, 100.0)

AMI = acute myocardial infarction; CI = confidence interval; CPRD = Clinical Practice Research Datalink; NPV = negative predictive value; PPV = positive predictive value.

Note: Exact binomial confidence intervals are reported for PPV and NPV.

Table ValCov2c. Results of Covariate Validation - Body Mass Index, Menopause, History of AMI and Stroke, Covariate Status From the CPRD Based on the Closest Data *to* the Endpoint Date

	Questionnaires				
CPRD Data	**Yes**	**No**	**Unknown**	**PPV (95% CI)**	**NPV (95% CI)**
Overall					
Body mass index ≥ 30					
Yes	377 (83.4%)	52 (11.5%)	23 (5.1%)	83.4 (79.7, 86.7)	
No	21 (2.2%)	862 (92.3%)	51 (5.5%)		92.3 (90.4, 93.9)
Unknown	36 (11.0%)	186 (56.9%)	105 (32.1%)		
Menopause					
Yes	213 (82.2%)	12 (4.6%)	34 (13.1%)	82.2 (77.0, 86.7)	
No	644 (77.4%)	95 (11.4%)	93 (11.2%)		11.4 (9.3, 13.8)
AMI questionnaire					
Body mass index ≥ 30					
Yes	253 (84.1%)	35 (11.6%)	13 (4.3%)	84.1 (79.4, 88.0)	
No	14 (2.5%)	513 (93.1%)	24 (4.4%)		93.1 (90.7, 95.1)
Unknown	20 (14.3%)	76 (54.3%)	44 (31.4%)		
Menopause					
Yes	155 (80.7%)	9 (4.7%)	28 (14.6%)	80.7 (74.4, 86.1)	
No	327 (72.5%)	66 (14.6%)	58 (12.9%)		14.6 (11.5, 18.2)
Stroke questionnaire					
Body mass index ≥ 30					
Yes	83 (79.0%)	13 (12.4%)	9 (8.6%)	79.0 (70.0, 86.4)	
No	7 (2.9%)	215 (87.8%)	23 (9.4%)		87.8 (83.0, 91.6)
Unknown	5 (6.0%)	49 (58.3%)	30 (35.7%)		
Menopause					
Yes	35 (94.6%)	2 (5.4%)	0	94.6 (81.8, 99.3)	
No	196 (85.6%)	12 (5.2%)	21 (9.2%)		5.2 (2.7, 9.0)
Non-case alive questionnaire					
Body mass index ≥ 30					
Yes	31 (93.9%)	2 (6.1%)	0	93.9 (79.8, 99.3)	
No	0	67 (98.5%)	1 (1.5%)		98.5 (92.1, 100.0)
Unknown	7 (15.9%)	27 (61.4%)	10 (22.7%)		
Menopause					
Yes	17 (73.9%)	1 (4.3%)	5 (21.7%)	73.9 (51.6, 89.8)	
No	50 (63.3%)	17 (21.5%)	12 (15.2%)		21.5 (13.1, 32.2)

CPRD Data	Questionnaires			PPV (95% CI)	NPV (95% CI)
	Yes	No	Unknown		
Non-case dead questionnaire					
Body mass index ≥ 30					
Yes	10 (76.9%)	2 (15.4%)	1 (7.7%)	76.9 (46.2, 95.0)	
No	0	67 (95.7%)	3 (4.3%)		95.7 (88.0, 99.1)
Unknown	4 (6.8%)	34 (57.6%)	21 (35.6%)		
Menopause					
Yes	6 (85.7%)	0	1 (14.3%)	85.7 (42.1, 99.6)	
No	71 (97.3%)	0	2 (2.7%)		n/a

AMI = acute myocardial infarction; CI = confidence interval; CPRD = Clinical Practice Research Datalink; NPV = negative predictive value; PPV = positive predictive value.

Note: Exact binomial confidence intervals are reported for PPV and NPV.

Table CV1. Characteristics of Subjects by Cardiovascular Event Type and Overall Mortality at Cohort Entry

	Patients Without CV Endpoint (n = 115,184)		Acute Myocardial Infarction (n = 1,983)		Stroke (n = 2,184)		Coronary Heart Disease Death (n = 1,126)		Cerebro-vascular Disease Death (n = 1,007)		Cardiovascular Mortality (n = 2,097)		Composite Endpoint (n = 4,728)		All-Cause Death (n = 9,487)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sex																
Male	34,265	29.7	876	44.2	785	35.9	502	44.6	365	36.2	853	40.7	1,914	40.5	3,732	39.3
Female	80,919	70.3	1,107	55.8	1,399	64.1	624	55.4	642	63.8	1,244	59.3	2,814	59.5	5,755	60.7
Age at cohort entry (years)																
18-24	2,215	1.9	1	0.1	1	0	1	0.1	0		1	0	2	0	5	0.1
25-34	5,002	4.3	5	0.3	4	0.2	1	0.1	0		1	0	9	0.2	25	0.3
35-44	11,940	10.4	32	1.6	30	1.4	5	0.4	4	0.4	9	0.4	65	1.4	75	0.8
45-54	18,226	15.8	99	5	83	3.8	18	1.6	14	1.4	32	1.5	185	3.9	225	2.4
55-64	23,510	20.4	222	11.2	199	9.1	58	5.2	33	3.3	91	4.3	441	9.3	575	6.1
65-74	24,352	21.1	490	24.7	506	23.2	222	19.7	151	15	365	17.4	1,077	22.8	1,593	16.8
75-84	21,722	18.9	736	37.1	898	41.1	493	43.8	456	45.3	929	44.3	1,890	40	3,954	41.7
85+	8,217	7.1	398	20.1	463	21.2	328	29.1	349	34.7	669	31.9	1,059	22.4	3,035	32
Calendar year at cohort entry																
2004	11,672	10.1	361	18.2	428	19.6	225	20	232	23	450	21.5	926	19.6	1,896	20
2005	11,816	10.3	382	19.3	412	18.9	219	19.4	203	20.2	416	19.8	870	18.4	1,727	18.2
2006	11,512	10	303	15.3	316	14.5	186	16.5	154	15.3	335	16	699	14.8	1,514	16
2007	11,789	10.2	268	13.5	300	13.7	155	13.8	137	13.6	287	13.7	645	13.6	1,276	13.4
2008	11,779	10.2	201	10.1	229	10.5	115	10.2	105	10.4	216	10.3	502	10.6	1,026	10.8
2009	12,959	11.3	182	9.2	216	9.9	102	9.1	76	7.5	173	8.2	434	9.2	835	8.8
2010	13,530	11.7	149	7.5	147	6.7	70	6.2	59	5.9	128	6.1	340	7.2	635	6.7
2011	14,758	12.8	97	4.9	112	5.1	43	3.8	35	3.5	75	3.6	240	5.1	429	4.5
2012	15,369	13.3	40	2	24	1.1	11	1	6	0.6	17	0.8	72	1.5	149	1.6
Index of Multiple Deprivation (Quintiles)																
Q1	25,694	22.3	454	22.9	487	22.3	257	22.8	231	22.9	474	22.6	1,059	22.4	2,096	22.1
Q2	23,590	20.5	389	19.6	479	21.9	247	21.9	247	24.5	486	23.2	986	20.9	1,966	20.7
Q3	23,134	20.1	417	21	455	20.8	223	19.8	204	20.3	424	20.2	988	20.9	2,014	21.2
Q4	23,413	20.3	393	19.8	390	17.9	214	19	179	17.8	388	18.5	898	19	1,884	19.9
Q5	19,353	16.8	330	16.6	373	17.1	185	16.4	146	14.5	325	15.5	797	16.9	1,527	16.1
Overactive bladder	57,355	49.8	883	44.5	1,018	46.6	506	44.9	446	44.3	933	44.5	2,147	45.4	3,843	40.5

Table CV1. Characteristics of Subjects by Cardiovascular Event Type and Overall Mortality at Cohort Entry

	Patients Without CV Endpoint (n = 115,184)		Acute Myocardial Infarction (n = 1,983)		Stroke (n = 2,184)		Coronary Heart Disease Death (n = 1,126)		Cerebro-vascular Disease Death (n = 1,007)		Cardiovascular Mortality (n = 2,097)		Composite Endpoint (n = 4,728)		All-Cause Death (n = 9,487)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypertension																
Diagnosis codes only	33,943	29.5	404	20.4	498	22.8	184	16.3	230	22.8	407	19.4	1,002	21.2	2,421	25.5
Medications only	4,938	4.3	45	2.3	36	1.6	20	1.8	11	1.1	31	1.5	95	2	200	2.1
Diagnosis codes and medications	53,334	46.3	1,446	72.9	1,551	71	894	79.4	724	71.9	1,590	75.8	3,426	72.5	6,405	67.5
Diabetes																
Diagnosis codes only	2,599	2.3	71	3.6	96	4.4	41	3.6	49	4.9	89	4.2	186	3.9	349	3.7
Medications only	334	0.3	1	0.1	5	0.2	3	0.3	3	0.3	6	0.3	8	0.2	21	0.2
Diagnosis codes and medications	9,673	8.4	313	15.8	285	13	209	18.6	124	12.3	328	15.6	695	14.7	1,394	14.7
Smoking																
Current	18,780	16.3	322	16.2	297	13.6	141	12.5	94	9.3	233	11.1	671	14.2	1,225	12.9
Former	40,264	35	826	41.7	880	40.3	496	44	417	41.4	894	42.6	1,965	41.6	3,968	41.8
Non-smoker	54,788	47.6	804	40.5	965	44.2	467	41.5	461	45.8	913	43.5	2,000	42.3	4,001	42.2
Unknown	1,352	1.2	31	1.6	42	1.9	22	2	35	3.5	57	2.7	92	1.9	293	3.1
History of acute myocardial infarction	4,220	3.7	306	15.4	177	8.1	244	21.7	93	9.2	331	15.8	590	12.5	1,070	11.3
History of stroke	7,367	6.4	251	12.7	529	24.2	182	16.2	335	33.3	505	24.1	942	19.9	1,737	18.3
History of transient ischemic attack	4,289	3.7	184	9.3	296	13.6	126	11.2	185	18.4	306	14.6	579	12.2	1,051	11.1
History of coronary heart disease	14,099	12.2	705	35.6	509	23.3	509	45.2	243	24.1	739	35.2	1,442	30.5	2,669	28.1
History of heart failure	3,352	2.9	229	11.5	173	7.9	238	21.1	122	12.1	350	16.7	517	10.9	1,279	13.5
History of peripheral artery disease or peripheral vascular disease	7,702	6.7	295	14.9	296	13.6	202	17.9	150	14.9	349	16.6	690	14.6	1,424	15
Dyslipidemia	14,569	12.6	392	19.8	329	15.1	208	18.5	130	12.9	333	15.9	810	17.1	1,195	12.6
Atrial fibrillation	6,108	5.3	266	13.4	379	17.4	248	22	246	24.4	484	23.1	797	16.9	1,705	18
Chronic obstructive pulmonary disease	6,816	5.9	224	11.3	179	8.2	159	14.1	89	8.8	246	11.7	484	10.2	1,363	14.4
Dementia	1,940	1.7	63	3.2	108	4.9	54	4.8	105	10.4	157	7.5	217	4.6	712	7.5
Hemiplegia and paraplegia	1,556	1.4	37	1.9	117	5.4	32	2.8	81	8	112	5.3	192	4.1	321	3.4
Liver disease	1,237	1.1	20	1	28	1.3	11	1	8	0.8	18	0.9	53	1.1	138	1.5
Peptic ulcer disease	5,782	5	178	9	178	8.2	113	10	104	10.3	212	10.1	409	8.7	846	8.9

Table CV1. Characteristics of Subjects by Cardiovascular Event Type and Overall Mortality at Cohort Entry

	Patients Without CV Endpoint (n = 115,184)		Acute Myocardial Infarction (n = 1,983)		Stroke (n = 2,184)		Coronary Heart Disease Death (n = 1,126)		Cerebro-vascular Disease Death (n = 1,007)		Cardiovascular Mortality (n = 2,097)		Composite Endpoint (n = 4,728)		All-Cause Death (n = 9,487)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Renal disease	11,840	10.3	357	18	335	15.3	251	22.3	173	17.2	418	19.9	826	17.5	1,850	19.5
Dialysis	71	0.1	2	0.1	1	0	3	0.3	0		3	0.1	5	0.1	16	0.2
Rheumatological disease	6,123	5.3	196	9.9	193	8.8	126	11.2	106	10.5	226	10.8	447	9.5	965	10.2
Gout	4,439	3.9	146	7.4	140	6.4	111	9.9	62	6.2	169	8.1	337	7.1	671	7.1
Organ transplantation	127	0.1	4	0.2	3	0.1	1	0.1	2	0.2	2	0.1	6	0.1	10	0.1
Menopause (females only)	19,454	24	170	15.4	194	13.9	65	10.4	55	8.6	118	9.5	385	13.7	499	8.7
Body mass index																
< 20	3,773	3.3	72	3.6	90	4.1	61	5.4	64	6.4	124	5.9	202	4.3	661	7
20 to < 25	20,087	17.4	346	17.4	408	18.7	210	18.7	203	20.2	404	19.3	860	18.2	1,883	19.8
25 to < 30	26,377	22.9	505	25.5	489	22.4	231	20.5	163	16.2	389	18.6	1,086	23	1,735	18.3
30 to < 40	22,892	19.9	415	20.9	368	16.8	196	17.4	103	10.2	294	14	847	17.9	1,195	12.6
40+	4,199	3.6	46	2.3	36	1.6	33	2.9	8	0.8	41	2	97	2.1	218	2.3
Unknown	37,856	32.9	599	30.2	793	36.3	395	35.1	466	46.3	845	40.3	1,636	34.6	3,795	40
Obesity treatment	6,096	5.3	57	2.9	54	2.5	23	2	6	0.6	29	1.4	119	2.5	148	1.6
History of alcohol use																
Non-drinker	15,601	13.5	314	15.8	299	13.7	182	16.2	141	14	319	15.2	688	14.6	1,576	16.6
Low-moderate intake (1-6 units/wk)	60,086	52.2	981	49.5	1,106	50.6	532	47.2	469	46.6	981	46.8	2,353	49.8	4,304	45.4
Heavy or very heavy intake (7+ units/wk)	21,142	18.4	368	18.6	399	18.3	204	18.1	167	16.6	367	17.5	866	18.3	1,565	16.5
Drinker - unknown quantity	6,790	5.9	146	7.4	143	6.5	78	6.9	70	7	143	6.8	326	6.9	712	7.5
Unknown	11,565	10	174	8.8	237	10.9	130	11.5	160	15.9	287	13.7	495	10.5	1,330	14
Alcoholism or alcohol-related diseases	3,353	2.9	67	3.4	77	3.5	32	2.8	25	2.5	57	2.7	153	3.2	342	3.6
Health services utilization [mean (SD)]																
Outpatient visits	11	9.29	13	10.85	13	11.41	14	11.96	13	11.46	14	11.76	13	11.42	14	13.11
Hospitalizations	1	1.25	1	2.23	1	1.34	1	2.57	1	1.43	1	2.12	1	1.78	1	2.21

Table CV1. Characteristics of Subjects by Cardiovascular Event Type and Overall Mortality at Cohort Entry

	Patients Without CV Endpoint (n = 115,184)		Acute Myocardial Infarction (n = 1,983)		Stroke (n = 2,184)		Coronary Heart Disease Death (n = 1,126)		Cerebro-vascular Disease Death (n = 1,007)		Cardiovascular Mortality (n = 2,097)		Composite Endpoint (n = 4,728)		All-Cause Death (n = 9,487)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of prescriptions for study drugs (during follow-up)	12	22.13	11	19.92	14	25.32	13	22.37	15	26.35	14	24.51	13	22.61	15	24.39
Number of different OAB drugs received (during follow-up)	1	0.68	1	0.63	1	0.62	1	0.58	1	0.55	1	0.57	1	0.62	1	0.59
Duration of enrollment prior to cohort entry (years)	9	5.46	9	5.13	9	5.17	9	5.2	9	5.07	9	5.14	9	5.17	9	5.14
Duration of follow-up (years)	3	2.46	2	1.97	2	1.95	2	1.83	2	1.87	2	1.85	2	1.95	3	2
Previous exposure to study drug in the year before cohort entry																
Oxybutynin	2,151	1.9	63	3.2	60	2.7	42	3.7	29	2.9	70	3.3	145	3.1	291	3.1
Tolterodine	2,613	2.3	79	4	74	3.4	33	2.9	22	2.2	52	2.5	162	3.4	276	2.9
Darifenacin	10	0	0		0		0		0		0					
Solifenacin	377	0.3	3	0.2	3	0.1	3	0.3	0		3	0.1	7	0.1	16	0.2
Trospium	423	0.4	14	0.7	11	0.5	8	0.7	5	0.5	13	0.6	31	0.7	57	0.6
Fesoterodine	33	0	0		0		0		0		0				1	0
Previous exposure to study drug in the 5 years before cohort entry																
Oxybutynin	5,949	5.2	173	8.7	198	9.1	95	8.4	83	8.2	172	8.2	416	8.8	802	8.5
Tolterodine	7,155	6.2	184	9.3	228	10.4	88	7.8	88	8.7	171	8.2	450	9.5	817	8.6
Darifenacin	15	0	0		0		0		0		0					
Solifenacin	794	0.7	6	0.3	6	0.3	5	0.4	1	0.1	6	0.3	14	0.3	31	0.3
Trospium	1,203	1	31	1.6	31	1.4	14	1.2	12	1.2	26	1.2	70	1.5	128	1.3
Fesoterodine	57	0	0		0		0		0		0				1	0
Previous exposure to study drug before cohort entry																
Oxybutynin	11,477	10	289	14.6	329	15.1	159	14.1	137	13.6	289	13.8	688	14.6	1,338	14.1
Tolterodine	9,875	8.6	234	11.8	280	12.8	116	10.3	104	10.3	214	10.2	562	11.9	1,014	10.7
Darifenacin	15	0	0		0		0		0		0					
Solifenacin	810	0.7	6	0.3	6	0.3	5	0.4	1	0.1	6	0.3	14	0.3	31	0.3
Trospium	1,473	1.3	35	1.8	32	1.5	17	1.5	12	1.2	29	1.4	75	1.6	142	1.5
Fesoterodine	57	0	0		0		0		0		0				1	0

Table CV1. Characteristics of Subjects by Cardiovascular Event Type and Overall Mortality at Cohort Entry

	Patients Without CV Endpoint (n = 115,184)		Acute Myocardial Infarction (n = 1,983)		Stroke (n = 2,184)		Coronary Heart Disease Death (n = 1,126)		Cerebro-vascular Disease Death (n = 1,007)		Cardiovascular Mortality (n = 2,097)		Composite Endpoint (n = 4,728)		All-Cause Death (n = 9,487)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Increased cardiovascular risk	48,914	42.5	1,397	70.4	1,512	69.2	864	76.7	732	72.7	1,571	74.9	3,355	71	6,608	69.7
Hormone replacement therapy (females only)	29,729	36.7	346	31.3	447	32	162	26	155	24.1	312	25.1	860	30.6	1,380	24
Tamoxifen	254	0.2	2	0.1	4	0.2	1	0.1	0		1	0	6	0.1	23	0.2
Letrozole	14	0	1	0.1	0		0		0		0		1	0	4	0
Thyroid hormone replacement	11,722	10.2	241	12.2	235	10.8	134	11.9	135	13.4	264	12.6	558	11.8	1,168	12.3
Digoxin	3,087	2.7	158	8	206	9.4	151	13.4	148	14.7	295	14.1	462	9.8	1,136	12
Nitrates and other anti-anginal drugs	8,276	7.2	472	23.8	322	14.7	321	28.5	146	14.5	458	21.8	933	19.7	1,617	17
Lipid-lowering drugs	36,431	31.6	995	50.2	1,007	46.1	586	52	445	44.2	1,009	48.1	2,274	48.1	3,861	40.7
Non-aspirin NSAIDs	85,562	74.3	1,461	73.7	1,587	72.7	777	69	667	66.2	1,423	67.9	3,423	72.4	6,421	67.7
Low-dose aspirin and other antiplatelets	35,217	30.6	1,191	60.1	1,323	60.6	763	67.8	664	65.9	1,405	67	2,919	61.7	5,677	59.8
Immunosuppressive agents	1,300	1.1	25	1.3	25	1.1	18	1.6	16	1.6	32	1.5	60	1.3	154	1.6
Antiarrhythmic drugs	2,948	2.6	109	5.5	133	6.1	76	6.7	77	7.6	150	7.2	281	5.9	615	6.5
Thrombolytic therapy	0		0		0		0		0		0					
Warfarin	6,173	5.4	228	11.5	285	13	194	17.2	180	17.9	368	17.5	637	13.5	1,297	13.7

CV = cardiovascular; NSAIDs = non-steroidal anti-inflammatory drugs; OAB = overactive bladder; SD = standard deviation.

Table CV2a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with current exposure to							
Any OAB drug	663	119,912	124,226	5.34	(4.94, 5.76)	4.90	(4.53, 5.29)
Oxybutynin	214	50,440	31,420	6.81	(5.93, 7.79)	5.94	(5.16, 6.80)
Tolterodine	241	46,641	41,292	5.84	(5.12, 6.62)	5.01	(4.39, 5.68)
Darifenacin	1	647	447	2.24	(0.06, 12.45)	2.45	(0.06, 13.67)
Solifenacin	165	48,718	41,824	3.95	(3.37, 4.60)	4.00	(3.41, 4.67)
Trospium	49	11,088	7,927	6.18	(4.57, 8.17)	5.58	(4.11, 7.39)
Fesoterodine	13	5,879	3,491	3.72	(1.98, 6.37)	3.95	(2.08, 6.79)
Overall, aged ≥ 65 years with current exposure to							
Any OAB drug	573	62,998	71,253	8.04	(7.40, 8.73)	8.02	(7.38, 8.71)
Oxybutynin	191	26,887	18,370	10.40	(8.97, 11.98)	9.94	(8.57, 11.47)
Tolterodine	212	24,905	24,806	8.55	(7.43, 9.78)	8.35	(7.26, 9.56)
Darifenacin	0	346	266	0.00	(0.00, 13.84)	0.00	not estimable
Solifenacin	133	24,669	22,622	5.88	(4.92, 6.97)	6.22	(5.20, 7.38)
Trospium	42	6,263	4,680	8.97	(6.47, 12.13)	8.94	(6.43, 12.09)
Fesoterodine	12	2,859	1,757	6.83	(3.53, 11.93)	7.23	(3.69, 12.69)
Overall, with high CV risk and with current exposure to							
Any OAB drug	483	52,269	57,743	8.36	(7.64, 9.15)	6.47	(5.82, 7.16)
Oxybutynin	157	22,225	15,178	10.34	(8.79, 12.09)	7.90	(6.46, 9.52)
Tolterodine	180	20,133	19,254	9.35	(8.03, 10.82)	6.71	(5.72, 7.82)
Darifenacin	1	269	213	4.70	(0.12, 26.21)	5.33	(0.13, 29.70)
Solifenacin	117	20,712	18,769	6.23	(5.16, 7.47)	5.23	(4.28, 6.32)
Trospium	33	4,974	3,857	8.56	(5.89, 12.02)	6.17	(4.19, 8.72)
Fesoterodine	11	2,399	1,493	7.37	(3.68, 13.18)	5.77	(2.84, 10.40)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with current exposure to							
Any OAB drug	371	83,733	88,913	4.17	(3.76, 4.62)	3.79	(3.41, 4.20)
Oxybutynin	122	34,844	21,790	5.60	(4.65, 6.69)	4.68	(3.87, 5.61)
Tolterodine	132	32,495	28,776	4.59	(3.84, 5.44)	3.95	(3.30, 4.69)
Darifenacin	1	492	309	3.23	(0.08, 18.01)	3.43	(0.09, 19.09)
Solifenacin	90	36,211	31,342	2.87	(2.31, 3.53)	2.86	(2.29, 3.52)
Trospium	30	7,917	5,649	5.31	(3.58, 7.58)	4.92	(3.30, 7.04)
Fesoterodine	8	4,388	2,614	3.06	(1.32, 6.03)	3.30	(1.39, 6.56)
Female, aged ≥ 65 with current exposure to							
Any OAB drug	321	41,510	48,713	6.59	(5.89, 7.35)	6.54	(5.85, 7.30)
Oxybutynin	111	17,845	12,494	8.88	(7.31, 10.70)	8.31	(6.82, 10.03)
Tolterodine	113	16,433	16,475	6.86	(5.65, 8.25)	6.71	(5.53, 8.07)
Darifenacin	0	249	165	0.00	(0.00, 22.31)	0.00	not estimable
Solifenacin	75	17,196	16,033	4.68	(3.68, 5.86)	4.91	(3.85, 6.16)
Trospium	25	4,206	3,193	7.83	(5.07, 11.56)	8.05	(5.20, 11.90)
Fesoterodine	7	1,978	1,221	5.73	(2.30, 11.81)	6.06	(2.37, 12.61)
Female, with high CV risk and with current exposure to							
Any OAB drug	252	33,672	38,042	6.62	(5.83, 7.49)	4.95	(4.33, 5.64)
Oxybutynin	87	14,320	9,804	8.87	(7.11, 10.95)	6.22	(4.84, 7.83)
Tolterodine	90	12,946	12,279	7.33	(5.89, 9.01)	5.29	(4.21, 6.55)
Darifenacin	1	189	126	7.93	(0.20, 44.19)	7.44	(0.19, 41.46)
Solifenacin	59	14,193	12,947	4.56	(3.47, 5.88)	3.76	(2.83, 4.89)
Trospium	18	3,262	2,544	7.08	(4.19, 11.18)	5.26	(3.08, 8.36)
Fesoterodine	6	1,656	1,023	5.86	(2.15, 12.76)	4.94	(1.78, 10.80)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with current exposure to							
Any OAB drug	292	36,179	35,313	8.27	(7.35, 9.27)	7.69	(6.83, 8.63)
Oxybutynin	92	15,596	9,630	9.55	(7.70, 11.72)	9.11	(7.34, 11.18)
Tolterodine	109	14,146	12,516	8.71	(7.15, 10.51)	7.67	(6.30, 9.26)
Darifenacin	0	155	138	0.00	(0.00, 26.73)	0.00	not estimable
Solifenacin	75	12,507	10,482	7.16	(5.63, 8.97)	6.89	(5.41, 8.65)
Trospium	19	3,171	2,278	8.34	(5.02, 13.03)	7.24	(4.33, 11.35)
Fesoterodine	5	1,491	878	5.70	(1.85, 13.29)	5.59	(1.81, 13.07)
Male, aged ≥ 65 years with current exposure to							
Any OAB drug	252	21,488	22,540	11.18	(9.84, 12.65)	11.19	(9.85, 12.66)
Oxybutynin	80	9,042	5,876	13.61	(10.80, 16.94)	13.41	(10.63, 16.70)
Tolterodine	99	8,472	8,331	11.88	(9.66, 14.47)	11.86	(9.63, 14.44)
Darifenacin	0	97	101	0.00	(0.00, 36.48)	0.00	not estimable
Solifenacin	58	7,473	6,588	8.80	(6.69, 11.38)	9.02	(6.84, 11.67)
Trospium	17	2,057	1,487	11.43	(6.66, 18.30)	10.83	(6.29, 17.37)
Fesoterodine	5	881	535	9.34	(3.03, 21.79)	9.71	(3.14, 22.70)
Male, with high CV risk and with current exposure to							
Any OAB drug	231	18,597	19,700	11.73	(10.26, 13.34)	10.29	(8.67, 12.07)
Oxybutynin	70	7,905	5,374	13.03	(10.15, 16.46)	12.13	(8.55, 16.41)
Tolterodine	90	7,187	6,976	12.90	(10.37, 15.86)	10.30	(8.21, 12.74)
Darifenacin	0	80	87	0.00	(0.00, 42.64)	0.00	not estimable
Solifenacin	58	6,519	5,821	9.96	(7.57, 12.88)	8.94	(6.66, 11.72)
Trospium	15	1,712	1,313	11.43	(6.40, 18.85)	8.46	(4.66, 14.06)
Fesoterodine	5	743	470	10.65	(3.46, 24.85)	7.88	(2.55, 18.39)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with current exposure to							
Any OAB drug	818	119,912	124,028	6.60	(6.15, 7.06)	6.00	(5.60, 6.43)
Oxybutynin	251	50,410	31,367	8.00	(7.04, 9.06)	6.76	(5.94, 7.65)
Tolterodine	299	46,628	41,251	7.25	(6.45, 8.12)	6.34	(5.63, 7.10)
Darifenacin	3	644	443	6.77	(1.40, 19.78)	5.11	(1.01, 15.06)
Solifenacin	212	48,703	41,752	5.08	(4.42, 5.81)	5.12	(4.45, 5.87)
Trospium	57	11,071	7,902	7.21	(5.46, 9.35)	6.54	(4.94, 8.49)
Fesoterodine	11	5,874	3,482	3.16	(1.58, 5.65)	3.47	(1.71, 6.23)
Overall, aged ≥ 65 years with current exposure to							
Any OAB drug	727	62,995	71,069	10.23	(9.50, 11.00)	10.18	(9.45, 10.95)
Oxybutynin	229	26,864	18,313	12.51	(10.94, 14.23)	11.70	(10.22, 13.33)
Tolterodine	266	24,893	24,779	10.73	(9.48, 12.11)	10.55	(9.32, 11.90)
Darifenacin	3	343	262	11.45	(2.36, 33.47)	9.98	(1.96, 29.39)
Solifenacin	187	24,663	22,553	8.29	(7.15, 9.57)	8.80	(7.58, 10.17)
Trospium	48	6,248	4,655	10.31	(7.60, 13.67)	10.37	(7.64, 13.76)
Fesoterodine	8	2,851	1,750	4.57	(1.97, 9.01)	5.16	(2.21, 10.21)
Overall, with high CV risk and with current exposure to							
Any OAB drug	589	52,269	57,622	10.22	(9.41, 11.08)	7.86	(7.19, 8.57)
Oxybutynin	199	22,206	15,112	13.17	(11.40, 15.13)	9.32	(7.99, 10.79)
Tolterodine	210	20,125	19,266	10.90	(9.48, 12.48)	8.77	(7.43, 10.26)
Darifenacin	3	266	209	14.34	(2.96, 41.91)	7.87	(1.42, 23.48)
Solifenacin	138	20,708	18,716	7.37	(6.19, 8.71)	5.99	(5.01, 7.10)
Trospium	42	4,966	3,845	10.92	(7.87, 14.77)	8.57	(6.05, 11.74)
Fesoterodine	8	2,398	1,489	5.37	(2.32, 10.58)	3.97	(1.67, 7.89)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with current exposure to							
Any OAB drug	524	83,733	88,715	5.91	(5.41, 6.43)	5.34	(4.89, 5.82)
Oxybutynin	162	34,821	21,732	7.45	(6.35, 8.69)	6.00	(5.10, 7.02)
Tolterodine	190	32,485	28,714	6.62	(5.71, 7.63)	5.77	(4.97, 6.66)
Darifenacin	1	491	308	3.24	(0.08, 18.06)	2.72	(0.07, 15.18)
Solifenacin	139	36,199	31,289	4.44	(3.73, 5.25)	4.55	(3.82, 5.38)
Trospium	38	7,901	5,626	6.75	(4.78, 9.27)	6.18	(4.36, 8.50)
Fesoterodine	4	4,386	2,608	1.53	(0.42, 3.93)	1.73	(0.44, 4.49)
Female, aged ≥ 65 with current exposure to							
Any OAB drug	463	41,497	48,552	9.54	(8.69, 10.45)	9.46	(8.62, 10.37)
Oxybutynin	150	17,827	12,444	12.05	(10.20, 14.14)	11.02	(9.31, 12.95)
Tolterodine	167	16,418	16,423	10.17	(8.69, 11.83)	9.98	(8.52, 11.61)
Darifenacin	1	248	164	6.09	(0.15, 33.94)	5.60	(0.14, 31.18)
Solifenacin	122	17,188	15,996	7.63	(6.33, 9.11)	8.23	(6.83, 9.84)
Trospium	31	4,191	3,173	9.77	(6.64, 13.87)	9.99	(6.78, 14.19)
Fesoterodine	2	1,975	1,218	1.64	(0.20, 5.93)	2.10	(0.23, 7.66)
Female, with high CV risk and with current exposure to							
Any OAB drug	355	33,672	37,916	9.36	(8.41, 10.39)	7.13	(6.36, 7.97)
Oxybutynin	121	14,304	9,750	12.41	(10.30, 14.83)	8.37	(6.85, 10.11)
Tolterodine	124	12,938	12,264	10.11	(8.41, 12.06)	8.02	(6.47, 9.80)
Darifenacin	1	188	126	7.94	(0.20, 44.22)	4.96	(0.13, 27.61)
Solifenacin	88	14,189	12,899	6.82	(5.47, 8.41)	5.55	(4.43, 6.86)
Trospium	26	3,252	2,532	10.27	(6.71, 15.05)	8.44	(5.38, 12.55)
Fesoterodine	2	1,658	1,022	1.96	(0.24, 7.07)	1.79	(0.21, 6.50)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with current exposure to							
Any OAB drug	294	36,179	35,313	8.33	(7.40, 9.33)	7.67	(6.81, 8.60)
Oxybutynin	89	15,589	9,635	9.24	(7.42, 11.37)	8.65	(6.94, 10.65)
Tolterodine	109	14,143	12,537	8.69	(7.14, 10.49)	7.77	(6.36, 9.39)
Darifenacin	2	153	135	14.85	(1.80, 53.64)	11.14	(1.23, 40.58)
Solifenacin	73	12,504	10,462	6.98	(5.47, 8.77)	6.56	(5.14, 8.25)
Trospium	19	3,170	2,276	8.35	(5.03, 13.04)	7.45	(4.47, 11.66)
Fesoterodine	7	1,488	875	8.00	(3.22, 16.49)	7.87	(3.15, 16.22)
Male, aged ≥ 65 years with current exposure to							
Any OAB drug	264	21,498	22,516	11.72	(10.35, 13.23)	11.71	(10.34, 13.21)
Oxybutynin	79	9,037	5,868	13.46	(10.66, 16.78)	13.16	(10.41, 16.40)
Tolterodine	99	8,475	8,356	11.85	(9.63, 14.42)	11.77	(9.57, 14.33)
Darifenacin	2	95	98	20.44	(2.48, 73.85)	19.34	(2.14, 70.45)
Solifenacin	65	7,475	6,557	9.91	(7.65, 12.64)	10.02	(7.73, 12.78)
Trospium	17	2,057	1,482	11.47	(6.68, 18.37)	11.20	(6.51, 17.94)
Fesoterodine	6	876	533	11.26	(4.13, 24.52)	11.70	(4.28, 25.49)
Male, with high CV risk and with current exposure to							
Any OAB drug	234	18,597	19,707	11.87	(10.40, 13.50)	9.69	(8.42, 11.09)
Oxybutynin	78	7,902	5,363	14.55	(11.50, 18.15)	11.72	(9.16, 14.74)
Tolterodine	86	7,187	7,003	12.28	(9.82, 15.17)	10.66	(8.13, 13.64)
Darifenacin	2	78	83	24.04	(2.91, 86.82)	15.21	(1.79, 55.09)
Solifenacin	50	6,519	5,817	8.60	(6.38, 11.33)	7.10	(5.23, 9.41)
Trospium	16	1,714	1,313	12.19	(6.97, 19.79)	8.89	(5.06, 14.47)
Fesoterodine	6	740	467	12.84	(4.71, 27.95)	9.47	(3.47, 20.61)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with current exposure to							
Any OAB drug	365	119,912	124,917	2.92	(2.63, 3.24)	2.63	(2.36, 2.91)
Oxybutynin	136	50,473	31,591	4.31	(3.61, 5.09)	3.60	(3.02, 4.27)
Tolterodine	133	46,655	41,541	3.20	(2.68, 3.79)	2.66	(2.22, 3.15)
Darifenacin	2	648	448	4.47	(0.54, 16.14)	4.70	(0.50, 17.16)
Solifenacin	62	48,790	42,039	1.47	(1.13, 1.89)	1.49	(1.14, 1.91)
Trospium	31	11,102	7,981	3.88	(2.64, 5.51)	3.33	(2.26, 4.74)
Fesoterodine	9	5,893	3,503	2.57	(1.17, 4.88)	2.92	(1.32, 5.56)
Overall, aged ≥ 65 years with current exposure to							
Any OAB drug	345	63,024	71,807	4.80	(4.31, 5.34)	4.78	(4.29, 5.31)
Oxybutynin	127	26,922	18,502	6.86	(5.72, 8.17)	6.38	(5.31, 7.60)
Tolterodine	130	24,924	25,008	5.20	(4.34, 6.17)	5.05	(4.21, 5.99)
Darifenacin	2	347	267	7.50	(0.91, 27.11)	9.17	(0.98, 33.51)
Solifenacin	58	24,737	22,792	2.54	(1.93, 3.29)	2.73	(2.07, 3.53)
Trospium	28	6,276	4,729	5.92	(3.93, 8.56)	5.72	(3.79, 8.28)
Fesoterodine	8	2,869	1,767	4.53	(1.95, 8.92)	5.07	(2.17, 10.04)
Overall, with high CV risk and with current exposure to							
Any OAB drug	281	52,269	58,217	4.83	(4.28, 5.43)	3.53	(3.04, 4.06)
Oxybutynin	107	22,250	15,282	7.00	(5.74, 8.46)	5.14	(3.94, 6.52)
Tolterodine	100	20,141	19,448	5.14	(4.18, 6.25)	3.34	(2.71, 4.08)
Darifenacin	1	269	213	4.70	(0.12, 26.19)	4.51	(0.11, 25.13)
Solifenacin	51	20,760	18,900	2.70	(2.01, 3.55)	2.10	(1.56, 2.77)
Trospium	22	4,987	3,899	5.64	(3.54, 8.54)	3.95	(2.44, 6.04)
Fesoterodine	7	2,409	1,501	4.67	(1.88, 9.61)	3.94	(1.52, 8.25)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with current exposure to							
Any OAB drug	193	83,733	89,303	2.16	(1.87, 2.49)	1.92	(1.66, 2.21)
Oxybutynin	72	34,863	21,876	3.29	(2.58, 4.14)	2.61	(2.03, 3.29)
Tolterodine	71	32,504	28,914	2.46	(1.92, 3.10)	2.04	(1.59, 2.57)
Darifenacin	2	493	310	6.46	(0.78, 23.33)	6.56	(0.70, 23.96)
Solifenacin	36	36,261	31,476	1.14	(0.80, 1.58)	1.15	(0.81, 1.60)
Trospium	13	7,922	5,677	2.29	(1.22, 3.92)	2.04	(1.09, 3.50)
Fesoterodine	5	4,399	2,624	1.91	(0.62, 4.45)	2.26	(0.71, 5.30)
Female, aged ≥ 65 with current exposure to							
Any OAB drug	182	41,519	49,030	3.71	(3.19, 4.29)	3.67	(3.16, 4.24)
Oxybutynin	67	17,863	12,565	5.33	(4.13, 6.77)	4.79	(3.70, 6.09)
Tolterodine	69	16,443	16,579	4.16	(3.24, 5.27)	4.05	(3.15, 5.12)
Darifenacin	2	250	165	12.09	(1.46, 43.68)	13.46	(1.44, 49.21)
Solifenacin	33	17,241	16,146	2.04	(1.41, 2.87)	2.18	(1.50, 3.07)
Trospium	12	4,209	3,220	3.73	(1.93, 6.51)	3.85	(1.99, 6.73)
Fesoterodine	5	1,987	1,230	4.06	(1.32, 9.48)	4.63	(1.46, 10.89)
Female, with high CV risk and with current exposure to							
Any OAB drug	140	33,672	38,282	3.66	(3.08, 4.32)	2.60	(2.17, 3.09)
Oxybutynin	53	14,332	9,857	5.38	(4.03, 7.03)	3.68	(2.61, 4.99)
Tolterodine	51	12,950	12,372	4.12	(3.07, 5.42)	2.69	(1.99, 3.55)
Darifenacin	1	189	126	7.92	(0.20, 44.13)	6.30	(0.16, 35.08)
Solifenacin	28	14,224	13,018	2.15	(1.43, 3.11)	1.70	(1.12, 2.47)
Trospium	9	3,266	2,563	3.51	(1.61, 6.67)	2.62	(1.19, 4.99)
Fesoterodine	3	1,664	1,030	2.91	(0.60, 8.52)	2.54	(0.51, 7.45)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with current exposure to							
Any OAB drug	172	36,179	35,614	4.83	(4.13, 5.61)	4.42	(3.78, 5.13)
Oxybutynin	64	15,610	9,714	6.59	(5.07, 8.41)	6.13	(4.71, 7.83)
Tolterodine	62	14,151	12,627	4.91	(3.76, 6.29)	4.21	(3.23, 5.40)
Darifenacin	0	155	138	0.00	(0.00, 26.73)	0.00	not estimable
Solifenacin	26	12,529	10,564	2.46	(1.61, 3.61)	2.34	(1.53, 3.44)
Trospium	18	3,180	2,304	7.81	(4.63, 12.35)	6.58	(3.87, 10.45)
Fesoterodine	4	1,494	879	4.55	(1.24, 11.65)	4.59	(1.25, 11.76)
Male, aged ≥ 65 years with current exposure to							
Any OAB drug	163	21,505	22,777	7.16	(6.10, 8.34)	7.15	(6.10, 8.34)
Oxybutynin	60	9,059	5,937	10.11	(7.71, 13.01)	9.79	(7.47, 12.60)
Tolterodine	61	8,481	8,429	7.24	(5.54, 9.30)	7.18	(5.49, 9.22)
Darifenacin	0	97	101	0.00	(0.00, 36.48)	0.00	not estimable
Solifenacin	25	7,496	6,646	3.76	(2.43, 5.55)	3.91	(2.52, 5.77)
Trospium	16	2,067	1,509	10.60	(6.06, 17.22)	9.71	(5.53, 15.79)
Fesoterodine	3	882	537	5.59	(1.15, 16.33)	6.02	(1.23, 17.60)
Male, with high CV risk and with current exposure to							
Any OAB drug	141	18,597	19,935	7.07	(5.95, 8.34)	5.87	(4.58, 7.32)
Oxybutynin	54	7,918	5,425	9.95	(7.48, 12.99)	8.82	(5.69, 12.65)
Tolterodine	49	7,191	7,075	6.93	(5.12, 9.16)	4.99	(3.69, 6.60)
Darifenacin	0	80	87	0.00	(0.00, 42.64)	0.00	not estimable
Solifenacin	23	6,536	5,883	3.91	(2.48, 5.87)	3.12	(1.97, 4.69)
Trospium	13	1,721	1,336	9.73	(5.18, 16.64)	7.31	(3.77, 12.68)
Fesoterodine	4	745	471	8.49	(2.31, 21.75)	7.49	(1.79, 19.71)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with current exposure to							
Any OAB drug	278	119,912	124,917	2.23	(1.97, 2.50)	1.99	(1.76, 2.24)
Oxybutynin	112	50,473	31,591	3.55	(2.92, 4.27)	2.89	(2.37, 3.48)
Tolterodine	104	46,655	41,541	2.50	(2.05, 3.03)	2.12	(1.73, 2.57)
Darifenacin	0	648	448	0.00	(0.00, 8.24)	0.00	not estimable
Solifenacin	42	48,790	42,039	1.00	(0.72, 1.35)	1.03	(0.74, 1.40)
Trospium	22	11,102	7,981	2.76	(1.73, 4.17)	2.46	(1.54, 3.74)
Fesoterodine	2	5,893	3,503	0.57	(0.07, 2.06)	0.63	(0.08, 2.29)
Overall, aged ≥ 65 years with current exposure to							
Any OAB drug	262	63,024	71,807	3.65	(3.22, 4.12)	3.62	(3.20, 4.09)
Oxybutynin	106	26,922	18,502	5.73	(4.69, 6.93)	5.17	(4.23, 6.26)
Tolterodine	100	24,924	25,008	4.00	(3.25, 4.86)	3.92	(3.19, 4.77)
Darifenacin	0	347	267	0.00	(0.00, 13.84)	0.00	not estimable
Solifenacin	40	24,737	22,792	1.76	(1.25, 2.39)	1.92	(1.37, 2.62)
Trospium	19	6,276	4,729	4.02	(2.42, 6.27)	4.10	(2.46, 6.42)
Fesoterodine	1	2,869	1,767	0.57	(0.01, 3.15)	0.62	(0.02, 3.43)
Overall, with high CV risk and with current exposure to							
Any OAB drug	210	52,269	58,217	3.61	(3.14, 4.13)	2.61	(2.25, 3.00)
Oxybutynin	83	22,250	15,282	5.43	(4.33, 6.73)	3.63	(2.82, 4.57)
Tolterodine	81	20,141	19,448	4.16	(3.31, 5.18)	2.93	(2.30, 3.68)
Darifenacin	0	269	213	0.00	(0.00, 17.34)	0.00	not estimable
Solifenacin	32	20,760	18,900	1.69	(1.16, 2.39)	1.33	(0.91, 1.88)
Trospium	16	4,987	3,899	4.10	(2.35, 6.66)	3.34	(1.86, 5.49)
Fesoterodine	2	2,409	1,501	1.33	(0.16, 4.81)	1.24	(0.10, 4.64)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with current exposure to							
Any OAB drug	188	83,733	89,303	2.11	(1.82, 2.43)	1.87	(1.61, 2.16)
Oxybutynin	74	34,863	21,876	3.38	(2.66, 4.25)	2.64	(2.06, 3.32)
Tolterodine	72	32,504	28,914	2.49	(1.95, 3.14)	2.07	(1.62, 2.61)
Darifenacin	0	493	310	0.00	(0.00, 11.91)	0.00	not estimable
Solifenacin	27	36,261	31,476	0.86	(0.57, 1.25)	0.90	(0.59, 1.31)
Trospium	16	7,922	5,677	2.82	(1.61, 4.58)	2.62	(1.49, 4.25)
Fesoterodine	0	4,399	2,624	0.00	(0.00, 1.41)	0.00	not estimable
Female, aged ≥ 65 with current exposure to							
Any OAB drug	177	41,519	49,030	3.61	(3.10, 4.18)	3.57	(3.06, 4.14)
Oxybutynin	68	17,863	12,565	5.41	(4.20, 6.86)	4.74	(3.67, 6.02)
Tolterodine	71	16,443	16,579	4.28	(3.34, 5.40)	4.16	(3.25, 5.25)
Darifenacin	0	250	165	0.00	(0.00, 22.30)	0.00	not estimable
Solifenacin	26	17,241	16,146	1.61	(1.05, 2.36)	1.79	(1.16, 2.62)
Trospium	13	4,209	3,220	4.04	(2.15, 6.90)	4.33	(2.30, 7.41)
Fesoterodine	0	1,987	1,230	0.00	(0.00, 3.00)	0.00	not estimable
Female, with high CV risk and with current exposure to							
Any OAB drug	132	33,672	38,282	3.45	(2.88, 4.09)	2.44	(2.02, 2.91)
Oxybutynin	50	14,332	9,857	5.07	(3.76, 6.69)	3.35	(2.39, 4.53)
Tolterodine	52	12,950	12,372	4.20	(3.14, 5.51)	2.79	(2.05, 3.69)
Darifenacin	0	189	126	0.00	(0.00, 29.22)	0.00	not estimable
Solifenacin	19	14,224	13,018	1.46	(0.88, 2.28)	1.14	(0.68, 1.78)
Trospium	12	3,266	2,563	4.68	(2.42, 8.18)	3.87	(1.96, 6.81)
Fesoterodine	0	1,664	1,030	0.00	(0.00, 3.58)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with current exposure to							
Any OAB drug	90	36,179	35,614	2.53	(2.03, 3.11)	2.30	(1.85, 2.83)
Oxybutynin	38	15,610	9,714	3.91	(2.77, 5.37)	3.52	(2.49, 4.83)
Tolterodine	32	14,151	12,627	2.53	(1.73, 3.58)	2.24	(1.53, 3.17)
Darifenacin	0	155	138	0.00	(0.00, 26.73)	0.00	not estimable
Solifenacin	15	12,529	10,564	1.42	(0.79, 2.34)	1.36	(0.76, 2.25)
Trospium	6	3,180	2,304	2.60	(0.96, 5.67)	2.08	(0.76, 4.53)
Fesoterodine	2	1,494	879	2.27	(0.28, 8.22)	2.24	(0.27, 8.08)
Male, aged ≥ 65 years with current exposure to							
Any OAB drug	85	21,505	22,777	3.73	(2.98, 4.61)	3.73	(2.98, 4.61)
Oxybutynin	38	9,059	5,937	6.40	(4.53, 8.79)	6.11	(4.32, 8.38)
Tolterodine	29	8,481	8,429	3.44	(2.30, 4.94)	3.41	(2.29, 4.90)
Darifenacin	0	97	101	0.00	(0.00, 36.48)	0.00	not estimable
Solifenacin	14	7,496	6,646	2.11	(1.15, 3.53)	2.20	(1.20, 3.70)
Trospium	6	2,067	1,509	3.98	(1.46, 8.65)	3.61	(1.32, 7.87)
Fesoterodine	1	882	537	1.86	(0.05, 10.38)	1.93	(0.05, 10.76)
Male, with high CV risk and with current exposure to							
Any OAB drug	78	18,597	19,935	3.91	(3.09, 4.88)	3.03	(2.37, 3.80)
Oxybutynin	33	7,918	5,425	6.08	(4.19, 8.54)	4.33	(2.97, 6.10)
Tolterodine	29	7,191	7,075	4.10	(2.74, 5.89)	3.30	(2.13, 4.84)
Darifenacin	0	80	87	0.00	(0.00, 42.64)	0.00	not estimable
Solifenacin	13	6,536	5,883	2.21	(1.18, 3.78)	1.81	(0.96, 3.11)
Trospium	4	1,721	1,336	2.99	(0.82, 7.67)	2.00	(0.54, 5.13)
Fesoterodine	2	745	471	4.25	(0.51, 15.34)	4.39	(0.36, 16.36)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with current exposure to							
Any OAB drug	630	119,912	124,917	5.04	(4.66, 5.45)	4.53	(4.18, 4.90)
Oxybutynin	243	50,473	31,591	7.69	(6.76, 8.72)	6.37	(5.59, 7.24)
Tolterodine	234	46,655	41,541	5.63	(4.93, 6.40)	4.71	(4.13, 5.36)
Darifenacin	2	648	448	4.47	(0.54, 16.14)	4.70	(0.50, 17.16)
Solifenacin	100	48,790	42,039	2.38	(1.94, 2.89)	2.43	(1.98, 2.96)
Trospium	53	11,102	7,981	6.64	(4.97, 8.69)	5.79	(4.33, 7.59)
Fesoterodine	10	5,893	3,503	2.85	(1.37, 5.25)	3.24	(1.54, 5.97)
Overall, aged ≥ 65 years with current exposure to							
Any OAB drug	594	63,024	71,807	8.27	(7.62, 8.96)	8.22	(7.57, 8.91)
Oxybutynin	228	26,922	18,502	12.32	(10.78, 14.03)	11.32	(9.89, 12.90)
Tolterodine	227	24,924	25,008	9.08	(7.93, 10.34)	8.85	(7.74, 10.08)
Darifenacin	2	347	267	7.50	(0.91, 27.11)	9.17	(0.98, 33.51)
Solifenacin	94	24,737	22,792	4.12	(3.33, 5.05)	4.48	(3.61, 5.48)
Trospium	47	6,276	4,729	9.94	(7.30, 13.22)	9.82	(7.20, 13.08)
Fesoterodine	8	2,869	1,767	4.53	(1.95, 8.92)	5.07	(2.17, 10.04)
Overall, with high CV risk and with current exposure to							
Any OAB drug	483	52,269	58,217	8.30	(7.57, 9.07)	6.04	(5.44, 6.68)
Oxybutynin	187	22,250	15,282	12.24	(10.55, 14.12)	8.66	(7.20, 10.28)
Tolterodine	180	20,141	19,448	9.26	(7.95, 10.71)	6.25	(5.34, 7.27)
Darifenacin	1	269	213	4.70	(0.12, 26.19)	4.51	(0.11, 25.13)
Solifenacin	80	20,760	18,900	4.23	(3.36, 5.27)	3.31	(2.61, 4.13)
Trospium	38	4,987	3,899	9.75	(6.90, 13.38)	7.29	(5.09, 10.10)
Fesoterodine	8	2,409	1,501	5.33	(2.30, 10.51)	4.75	(1.97, 9.52)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with current exposure to							
Any OAB drug	373	83,733	89,303	4.18	(3.76, 4.62)	3.71	(3.34, 4.11)
Oxybutynin	144	34,863	21,876	6.58	(5.55, 7.75)	5.18	(4.35, 6.12)
Tolterodine	141	32,504	28,914	4.88	(4.10, 5.75)	4.05	(3.41, 4.78)
Darifenacin	2	493	310	6.46	(0.78, 23.33)	6.56	(0.70, 23.96)
Solifenacin	59	36,261	31,476	1.87	(1.43, 2.42)	1.93	(1.47, 2.49)
Trospium	29	7,922	5,677	5.11	(3.42, 7.34)	4.66	(3.12, 6.69)
Fesoterodine	5	4,399	2,624	1.91	(0.62, 4.45)	2.26	(0.71, 5.30)
Female, aged ≥ 65 with current exposure to							
Any OAB drug	351	41,519	49,030	7.16	(6.43, 7.95)	7.08	(6.36, 7.86)
Oxybutynin	133	17,863	12,565	10.58	(8.86, 12.54)	9.40	(7.86, 11.15)
Tolterodine	138	16,443	16,579	8.32	(6.99, 9.83)	8.09	(6.80, 9.56)
Darifenacin	2	250	165	12.09	(1.46, 43.68)	13.46	(1.44, 49.21)
Solifenacin	55	17,241	16,146	3.41	(2.57, 4.43)	3.71	(2.79, 4.84)
Trospium	25	4,209	3,220	7.76	(5.03, 11.46)	8.18	(5.29, 12.08)
Fesoterodine	5	1,987	1,230	4.06	(1.32, 9.48)	4.63	(1.46, 10.89)
Female, with high CV risk and with current exposure to							
Any OAB drug	268	33,672	38,282	7.00	(6.19, 7.89)	4.97	(4.36, 5.63)
Oxybutynin	102	14,332	9,857	10.35	(8.44, 12.56)	6.98	(5.52, 8.67)
Tolterodine	103	12,950	12,372	8.32	(6.80, 10.10)	5.48	(4.44, 6.68)
Darifenacin	1	189	126	7.92	(0.20, 44.13)	6.30	(0.16, 35.08)
Solifenacin	44	14,224	13,018	3.38	(2.46, 4.54)	2.66	(1.92, 3.59)
Trospium	21	3,266	2,563	8.19	(5.07, 12.52)	6.49	(3.98, 9.98)
Fesoterodine	3	1,664	1,030	2.91	(0.60, 8.52)	2.54	(0.51, 7.45)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with current exposure to							
Any OAB drug	257	36,179	35,614	7.22	(6.36, 8.15)	6.59	(5.81, 7.45)
Oxybutynin	99	15,610	9,714	10.19	(8.28, 12.41)	9.38	(7.62, 11.42)
Tolterodine	93	14,151	12,627	7.37	(5.94, 9.02)	6.39	(5.15, 7.83)
Darifenacin	0	155	138	0.00	(0.00, 26.73)	0.00	not estimable
Solifenacin	41	12,529	10,564	3.88	(2.79, 5.27)	3.71	(2.66, 5.03)
Trospium	24	3,180	2,304	10.42	(6.68, 15.50)	8.66	(5.52, 12.93)
Fesoterodine	5	1,494	879	5.69	(1.85, 13.27)	5.72	(1.85, 13.35)
Male, aged ≥ 65 years with current exposure to							
Any OAB drug	243	21,505	22,777	10.67	(9.37, 12.10)	10.67	(9.37, 12.09)
Oxybutynin	95	9,059	5,937	16.00	(12.95, 19.56)	15.43	(12.48, 18.87)
Tolterodine	89	8,481	8,429	10.56	(8.48, 12.99)	10.48	(8.41, 12.89)
Darifenacin	0	97	101	0.00	(0.00, 36.48)	0.00	not estimable
Solifenacin	39	7,496	6,646	5.87	(4.17, 8.02)	6.11	(4.34, 8.36)
Trospium	22	2,067	1,509	14.58	(9.14, 22.07)	13.32	(8.33, 20.19)
Fesoterodine	3	882	537	5.59	(1.15, 16.33)	6.02	(1.23, 17.60)
Male, with high CV risk and with current exposure to							
Any OAB drug	215	18,597	19,935	10.79	(9.39, 12.33)	8.75	(7.30, 10.35)
Oxybutynin	85	7,918	5,425	15.67	(12.51, 19.37)	12.90	(9.44, 16.97)
Tolterodine	77	7,191	7,075	10.88	(8.59, 13.60)	8.19	(6.40, 10.31)
Darifenacin	0	80	87	0.00	(0.00, 42.64)	0.00	not estimable
Solifenacin	36	6,536	5,883	6.12	(4.29, 8.47)	4.93	(3.44, 6.84)
Trospium	17	1,721	1,336	12.72	(7.41, 20.37)	9.31	(5.31, 15.08)
Fesoterodine	5	745	471	10.62	(3.45, 24.78)	10.35	(3.03, 24.81)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with current exposure to							
Any OAB drug	1,644	119,912	123,356	13.33	(12.69, 13.99)	12.19	(11.61, 12.80)
Oxybutynin	521	50,378	31,199	16.70	(15.30, 18.20)	14.32	(13.10, 15.62)
Tolterodine	599	46,614	41,012	14.61	(13.46, 15.82)	12.63	(11.63, 13.69)
Darifenacin	6	643	443	13.55	(4.97, 29.49)	12.31	(4.32, 27.16)
Solifenacin	400	48,633	41,542	9.63	(8.71, 10.62)	9.82	(8.88, 10.84)
Trospium	126	11,058	7,848	16.05	(13.37, 19.11)	14.52	(12.07, 17.31)
Fesoterodine	27	5,860	3,470	7.78	(5.13, 11.32)	8.47	(5.55, 12.36)
Overall, aged ≥ 65 years with current exposure to							
Any OAB drug	1,456	62,969	70,530	20.64	(19.60, 21.73)	20.60	(19.55, 21.68)
Oxybutynin	472	26,830	18,182	25.96	(23.67, 28.41)	24.51	(22.34, 26.84)
Tolterodine	537	24,874	24,587	21.84	(20.03, 23.77)	21.41	(19.64, 23.30)
Darifenacin	5	342	262	19.09	(6.20, 44.55)	19.24	(5.89, 45.61)
Solifenacin	344	24,596	22,387	15.37	(13.78, 17.08)	16.42	(14.72, 18.26)
Trospium	108	6,235	4,607	23.44	(19.23, 28.30)	23.44	(19.22, 28.32)
Fesoterodine	21	2,841	1,739	12.07	(7.47, 18.45)	13.19	(8.11, 20.23)
Overall, with high CV risk and with current exposure to							
Any OAB drug	1,204	52,269	57,155	21.07	(19.89, 22.29)	16.09	(15.11, 17.12)
Oxybutynin	405	22,182	15,009	26.98	(24.42, 29.74)	19.69	(17.57, 21.97)
Tolterodine	437	20,117	19,076	22.91	(20.81, 25.16)	17.23	(15.47, 19.12)
Darifenacin	5	266	209	23.92	(7.77, 55.82)	17.71	(5.01, 42.79)
Solifenacin	276	20,662	18,587	14.85	(13.15, 16.71)	12.18	(10.74, 13.75)
Trospium	87	4,954	3,802	22.88	(18.33, 28.22)	17.33	(13.75, 21.53)
Fesoterodine	22	2,388	1,482	14.85	(9.31, 22.48)	11.90	(7.34, 18.17)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with current exposure to							
Any OAB drug	979	83,733	88,336	11.08	(10.40, 11.80)	10.06	(9.44, 10.71)
Oxybutynin	313	34,803	21,646	14.46	(12.90, 16.15)	11.86	(10.56, 13.28)
Tolterodine	357	32,476	28,584	12.49	(11.23, 13.85)	10.80	(9.70, 11.99)
Darifenacin	4	490	308	12.98	(3.54, 33.23)	12.77	(3.37, 32.94)
Solifenacin	238	36,150	31,157	7.64	(6.70, 8.67)	7.81	(6.84, 8.88)
Trospium	77	7,897	5,598	13.75	(10.85, 17.19)	12.65	(9.96, 15.83)
Fesoterodine	12	4,375	2,597	4.62	(2.39, 8.07)	5.07	(2.57, 8.95)
Female, aged ≥ 65 with current exposure to							
Any OAB drug	866	41,488	48,244	17.95	(16.77, 19.19)	17.84	(16.68, 19.07)
Oxybutynin	286	17,810	12,374	23.11	(20.51, 25.95)	21.31	(18.89, 23.95)
Tolterodine	316	16,408	16,327	19.35	(17.28, 21.61)	18.98	(16.94, 21.19)
Darifenacin	3	247	164	18.28	(3.77, 53.43)	19.20	(3.72, 56.67)
Solifenacin	207	17,143	15,885	13.03	(11.32, 14.93)	14.02	(12.16, 16.08)
Trospium	65	4,188	3,147	20.65	(15.94, 26.33)	21.22	(16.37, 27.06)
Fesoterodine	9	1,966	1,208	7.45	(3.41, 14.14)	8.26	(3.69, 15.84)
Female, with high CV risk and with current exposure to							
Any OAB drug	670	33,672	37,680	17.78	(16.46, 19.18)	13.38	(12.32, 14.49)
Oxybutynin	230	14,293	9,698	23.72	(20.75, 26.99)	16.48	(14.23, 18.95)
Tolterodine	242	12,934	12,172	19.88	(17.46, 22.55)	14.85	(12.85, 17.05)
Darifenacin	3	188	126	23.85	(4.92, 69.69)	18.69	(3.66, 55.10)
Solifenacin	153	14,159	12,830	11.93	(10.11, 13.97)	9.73	(8.21, 11.44)
Trospium	50	3,249	2,513	19.90	(14.77, 26.23)	15.60	(11.45, 20.72)
Fesoterodine	8	1,650	1,016	7.88	(3.40, 15.52)	6.79	(2.90, 13.44)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with current exposure to							
Any OAB drug	665	36,179	35,019	18.99	(17.57, 20.49)	17.58	(16.26, 18.97)
Oxybutynin	208	15,575	9,553	21.77	(18.92, 24.94)	20.53	(17.83, 23.53)
Tolterodine	242	14,138	12,427	19.47	(17.10, 22.09)	17.25	(15.13, 19.58)
Darifenacin	2	153	135	14.85	(1.80, 53.64)	11.14	(1.23, 40.58)
Solifenacin	162	12,483	10,385	15.60	(13.29, 18.20)	14.90	(12.69, 17.39)
Trospium	49	3,161	2,250	21.78	(16.11, 28.79)	19.24	(14.20, 25.49)
Fesoterodine	15	1,485	873	17.18	(9.61, 28.33)	17.03	(9.52, 28.11)
Male, aged ≥ 65 years with current exposure to							
Any OAB drug	590	21,481	22,286	26.47	(24.38, 28.70)	26.48	(24.38, 28.70)
Oxybutynin	186	9,020	5,809	32.02	(27.58, 36.97)	31.36	(27.01, 36.21)
Tolterodine	221	8,466	8,260	26.75	(23.34, 30.52)	26.61	(23.22, 30.37)
Darifenacin	2	95	98	20.44	(2.48, 73.85)	19.34	(2.14, 70.45)
Solifenacin	137	7,453	6,502	21.07	(17.69, 24.91)	21.54	(18.07, 25.48)
Trospium	43	2,047	1,460	29.46	(21.32, 39.68)	28.18	(20.37, 37.98)
Fesoterodine	12	875	531	22.59	(11.67, 39.45)	23.70	(12.22, 41.44)
Male, with high CV risk and with current exposure to							
Any OAB drug	534	18,597	19,475	27.42	(25.14, 29.85)	22.96	(20.76, 25.30)
Oxybutynin	175	7,889	5,311	32.95	(28.25, 38.21)	27.81	(23.08, 33.09)
Tolterodine	195	7,183	6,904	28.24	(24.42, 32.50)	23.23	(19.73, 27.11)
Darifenacin	2	78	83	24.04	(2.91, 86.82)	15.21	(1.79, 55.09)
Solifenacin	123	6,503	5,757	21.36	(17.76, 25.49)	18.35	(15.12, 22.03)
Trospium	37	1,705	1,290	28.69	(20.20, 39.54)	21.69	(15.15, 30.06)
Fesoterodine	14	738	466	30.05	(16.43, 50.42)	24.79	(13.19, 42.12)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with current exposure to							
Any OAB drug	2,744	119,912	124,917	21.97	(21.15, 22.80)	19.87	(19.13, 20.63)
Oxybutynin	969	50,473	31,591	30.67	(28.77, 32.67)	25.61	(24.00, 27.30)
Tolterodine	940	46,655	41,541	22.63	(21.20, 24.12)	19.21	(18.00, 20.49)
Darifenacin	7	648	448	15.64	(6.29, 32.22)	16.31	(6.13, 34.38)
Solifenacin	620	48,790	42,039	14.75	(13.61, 15.96)	15.37	(14.18, 16.64)
Trospium	212	11,102	7,981	26.56	(23.11, 30.39)	23.42	(20.35, 26.82)
Fesoterodine	35	5,893	3,503	9.99	(6.96, 13.89)	11.85	(8.21, 16.54)
Overall, aged ≥ 65 years with current exposure to							
Any OAB drug	2,504	63,024	71,807	34.87	(33.52, 36.26)	34.69	(33.35, 36.08)
Oxybutynin	864	26,922	18,502	46.70	(43.63, 49.92)	42.76	(39.94, 45.73)
Tolterodine	886	24,924	25,008	35.43	(33.13, 37.84)	34.59	(32.35, 36.95)
Darifenacin	7	347	267	26.26	(10.56, 54.11)	31.85	(11.96, 67.12)
Solifenacin	559	24,737	22,792	24.53	(22.54, 26.65)	27.01	(24.81, 29.36)
Trospium	191	6,276	4,729	40.39	(34.87, 46.54)	40.27	(34.74, 46.43)
Fesoterodine	31	2,869	1,767	17.54	(11.92, 24.90)	20.77	(14.02, 29.59)
Overall, with high CV risk and with current exposure to							
Any OAB drug	1,963	52,269	58,217	33.72	(32.24, 35.24)	24.77	(23.60, 25.99)
Oxybutynin	698	22,250	15,282	45.67	(42.35, 49.19)	31.58	(29.01, 34.31)
Tolterodine	670	20,141	19,448	34.45	(31.89, 37.16)	23.58	(21.74, 25.52)
Darifenacin	6	269	213	28.20	(10.35, 61.38)	26.32	(9.02, 58.46)
Solifenacin	448	20,760	18,900	23.70	(21.56, 26.00)	19.62	(17.74, 21.62)
Trospium	142	4,987	3,899	36.42	(30.67, 42.92)	27.21	(22.72, 32.29)
Fesoterodine	25	2,409	1,501	16.66	(10.78, 24.59)	14.32	(9.06, 21.43)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with current exposure to							
Any OAB drug	1,656	83,733	89,303	18.54	(17.66, 19.46)	16.60	(15.81, 17.43)
Oxybutynin	583	34,863	21,876	26.65	(24.53, 28.90)	21.24	(19.52, 23.08)
Tolterodine	570	32,504	28,914	19.71	(18.13, 21.40)	16.51	(15.18, 17.94)
Darifenacin	5	493	310	16.15	(5.24, 37.68)	15.03	(4.77, 35.30)
Solifenacin	379	36,261	31,476	12.04	(10.86, 13.32)	12.63	(11.38, 13.98)
Trospium	124	7,922	5,677	21.84	(18.17, 26.04)	19.81	(16.46, 23.63)
Fesoterodine	18	4,399	2,624	6.86	(4.07, 10.84)	8.77	(5.12, 13.97)
Female, aged ≥ 65 with current exposure to							
Any OAB drug	1,516	41,519	49,030	30.92	(29.38, 32.52)	30.60	(29.08, 32.18)
Oxybutynin	520	17,863	12,565	41.38	(37.90, 45.10)	36.70	(33.58, 40.02)
Tolterodine	546	16,443	16,579	32.93	(30.23, 35.81)	31.94	(29.31, 34.74)
Darifenacin	5	250	165	30.23	(9.82, 70.54)	30.87	(9.80, 72.49)
Solifenacin	339	17,241	16,146	21.00	(18.82, 23.35)	23.28	(20.85, 25.91)
Trospium	111	4,209	3,220	34.48	(28.36, 41.52)	35.91	(29.53, 43.26)
Fesoterodine	17	1,987	1,230	13.82	(8.05, 22.12)	17.28	(9.93, 27.86)
Female, with high CV risk and with current exposure to							
Any OAB drug	1,137	33,672	38,282	29.70	(28.00, 31.48)	21.39	(20.09, 22.75)
Oxybutynin	400	14,332	9,857	40.58	(36.70, 44.76)	26.66	(23.85, 29.69)
Tolterodine	392	12,950	12,372	31.68	(28.62, 34.98)	20.87	(18.76, 23.13)
Darifenacin	4	189	126	31.68	(8.63, 81.11)	26.33	(6.91, 67.96)
Solifenacin	267	14,224	13,018	20.51	(18.12, 23.12)	17.16	(15.04, 19.48)
Trospium	79	3,266	2,563	30.82	(24.40, 38.41)	24.03	(18.84, 30.18)
Fesoterodine	9	1,664	1,030	8.74	(4.00, 16.59)	8.49	(3.76, 16.31)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV2g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with current exposure to							
Any OAB drug	1,088	36,179	35,614	30.55	(28.76, 32.42)	28.12	(26.47, 29.85)
Oxybutynin	386	15,610	9,714	39.74	(35.87, 43.90)	36.66	(33.08, 40.51)
Tolterodine	370	14,151	12,627	29.30	(26.39, 32.45)	26.03	(23.42, 28.85)
Darifenacin	2	155	138	14.49	(1.76, 52.36)	19.55	(1.08, 74.45)
Solifenacin	241	12,529	10,564	22.81	(20.02, 25.88)	22.29	(19.55, 25.30)
Trospium	88	3,180	2,304	38.20	(30.64, 47.07)	32.53	(26.03, 40.16)
Fesoterodine	17	1,494	879	19.34	(11.26, 30.96)	19.62	(11.41, 31.45)
Male, aged ≥ 65 years with current exposure to							
Any OAB drug	988	21,505	22,777	43.38	(40.71, 46.17)	43.43	(40.76, 46.22)
Oxybutynin	344	9,059	5,937	57.94	(51.98, 64.40)	55.71	(49.97, 61.93)
Tolterodine	340	8,481	8,429	40.34	(36.16, 44.86)	40.25	(36.08, 44.77)
Darifenacin	2	97	101	19.78	(2.40, 71.44)	33.94	(1.87, 129.3)
Solifenacin	220	7,496	6,646	33.10	(28.87, 37.78)	34.98	(30.50, 39.94)
Trospium	80	2,067	1,509	53.01	(42.04, 65.98)	49.58	(39.26, 61.76)
Fesoterodine	14	882	537	26.08	(14.26, 43.76)	28.21	(15.38, 47.38)
Male, with high CV risk and with current exposure to							
Any OAB drug	826	18,597	19,935	41.44	(38.66, 44.36)	33.32	(30.83, 35.95)
Oxybutynin	298	7,918	5,425	54.93	(48.87, 61.53)	44.02	(38.46, 50.07)
Tolterodine	278	7,191	7,075	39.29	(34.81, 44.19)	30.43	(26.82, 34.37)
Darifenacin	2	80	87	23.12	(2.80, 83.52)	26.30	(1.10, 101.2)
Solifenacin	181	6,536	5,883	30.77	(26.45, 35.59)	25.81	(22.04, 30.01)
Trospium	63	1,721	1,336	47.15	(36.23, 60.33)	35.22	(26.87, 45.29)
Fesoterodine	16	745	471	33.98	(19.42, 55.18)	29.07	(16.14, 47.88)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Number of prescriptions							
0	1,143	78,205	241,890	4.73	(4.46, 5.01)	4.90	(4.62, 5.19)
1	28	50,440	4,431	6.32	(4.20, 9.13)	6.48	(4.30, 9.38)
2-3	39	27,972	4,376	8.91	(6.34, 12.18)	8.36	(5.93, 11.44)
4-5	20	17,790	2,978	6.72	(4.10, 10.37)	5.78	(3.52, 8.94)
6-9	32	13,855	4,288	7.46	(5.10, 10.54)	6.60	(4.48, 9.36)
10+	95	9,970	15,347	6.19	(5.01, 7.57)	5.00	(4.02, 6.14)
Cumulative duration							
0 days	1,143	78,205	241,890	4.73	(4.46, 5.01)	4.90	(4.62, 5.19)
1 - 45 days	43	50,440	5,548	7.75	(5.61, 10.44)	7.60	(5.50, 10.24)
46 - 180 days	61	29,178	7,070	8.63	(6.60, 11.08)	7.72	(5.89, 9.94)
181 - 365 days	35	13,605	5,460	6.41	(4.47, 8.92)	5.42	(3.75, 7.57)
> 365 days	75	8,582	13,342	5.62	(4.42, 7.05)	4.62	(3.61, 5.82)
Time since first exposure							
0 days	1,143	78,205	241,890	4.73	(4.46, 5.01)	4.90	(4.62, 5.19)
1 - 45 days	41	50,440	5,274	7.77	(5.58, 10.55)	7.67	(5.50, 10.41)
46 - 180 days	49	26,316	5,279	9.28	(6.87, 12.27)	8.41	(6.19, 11.16)
181 - 365 days	34	15,364	4,624	7.35	(5.09, 10.27)	6.08	(4.20, 8.51)
> 365 days	90	13,515	16,243	5.54	(4.46, 6.81)	4.66	(3.72, 5.75)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Number of prescriptions							
0	1,016	81,003	207,148	4.90	(4.61, 5.22)	5.01	(4.70, 5.33)
1	27	46,641	4,231	6.38	(4.21, 9.28)	6.82	(4.48, 9.95)
2-3	30	28,063	4,916	6.10	(4.12, 8.71)	5.85	(3.94, 8.37)
4-5	15	19,083	3,606	4.16	(2.33, 6.86)	3.79	(2.10, 6.27)
6-9	33	15,432	5,475	6.03	(4.15, 8.46)	5.37	(3.69, 7.55)
10+	136	11,526	23,064	5.90	(4.95, 6.97)	4.70	(3.94, 5.57)
Cumulative duration							
0 days	1,016	81,003	207,148	4.90	(4.61, 5.22)	5.01	(4.70, 5.33)
1 - 45 days	32	46,641	5,230	6.12	(4.18, 8.64)	6.21	(4.24, 8.78)
46 - 180 days	53	29,880	7,786	6.81	(5.10, 8.90)	6.23	(4.66, 8.15)
181 - 365 days	34	15,921	6,594	5.16	(3.57, 7.21)	4.39	(3.04, 6.15)
> 365 days	122	10,847	21,681	5.63	(4.67, 6.72)	4.55	(3.77, 5.44)
Time since first exposure							
0 days	1,016	81,003	207,148	4.90	(4.61, 5.22)	5.01	(4.70, 5.33)
1 - 45 days	31	46,641	5,005	6.19	(4.21, 8.79)	6.33	(4.29, 8.99)
46 - 180 days	40	27,457	6,139	6.52	(4.65, 8.87)	5.90	(4.21, 8.05)
181 - 365 days	34	16,956	5,676	5.99	(4.15, 8.37)	5.14	(3.55, 7.18)
> 365 days	136	15,018	24,471	5.56	(4.66, 6.57)	4.56	(3.82, 5.40)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Number of prescriptions							
0	1,976	119,754	394,995	5.00	(4.78, 5.23)	5.03	(4.81, 5.25)
1	1	647	54	18.46	(0.47, 102.83)	15.48	(0.39, 86.24)
2-3	0	442	68	0.00	(0.00, 54.43)	0.00	not estimable
4-5	0	289	48	0.00	(0.00, 77.49)	0.00	not estimable
6-9	0	214	67	0.00	(0.00, 54.98)	0.00	not estimable
10+	0	145	211	0.00	(0.00, 17.50)	0.00	not estimable
Cumulative duration							
0 days	1,976	119,754	394,995	5.00	(4.78, 5.23)	5.03	(4.81, 5.25)
1 - 45 days	1	647	74	13.58	(0.34, 75.67)	11.71	(0.30, 65.27)
46 - 180 days	0	449	111	0.00	(0.00, 33.25)	0.00	not estimable
181 - 365 days	0	211	80	0.00	(0.00, 46.26)	0.00	not estimable
> 365 days	0	122	183	0.00	(0.00, 20.15)	0.00	not estimable
Time since first exposure							
0 days	1,976	119,754	394,995	5.00	(4.78, 5.23)	5.03	(4.81, 5.25)
1 - 45 days	1	647	71	14.10	(0.36, 78.59)	12.17	(0.31, 67.81)
46 - 180 days	0	435	97	0.00	(0.00, 38.23)	0.00	not estimable
181 - 365 days	0	235	77	0.00	(0.00, 48.02)	0.00	not estimable
> 365 days	0	154	203	0.00	(0.00, 18.15)	0.00	not estimable

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Number of prescriptions							
0	1,472	86,623	270,580	5.44	(5.17, 5.73)	5.29	(5.02, 5.57)
1	20	48,718	4,425	4.52	(2.76, 6.98)	5.23	(3.16, 8.11)
2-3	27	32,678	5,693	4.74	(3.13, 6.90)	5.30	(3.46, 7.75)
4-5	19	23,056	4,294	4.43	(2.66, 6.91)	4.76	(2.83, 7.47)
6-9	24	18,524	6,450	3.72	(2.38, 5.54)	3.80	(2.42, 5.67)
10+	75	13,614	20,962	3.58	(2.81, 4.48)	3.47	(2.72, 4.36)
Cumulative duration							
0 days	1,472	86,623	270,580	5.44	(5.17, 5.73)	5.29	(5.02, 5.57)
1 - 45 days	26	48,718	5,601	4.64	(3.03, 6.80)	5.24	(3.41, 7.70)
46 - 180 days	40	33,641	9,208	4.34	(3.10, 5.92)	4.48	(3.19, 6.11)
181 - 365 days	36	19,143	7,854	4.58	(3.21, 6.35)	4.76	(3.32, 6.60)
> 365 days	63	12,629	19,162	3.29	(2.53, 4.21)	3.23	(2.48, 4.15)
Time since first exposure							
0 days	1,472	86,623	270,580	5.44	(5.17, 5.73)	5.29	(5.02, 5.57)
1 - 45 days	25	48,718	5,402	4.63	(2.99, 6.83)	5.24	(3.38, 7.76)
46 - 180 days	33	31,320	7,427	4.44	(3.06, 6.24)	4.55	(3.12, 6.40)
181 - 365 days	29	20,404	6,923	4.19	(2.81, 6.02)	4.39	(2.93, 6.32)
> 365 days	78	16,949	22,071	3.53	(2.79, 4.41)	3.47	(2.74, 4.35)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Number of prescriptions							
0	1,755	113,633	356,422	4.92	(4.70, 5.16)	4.97	(4.74, 5.21)
1	5	11,088	984	5.08	(1.65, 11.85)	5.34	(1.72, 12.48)
2-3	10	6,587	1,062	9.42	(4.52, 17.32)	9.45	(4.49, 17.45)
4-5	4	4,261	725	5.52	(1.50, 14.13)	4.96	(1.32, 12.74)
6-9	8	3,319	1,055	7.58	(3.27, 14.94)	6.90	(2.97, 13.63)
10+	22	2,396	4,101	5.36	(3.36, 8.12)	4.45	(2.77, 6.76)
Cumulative duration							
0 days	1,755	113,633	356,422	4.92	(4.70, 5.16)	4.97	(4.74, 5.21)
1 - 45 days	8	11,088	1,240	6.45	(2.78, 12.71)	6.45	(2.78, 12.71)
46 - 180 days	15	6,740	1,702	8.81	(4.93, 14.53)	8.36	(4.65, 13.83)
181 - 365 days	6	3,299	1,330	4.51	(1.66, 9.82)	3.95	(1.43, 8.63)
> 365 days	20	2,146	3,654	5.47	(3.34, 8.45)	4.60	(2.80, 7.13)
Time since first exposure							
0 days	1,755	113,633	356,422	4.92	(4.70, 5.16)	4.97	(4.74, 5.21)
1 - 45 days	8	11,088	1,190	6.72	(2.90, 13.25)	6.73	(2.90, 13.27)
46 - 180 days	11	6,335	1,373	8.01	(4.00, 14.34)	7.60	(3.75, 13.67)
181 - 365 days	9	3,697	1,168	7.71	(3.52, 14.63)	6.92	(3.15, 13.17)
> 365 days	21	2,932	4,196	5.00	(3.10, 7.65)	4.20	(2.58, 6.43)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Number of prescriptions							
0	1,938	117,556	386,852	5.01	(4.79, 5.24)	5.02	(4.80, 5.25)
1	2	5,879	510	3.92	(0.47, 14.17)	4.66	(0.56, 16.85)
2-3	1	3,861	629	1.59	(0.04, 8.86)	1.48	(0.04, 8.22)
4-5	1	2,571	459	2.18	(0.06, 12.13)	2.40	(0.06, 13.39)
6-9	0	1,967	638	0.00	(0.00, 5.79)	0.00	not estimable
10+	9	1,284	1,256	7.17	(3.28, 13.61)	7.15	(3.22, 13.66)
Cumulative duration							
0 days	1,938	117,556	386,852	5.01	(4.79, 5.24)	5.02	(4.80, 5.25)
1 - 45 days	2	5,879	664	3.01	(0.36, 10.88)	3.44	(0.42, 12.43)
46 - 180 days	2	3,946	1,014	1.97	(0.24, 7.13)	2.02	(0.24, 7.34)
181 - 365 days	3	1,998	764	3.93	(0.81, 11.47)	4.54	(0.90, 13.37)
> 365 days	6	1,140	1,049	5.72	(2.10, 12.45)	5.26	(1.90, 11.51)
Time since first exposure							
0 days	1,938	117,556	386,852	5.01	(4.79, 5.24)	5.02	(4.80, 5.25)
1 - 45 days	2	5,879	640	3.12	(0.38, 11.28)	3.56	(0.43, 12.87)
46 - 180 days	2	3,813	879	2.28	(0.28, 8.22)	2.35	(0.27, 8.52)
181 - 365 days	3	2,245	734	4.09	(0.84, 11.94)	4.80	(0.94, 14.12)
> 365 days	6	1,506	1,238	4.85	(1.78, 10.55)	4.53	(1.63, 9.90)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Number of prescriptions							
0	1,222	78,205	241,842	5.05	(4.77, 5.34)	5.27	(4.98, 5.58)
1	38	50,410	4,428	8.58	(6.07, 11.78)	8.71	(6.16, 11.96)
2-3	24	27,933	4,370	5.49	(3.52, 8.17)	5.12	(3.27, 7.62)
4-5	24	17,745	2,971	8.08	(5.18, 12.02)	6.88	(4.40, 10.24)
6-9	33	13,815	4,278	7.71	(5.31, 10.83)	6.60	(4.52, 9.29)
10+	132	9,950	15,320	8.62	(7.21, 10.22)	6.64	(5.52, 7.90)
Cumulative duration							
0 days	1,222	78,205	241,842	5.05	(4.77, 5.34)	5.27	(4.98, 5.58)
1 - 45 days	44	50,410	5,543	7.94	(5.77, 10.66)	7.84	(5.69, 10.53)
46 - 180 days	56	29,138	7,055	7.94	(6.00, 10.31)	6.92	(5.21, 8.99)
181 - 365 days	40	13,559	5,445	7.35	(5.25, 10.00)	5.86	(4.17, 8.00)
> 365 days	111	8,564	13,324	8.33	(6.85, 10.03)	6.62	(5.42, 8.00)
Time since first exposure							
0 days	1,222	78,205	241,842	5.05	(4.77, 5.34)	5.27	(4.98, 5.58)
1 - 45 days	42	50,410	5,270	7.97	(5.74, 10.77)	7.88	(5.68, 10.66)
46 - 180 days	42	26,285	5,272	7.97	(5.74, 10.77)	6.83	(4.91, 9.25)
181 - 365 days	39	15,326	4,616	8.45	(6.01, 11.55)	6.77	(4.80, 9.27)
> 365 days	128	13,480	16,209	7.90	(6.59, 9.39)	6.37	(5.29, 7.60)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Number of prescriptions							
0	1,159	81,003	206,925	5.60	(5.28, 5.93)	5.74	(5.42, 6.08)
1	32	46,628	4,230	7.57	(5.18, 10.68)	8.08	(5.51, 11.43)
2-3	29	28,047	4,913	5.90	(3.95, 8.48)	5.88	(3.92, 8.45)
4-5	19	19,068	3,602	5.27	(3.18, 8.24)	4.87	(2.92, 7.63)
6-9	36	15,418	5,470	6.58	(4.61, 9.11)	5.90	(4.11, 8.20)
10+	183	11,509	23,036	7.94	(6.83, 9.18)	6.52	(5.58, 7.56)
Cumulative duration							
0 days	1,159	81,003	206,925	5.60	(5.28, 5.93)	5.74	(5.42, 6.08)
1 - 45 days	42	46,628	5,227	8.03	(5.79, 10.86)	8.19	(5.89, 11.08)
46 - 180 days	45	29,862	7,781	5.78	(4.22, 7.74)	5.44	(3.96, 7.29)
181 - 365 days	52	15,912	6,588	7.89	(5.89, 10.35)	6.64	(4.95, 8.72)
> 365 days	160	10,825	21,655	7.39	(6.29, 8.63)	6.21	(5.26, 7.28)
Time since first exposure							
0 days	1,159	81,003	206,925	5.60	(5.28, 5.93)	5.74	(5.42, 6.08)
1 - 45 days	41	46,628	5,002	8.20	(5.88, 11.12)	8.39	(6.01, 11.39)
46 - 180 days	34	27,439	6,136	5.54	(3.84, 7.74)	5.22	(3.60, 7.31)
181 - 365 days	48	16,947	5,672	8.46	(6.24, 11.22)	7.29	(5.35, 9.70)
> 365 days	176	14,991	24,440	7.20	(6.18, 8.35)	6.07	(5.19, 7.05)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Number of prescriptions							
0	2,172	119,754	394,719	5.50	(5.27, 5.74)	5.54	(5.31, 5.78)
1	0	644	54	0.00	(0.00, 68.08)	0.00	not estimable
2-3	0	439	67	0.00	(0.00, 54.76)	0.00	not estimable
4-5	0	285	47	0.00	(0.00, 78.17)	0.00	not estimable
6-9	0	210	66	0.00	(0.00, 55.55)	0.00	not estimable
10+	3	142	208	14.42	(2.97, 42.15)	8.60	(1.63, 25.48)
Cumulative duration							
0 days	2,172	119,754	394,719	5.50	(5.27, 5.74)	5.54	(5.31, 5.78)
1 - 45 days	0	644	73	0.00	(0.00, 50.31)	0.00	not estimable
46 - 180 days	0	446	110	0.00	(0.00, 33.57)	0.00	not estimable
181 - 365 days	0	209	79	0.00	(0.00, 46.58)	0.00	not estimable
> 365 days	3	122	181	16.60	(3.42, 48.51)	9.92	(1.87, 29.39)
Time since first exposure							
0 days	2,172	119,754	394,719	5.50	(5.27, 5.74)	5.54	(5.31, 5.78)
1 - 45 days	0	644	71	0.00	(0.00, 52.27)	0.00	not estimable
46 - 180 days	0	432	96	0.00	(0.00, 38.53)	0.00	not estimable
181 - 365 days	0	233	76	0.00	(0.00, 48.45)	0.00	not estimable
> 365 days	3	152	201	14.95	(3.08, 43.69)	9.20	(1.77, 27.18)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Number of prescriptions							
0	1,594	86,623	270,396	5.90	(5.61, 6.19)	5.77	(5.49, 6.06)
1	15	48,703	4,424	3.39	(1.90, 5.59)	4.11	(2.28, 6.81)
2-3	39	32,658	5,688	6.86	(4.88, 9.37)	7.68	(5.43, 10.54)
4-5	21	23,031	4,290	4.89	(3.03, 7.48)	5.21	(3.19, 8.00)
6-9	26	18,503	6,448	4.03	(2.63, 5.91)	4.18	(2.71, 6.15)
10+	111	13,600	20,901	5.31	(4.37, 6.40)	5.07	(4.16, 6.13)
Cumulative duration							
0 days	1,594	86,623	270,396	5.90	(5.61, 6.19)	5.77	(5.49, 6.06)
1 - 45 days	25	48,703	5,599	4.47	(2.89, 6.59)	5.05	(3.26, 7.47)
46 - 180 days	55	33,619	9,197	5.98	(4.51, 7.78)	6.27	(4.71, 8.17)
181 - 365 days	34	19,120	7,843	4.34	(3.00, 6.06)	4.32	(2.98, 6.05)
> 365 days	98	12,611	19,113	5.13	(4.16, 6.25)	5.06	(4.09, 6.19)
Time since first exposure							
0 days	1,594	86,623	270,396	5.90	(5.61, 6.19)	5.77	(5.49, 6.06)
1 - 45 days	24	48,703	5,400	4.44	(2.85, 6.61)	5.00	(3.19, 7.45)
46 - 180 days	49	31,296	7,419	6.60	(4.89, 8.73)	6.96	(5.13, 9.22)
181 - 365 days	29	20,384	6,918	4.19	(2.81, 6.02)	4.11	(2.75, 5.92)
> 365 days	110	16,925	22,015	5.00	(4.11, 6.02)	4.97	(4.07, 6.01)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Number of prescriptions							
0	1,953	113,633	356,150	5.48	(5.24, 5.73)	5.55	(5.30, 5.80)
1	6	11,071	983	6.10	(2.24, 13.28)	6.14	(2.23, 13.40)
2-3	11	6,570	1,060	10.38	(5.18, 18.57)	9.72	(4.83, 17.44)
4-5	6	4,249	724	8.29	(3.04, 18.05)	7.40	(2.69, 16.16)
6-9	5	3,307	1,053	4.75	(1.54, 11.09)	4.90	(1.55, 11.50)
10+	29	2,389	4,083	7.10	(4.76, 10.20)	5.99	(4.00, 8.63)
Cumulative duration							
0 days	1,953	113,633	356,150	5.48	(5.24, 5.73)	5.55	(5.30, 5.80)
1 - 45 days	7	11,071	1,238	5.65	(2.27, 11.65)	5.55	(2.22, 11.46)
46 - 180 days	18	6,724	1,698	10.60	(6.28, 16.75)	9.58	(5.66, 15.16)
181 - 365 days	6	3,293	1,328	4.52	(1.66, 9.83)	4.44	(1.58, 9.76)
> 365 days	26	2,141	3,638	7.15	(4.67, 10.47)	6.09	(3.96, 8.94)
Time since first exposure							
0 days	1,953	113,633	356,150	5.48	(5.24, 5.73)	5.55	(5.30, 5.80)
1 - 45 days	7	11,071	1,188	5.89	(2.37, 12.14)	5.79	(2.31, 11.95)
46 - 180 days	16	6,319	1,369	11.69	(6.68, 18.98)	10.42	(5.93, 16.95)
181 - 365 days	6	3,688	1,165	5.15	(1.89, 11.21)	4.88	(1.77, 10.66)
> 365 days	28	2,927	4,180	6.70	(4.45, 9.68)	5.88	(3.88, 8.53)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Number of prescriptions							
0	2,146	117,556	386,584	5.55	(5.32, 5.79)	5.57	(5.34, 5.81)
1	0	5,874	510	0.00	(0.00, 7.24)	0.00	not estimable
2-3	1	3,856	628	1.59	(0.04, 8.87)	1.47	(0.04, 8.21)
4-5	1	2,562	458	2.18	(0.06, 12.17)	2.04	(0.05, 11.36)
6-9	4	1,957	634	6.31	(1.72, 16.15)	6.73	(1.83, 17.22)
10+	5	1,273	1,253	3.99	(1.30, 9.31)	4.37	(1.40, 10.22)
Cumulative duration							
0 days	2,146	117,556	386,584	5.55	(5.32, 5.79)	5.57	(5.34, 5.81)
1 - 45 days	1	5,874	663	1.51	(0.04, 8.40)	1.41	(0.04, 7.84)
46 - 180 days	3	3,939	1,011	2.97	(0.61, 8.67)	3.23	(0.67, 9.45)
181 - 365 days	3	1,987	759	3.95	(0.81, 11.55)	4.12	(0.84, 12.04)
> 365 days	4	1,134	1,049	3.81	(1.04, 9.76)	4.44	(1.19, 11.41)
Time since first exposure							
0 days	2,146	117,556	386,584	5.55	(5.32, 5.79)	5.57	(5.34, 5.81)
1 - 45 days	1	5,874	640	1.56	(0.04, 8.71)	1.46	(0.04, 8.11)
46 - 180 days	3	3,806	876	3.42	(0.71, 10.01)	3.70	(0.76, 10.81)
181 - 365 days	3	2,234	730	4.11	(0.85, 12.02)	4.32	(0.88, 12.63)
> 365 days	4	1,498	1,237	3.23	(0.88, 8.28)	3.75	(1.00, 9.65)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Number of prescriptions							
0	615	78,205	243,482	2.53	(2.33, 2.73)	2.64	(2.44, 2.86)
1	16	50,473	4,435	3.61	(2.06, 5.86)	3.61	(2.06, 5.87)
2-3	26	28,015	4,384	5.93	(3.87, 8.69)	5.47	(3.57, 8.03)
4-5	10	17,829	2,985	3.35	(1.61, 6.16)	2.79	(1.34, 5.14)
6-9	19	13,894	4,303	4.42	(2.66, 6.90)	3.80	(2.26, 5.96)
10+	65	10,023	15,485	4.20	(3.24, 5.35)	3.23	(2.48, 4.14)
Cumulative duration							
0 days	615	78,205	243,482	2.53	(2.33, 2.73)	2.64	(2.44, 2.86)
1 - 45 days	27	50,473	5,554	4.86	(3.20, 7.07)	4.67	(3.08, 6.80)
46 - 180 days	41	29,225	7,087	5.79	(4.15, 7.85)	5.07	(3.62, 6.89)
181 - 365 days	19	13,644	5,483	3.47	(2.09, 5.41)	2.79	(1.67, 4.38)
> 365 days	49	8,630	13,467	3.64	(2.69, 4.81)	2.82	(2.08, 3.75)
Time since first exposure							
0 days	615	78,205	243,482	2.53	(2.33, 2.73)	2.64	(2.44, 2.86)
1 - 45 days	27	50,473	5,279	5.11	(3.37, 7.44)	4.91	(3.24, 7.15)
46 - 180 days	36	26,345	5,288	6.81	(4.77, 9.42)	5.95	(4.14, 8.26)
181 - 365 days	18	15,400	4,641	3.88	(2.30, 6.13)	3.19	(1.88, 5.05)
> 365 days	55	13,585	16,383	3.36	(2.53, 4.37)	2.62	(1.96, 3.42)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Number of prescriptions							
0	580	81,003	208,308	2.78	(2.56, 3.02)	2.83	(2.60, 3.07)
1	9	46,655	4,233	2.13	(0.97, 4.04)	2.30	(1.04, 4.38)
2-3	17	28,095	4,923	3.45	(2.01, 5.53)	3.31	(1.92, 5.31)
4-5	8	19,125	3,614	2.21	(0.96, 4.36)	2.01	(0.86, 3.98)
6-9	19	15,479	5,494	3.46	(2.08, 5.40)	3.00	(1.80, 4.69)
10+	80	11,570	23,277	3.44	(2.73, 4.28)	2.57	(2.04, 3.20)
Cumulative duration							
0 days	580	81,003	208,308	2.78	(2.56, 3.02)	2.83	(2.60, 3.07)
1 - 45 days	14	46,655	5,233	2.68	(1.46, 4.49)	2.67	(1.45, 4.48)
46 - 180 days	28	29,916	7,803	3.59	(2.38, 5.19)	3.24	(2.15, 4.69)
181 - 365 days	23	15,972	6,620	3.47	(2.20, 5.21)	2.92	(1.85, 4.38)
> 365 days	68	10,892	21,885	3.11	(2.41, 3.94)	2.38	(1.85, 3.02)
Time since first exposure							
0 days	580	81,003	208,308	2.78	(2.56, 3.02)	2.83	(2.60, 3.07)
1 - 45 days	13	46,655	5,008	2.60	(1.38, 4.44)	2.61	(1.38, 4.47)
46 - 180 days	20	27,482	6,148	3.25	(1.99, 5.02)	2.93	(1.78, 4.53)
181 - 365 days	21	16,997	5,694	3.69	(2.28, 5.64)	3.07	(1.90, 4.70)
> 365 days	79	15,072	24,691	3.20	(2.53, 3.99)	2.50	(1.98, 3.12)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Number of prescriptions							
0	1,121	119,754	397,669	2.82	(2.66, 2.99)	2.82	(2.66, 2.99)
1	0	648	54	0.00	(0.00, 67.88)	0.00	not estimable
2-3	1	443	68	14.73	(0.37, 82.09)	15.10	(0.38, 84.12)
4-5	0	289	48	0.00	(0.00, 77.49)	0.00	not estimable
6-9	1	214	67	14.90	(0.38, 83.04)	19.33	(0.49, 107.68)
10+	0	145	211	0.00	(0.00, 17.50)	0.00	not estimable
Cumulative duration							
0 days	1,121	119,754	397,669	2.82	(2.66, 2.99)	2.82	(2.66, 2.99)
1 - 45 days	1	648	74	13.55	(0.34, 75.48)	12.68	(0.32, 70.64)
46 - 180 days	0	450	111	0.00	(0.00, 33.23)	0.00	not estimable
181 - 365 days	1	211	80	12.54	(0.32, 69.86)	16.93	(0.43, 94.35)
> 365 days	0	122	183	0.00	(0.00, 20.15)	0.00	not estimable
Time since first exposure							
0 days	1,121	119,754	397,669	2.82	(2.66, 2.99)	2.82	(2.66, 2.99)
1 - 45 days	1	648	71	14.07	(0.36, 78.41)	13.09	(0.33, 72.92)
46 - 180 days	0	436	97	0.00	(0.00, 38.19)	0.00	not estimable
181 - 365 days	1	235	77	13.02	(0.33, 72.53)	16.67	(0.42, 92.91)
> 365 days	0	154	203	0.00	(0.00, 18.15)	0.00	not estimable

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Number of prescriptions							
0	897	86,623	272,485	3.29	(3.08, 3.51)	3.16	(2.96, 3.37)
1	8	48,790	4,432	1.81	(0.78, 3.56)	2.18	(0.92, 4.32)
2-3	13	32,746	5,705	2.28	(1.21, 3.90)	2.56	(1.35, 4.40)
4-5	6	23,124	4,307	1.39	(0.51, 3.03)	1.50	(0.54, 3.29)
6-9	6	18,596	6,478	0.93	(0.34, 2.02)	1.00	(0.36, 2.20)
10+	29	13,689	21,117	1.37	(0.92, 1.97)	1.28	(0.86, 1.84)
Cumulative duration							
0 days	897	86,623	272,485	3.29	(3.08, 3.51)	3.16	(2.96, 3.37)
1 - 45 days	14	48,790	5,611	2.50	(1.36, 4.19)	2.88	(1.56, 4.84)
46 - 180 days	14	33,712	9,234	1.52	(0.83, 2.54)	1.57	(0.86, 2.64)
181 - 365 days	12	19,216	7,889	1.52	(0.79, 2.66)	1.55	(0.80, 2.72)
> 365 days	22	12,696	19,306	1.14	(0.71, 1.73)	1.09	(0.68, 1.65)
Time since first exposure							
0 days	897	86,623	272,485	3.29	(3.08, 3.51)	3.16	(2.96, 3.37)
1 - 45 days	13	48,790	5,411	2.40	(1.28, 4.11)	2.79	(1.48, 4.79)
46 - 180 days	12	31,378	7,444	1.61	(0.83, 2.82)	1.65	(0.85, 2.89)
181 - 365 days	9	20,471	6,950	1.29	(0.59, 2.46)	1.31	(0.59, 2.48)
> 365 days	28	17,031	22,234	1.26	(0.84, 1.82)	1.22	(0.81, 1.77)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Number of prescriptions							
0	995	113,633	358,729	2.77	(2.60, 2.95)	2.79	(2.62, 2.97)
1	4	11,102	986	4.06	(1.11, 10.39)	3.95	(1.07, 10.12)
2-3	5	6,598	1,064	4.70	(1.53, 10.96)	4.34	(1.39, 10.16)
4-5	3	4,277	728	4.12	(0.85, 12.05)	3.82	(0.76, 11.24)
6-9	5	3,329	1,059	4.72	(1.53, 11.02)	4.05	(1.30, 9.46)
10+	14	2,406	4,144	3.38	(1.85, 5.67)	2.80	(1.50, 4.75)
Cumulative duration							
0 days	995	113,633	358,729	2.77	(2.60, 2.95)	2.79	(2.62, 2.97)
1 - 45 days	6	11,102	1,242	4.83	(1.77, 10.51)	4.65	(1.70, 10.14)
46 - 180 days	7	6,754	1,708	4.10	(1.65, 8.45)	3.54	(1.41, 7.32)
181 - 365 days	4	3,313	1,336	2.99	(0.82, 7.67)	2.39	(0.64, 6.13)
> 365 days	14	2,157	3,695	3.79	(2.07, 6.36)	3.24	(1.75, 5.48)
Time since first exposure							
0 days	995	113,633	358,729	2.77	(2.60, 2.95)	2.79	(2.62, 2.97)
1 - 45 days	6	11,102	1,191	5.04	(1.85, 10.96)	4.84	(1.77, 10.55)
46 - 180 days	7	6,346	1,377	5.08	(2.04, 10.48)	4.40	(1.76, 9.10)
181 - 365 days	3	3,709	1,172	2.56	(0.53, 7.48)	2.06	(0.41, 6.05)
> 365 days	15	2,948	4,241	3.54	(1.98, 5.83)	3.04	(1.68, 5.05)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Number of prescriptions							
0	1,110	117,556	389,485	2.85	(2.68, 3.02)	2.84	(2.67, 3.01)
1	1	5,893	511	1.96	(0.05, 10.90)	2.29	(0.06, 12.74)
2-3	1	3,872	630	1.59	(0.04, 8.84)	1.56	(0.04, 8.68)
4-5	2	2,575	460	4.35	(0.53, 15.70)	5.35	(0.62, 19.42)
6-9	1	1,971	640	1.56	(0.04, 8.71)	1.64	(0.04, 9.11)
10+	4	1,286	1,262	3.17	(0.86, 8.12)	3.37	(0.89, 8.69)
Cumulative duration							
0 days	1,110	117,556	389,485	2.85	(2.68, 3.02)	2.84	(2.67, 3.01)
1 - 45 days	1	5,893	666	1.50	(0.04, 8.37)	1.72	(0.04, 9.59)
46 - 180 days	3	3,956	1,016	2.95	(0.61, 8.63)	3.45	(0.70, 10.12)
181 - 365 days	3	2,003	766	3.92	(0.81, 11.44)	4.54	(0.90, 13.37)
> 365 days	2	1,143	1,056	1.89	(0.23, 6.84)	1.75	(0.21, 6.33)
Time since first exposure							
0 days	1,110	117,556	389,485	2.85	(2.68, 3.02)	2.84	(2.67, 3.01)
1 - 45 days	1	5,893	642	1.56	(0.04, 8.68)	1.78	(0.05, 9.93)
46 - 180 days	3	3,822	881	3.41	(0.70, 9.96)	3.93	(0.80, 11.52)
181 - 365 days	3	2,249	736	4.08	(0.84, 11.92)	4.79	(0.94, 14.12)
> 365 days	2	1,511	1,245	1.61	(0.19, 5.80)	1.49	(0.18, 5.38)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Number of prescriptions							
0	534	78,205	243,482	2.19	(2.01, 2.39)	2.31	(2.12, 2.52)
1	9	50,473	4,435	2.03	(0.93, 3.85)	2.08	(0.95, 3.96)
2-3	9	28,015	4,384	2.05	(0.94, 3.90)	1.99	(0.90, 3.79)
4-5	10	17,829	2,985	3.35	(1.61, 6.16)	2.80	(1.34, 5.15)
6-9	12	13,894	4,303	2.79	(1.44, 4.87)	2.29	(1.18, 4.00)
10+	72	10,023	15,485	4.65	(3.64, 5.86)	3.45	(2.68, 4.37)
Cumulative duration							
0 days	534	78,205	243,482	2.19	(2.01, 2.39)	2.31	(2.12, 2.52)
1 - 45 days	11	50,473	5,554	1.98	(0.99, 3.54)	1.92	(0.96, 3.44)
46 - 180 days	23	29,225	7,087	3.25	(2.06, 4.87)	2.83	(1.78, 4.26)
181 - 365 days	26	13,644	5,483	4.74	(3.10, 6.95)	3.63	(2.36, 5.33)
> 365 days	52	8,630	13,467	3.86	(2.88, 5.06)	2.95	(2.18, 3.89)
Time since first exposure							
0 days	534	78,205	243,482	2.19	(2.01, 2.39)	2.31	(2.12, 2.52)
1 - 45 days	11	50,473	5,279	2.08	(1.04, 3.73)	2.03	(1.01, 3.63)
46 - 180 days	19	26,345	5,288	3.59	(2.16, 5.61)	3.15	(1.88, 4.95)
181 - 365 days	24	15,400	4,641	5.17	(3.31, 7.70)	3.97	(2.54, 5.92)
> 365 days	58	13,585	16,383	3.54	(2.69, 4.58)	2.73	(2.05, 3.55)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Number of prescriptions							
0	548	81,003	208,308	2.63	(2.42, 2.86)	2.67	(2.46, 2.91)
1	5	46,655	4,233	1.18	(0.38, 2.76)	1.33	(0.42, 3.12)
2-3	11	28,095	4,923	2.23	(1.12, 4.00)	2.17	(1.08, 3.90)
4-5	6	19,125	3,614	1.66	(0.61, 3.61)	1.67	(0.61, 3.65)
6-9	17	15,479	5,494	3.09	(1.80, 4.95)	2.74	(1.59, 4.39)
10+	65	11,570	23,277	2.79	(2.16, 3.56)	2.11	(1.62, 2.69)
Cumulative duration							
0 days	548	81,003	208,308	2.63	(2.42, 2.86)	2.67	(2.46, 2.91)
1 - 45 days	8	46,655	5,233	1.53	(0.66, 3.01)	1.60	(0.69, 3.16)
46 - 180 days	18	29,916	7,803	2.31	(1.37, 3.65)	2.16	(1.28, 3.42)
181 - 365 days	26	15,972	6,620	3.93	(2.57, 5.75)	3.37	(2.19, 4.94)
> 365 days	52	10,892	21,885	2.38	(1.77, 3.12)	1.82	(1.36, 2.39)
Time since first exposure							
0 days	548	81,003	208,308	2.63	(2.42, 2.86)	2.67	(2.46, 2.91)
1 - 45 days	8	46,655	5,008	1.60	(0.69, 3.15)	1.68	(0.72, 3.32)
46 - 180 days	16	27,482	6,148	2.60	(1.49, 4.23)	2.44	(1.39, 3.96)
181 - 365 days	24	16,997	5,694	4.22	(2.70, 6.27)	3.66	(2.34, 5.46)
> 365 days	56	15,072	24,691	2.27	(1.71, 2.95)	1.77	(1.33, 2.30)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Number of prescriptions							
0	1,006	119,754	397,669	2.53	(2.38, 2.69)	2.53	(2.38, 2.69)
1	0	648	54	0.00	(0.00, 67.88)	0.00	not estimable
2-3	0	443	68	0.00	(0.00, 54.35)	0.00	not estimable
4-5	0	289	48	0.00	(0.00, 77.49)	0.00	not estimable
6-9	0	214	67	0.00	(0.00, 54.98)	0.00	not estimable
10+	0	145	211	0.00	(0.00, 17.50)	0.00	not estimable
Cumulative duration							
0 days	1,006	119,754	397,669	2.53	(2.38, 2.69)	2.53	(2.38, 2.69)
1 - 45 days	0	648	74	0.00	(0.00, 49.97)	0.00	not estimable
46 - 180 days	0	450	111	0.00	(0.00, 33.23)	0.00	not estimable
181 - 365 days	0	211	80	0.00	(0.00, 46.26)	0.00	not estimable
> 365 days	0	122	183	0.00	(0.00, 20.15)	0.00	not estimable
Time since first exposure							
0 days	1,006	119,754	397,669	2.53	(2.38, 2.69)	2.53	(2.38, 2.69)
1 - 45 days	0	648	71	0.00	(0.00, 51.91)	0.00	not estimable
46 - 180 days	0	436	97	0.00	(0.00, 38.19)	0.00	not estimable
181 - 365 days	0	235	77	0.00	(0.00, 48.02)	0.00	not estimable
> 365 days	0	154	203	0.00	(0.00, 18.15)	0.00	not estimable

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Number of prescriptions							
0	812	86,623	272,485	2.98	(2.78, 3.19)	2.86	(2.67, 3.06)
1	4	48,790	4,432	0.90	(0.25, 2.31)	1.11	(0.29, 2.85)
2-3	5	32,746	5,705	0.88	(0.28, 2.05)	1.04	(0.33, 2.46)
4-5	6	23,124	4,307	1.39	(0.51, 3.03)	1.65	(0.59, 3.61)
6-9	2	18,596	6,478	0.31	(0.04, 1.12)	0.30	(0.04, 1.07)
10+	25	13,689	21,117	1.18	(0.77, 1.75)	1.12	(0.72, 1.66)
Cumulative duration							
0 days	812	86,623	272,485	2.98	(2.78, 3.19)	2.86	(2.67, 3.06)
1 - 45 days	6	48,790	5,611	1.07	(0.39, 2.33)	1.25	(0.45, 2.73)
46 - 180 days	11	33,712	9,234	1.19	(0.59, 2.13)	1.30	(0.64, 2.34)
181 - 365 days	4	19,216	7,889	0.51	(0.14, 1.30)	0.53	(0.14, 1.36)
> 365 days	21	12,696	19,306	1.09	(0.67, 1.66)	1.07	(0.66, 1.64)
Time since first exposure							
0 days	812	86,623	272,485	2.98	(2.78, 3.19)	2.86	(2.67, 3.06)
1 - 45 days	6	48,790	5,411	1.11	(0.41, 2.41)	1.29	(0.47, 2.82)
46 - 180 days	8	31,378	7,444	1.07	(0.46, 2.12)	1.17	(0.50, 2.32)
181 - 365 days	4	20,471	6,950	0.58	(0.16, 1.47)	0.58	(0.16, 1.48)
> 365 days	24	17,031	22,234	1.08	(0.69, 1.61)	1.09	(0.69, 1.62)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Number of prescriptions							
0	879	113,633	358,729	2.45	(2.29, 2.62)	2.46	(2.30, 2.63)
1	3	11,102	986	3.04	(0.63, 8.89)	3.54	(0.72, 10.36)
2-3	2	6,598	1,064	1.88	(0.23, 6.79)	1.97	(0.23, 7.14)
4-5	3	4,277	728	4.12	(0.85, 12.05)	3.72	(0.74, 10.95)
6-9	4	3,329	1,059	3.78	(1.03, 9.67)	3.32	(0.89, 8.53)
10+	10	2,406	4,144	2.41	(1.16, 4.44)	2.03	(0.97, 3.75)
Cumulative duration							
0 days	879	113,633	358,729	2.45	(2.29, 2.62)	2.46	(2.30, 2.63)
1 - 45 days	3	11,102	1,242	2.42	(0.50, 7.06)	2.59	(0.53, 7.57)
46 - 180 days	6	6,754	1,708	3.51	(1.29, 7.65)	3.31	(1.20, 7.21)
181 - 365 days	4	3,313	1,336	2.99	(0.82, 7.67)	2.49	(0.67, 6.40)
> 365 days	9	2,157	3,695	2.44	(1.11, 4.62)	2.09	(0.95, 3.98)
Time since first exposure							
0 days	879	113,633	358,729	2.45	(2.29, 2.62)	2.46	(2.30, 2.63)
1 - 45 days	3	11,102	1,191	2.52	(0.52, 7.36)	2.70	(0.55, 7.90)
46 - 180 days	6	6,346	1,377	4.36	(1.60, 9.49)	4.08	(1.48, 8.91)
181 - 365 days	2	3,709	1,172	1.71	(0.21, 6.16)	1.56	(0.19, 5.66)
> 365 days	11	2,948	4,241	2.59	(1.29, 4.64)	2.19	(1.09, 3.93)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Number of prescriptions							
0	990	117,556	389,485	2.54	(2.39, 2.71)	2.53	(2.37, 2.69)
1	0	5,893	511	0.00	(0.00, 7.22)	0.00	not estimable
2-3	0	3,872	630	0.00	(0.00, 5.85)	0.00	not estimable
4-5	0	2,575	460	0.00	(0.00, 8.02)	0.00	not estimable
6-9	1	1,971	640	1.56	(0.04, 8.71)	1.64	(0.04, 9.11)
10+	1	1,286	1,262	0.79	(0.02, 4.42)	1.04	(0.03, 5.80)
Cumulative duration							
0 days	990	117,556	389,485	2.54	(2.39, 2.71)	2.53	(2.37, 2.69)
1 - 45 days	0	5,893	666	0.00	(0.00, 5.54)	0.00	not estimable
46 - 180 days	0	3,956	1,016	0.00	(0.00, 3.63)	0.00	not estimable
181 - 365 days	1	2,003	766	1.31	(0.03, 7.27)	1.36	(0.03, 7.56)
> 365 days	1	1,143	1,056	0.95	(0.02, 5.28)	1.14	(0.03, 6.37)
Time since first exposure							
0 days	990	117,556	389,485	2.54	(2.39, 2.71)	2.53	(2.37, 2.69)
1 - 45 days	0	5,893	642	0.00	(0.00, 5.75)	0.00	not estimable
46 - 180 days	0	3,822	881	0.00	(0.00, 4.19)	0.00	not estimable
181 - 365 days	1	2,249	736	1.36	(0.03, 7.57)	1.42	(0.04, 7.93)
> 365 days	1	1,511	1,245	0.80	(0.02, 4.47)	0.96	(0.02, 5.37)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Number of prescriptions							
0	1,130	78,205	243,482	4.64	(4.37, 4.92)	4.88	(4.60, 5.17)
1	24	50,473	4,435	5.41	(3.47, 8.05)	5.47	(3.50, 8.15)
2-3	34	28,015	4,384	7.76	(5.37, 10.84)	7.26	(5.02, 10.16)
4-5	20	17,829	2,985	6.70	(4.09, 10.35)	5.59	(3.41, 8.64)
6-9	31	13,894	4,303	7.20	(4.90, 10.23)	6.08	(4.11, 8.66)
10+	134	10,023	15,485	8.65	(7.25, 10.25)	6.56	(5.47, 7.80)
Cumulative duration							
0 days	1,130	78,205	243,482	4.64	(4.37, 4.92)	4.88	(4.60, 5.17)
1 - 45 days	37	50,473	5,554	6.66	(4.69, 9.18)	6.43	(4.52, 8.86)
46 - 180 days	63	29,225	7,087	8.89	(6.83, 11.37)	7.78	(5.96, 9.97)
181 - 365 days	44	13,644	5,483	8.02	(5.83, 10.77)	6.30	(4.56, 8.47)
> 365 days	99	8,630	13,467	7.35	(5.97, 8.95)	5.67	(4.59, 6.93)
Time since first exposure							
0 days	1,130	78,205	243,482	4.64	(4.37, 4.92)	4.88	(4.60, 5.17)
1 - 45 days	37	50,473	5,279	7.01	(4.94, 9.66)	6.77	(4.76, 9.33)
46 - 180 days	54	26,345	5,288	10.21	(7.67, 13.32)	8.95	(6.70, 11.71)
181 - 365 days	41	15,400	4,641	8.83	(6.34, 11.99)	7.01	(5.01, 9.52)
> 365 days	111	13,585	16,383	6.78	(5.57, 8.16)	5.26	(4.31, 6.36)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Number of prescriptions							
0	1,108	81,003	208,308	5.32	(5.01, 5.64)	5.41	(5.09, 5.73)
1	14	46,655	4,233	3.31	(1.81, 5.55)	3.63	(1.97, 6.12)
2-3	28	28,095	4,923	5.69	(3.78, 8.22)	5.48	(3.63, 7.94)
4-5	14	19,125	3,614	3.87	(2.12, 6.50)	3.69	(2.01, 6.20)
6-9	33	15,479	5,494	6.01	(4.13, 8.44)	5.27	(3.62, 7.40)
10+	145	11,570	23,277	6.23	(5.26, 7.33)	4.68	(3.94, 5.51)
Cumulative duration							
0 days	1,108	81,003	208,308	5.32	(5.01, 5.64)	5.41	(5.09, 5.73)
1 - 45 days	22	46,655	5,233	4.20	(2.63, 6.36)	4.26	(2.67, 6.47)
46 - 180 days	45	29,916	7,803	5.77	(4.21, 7.72)	5.29	(3.85, 7.08)
181 - 365 days	47	15,972	6,620	7.10	(5.22, 9.44)	6.02	(4.42, 8.02)
> 365 days	120	10,892	21,885	5.48	(4.55, 6.56)	4.20	(3.48, 5.03)
Time since first exposure							
0 days	1,108	81,003	208,308	5.32	(5.01, 5.64)	5.41	(5.09, 5.73)
1 - 45 days	21	46,655	5,008	4.19	(2.60, 6.41)	4.29	(2.65, 6.56)
46 - 180 days	35	27,482	6,148	5.69	(3.97, 7.92)	5.21	(3.62, 7.26)
181 - 365 days	43	16,997	5,694	7.55	(5.47, 10.17)	6.43	(4.65, 8.67)
> 365 days	135	15,072	24,691	5.47	(4.58, 6.47)	4.27	(3.58, 5.06)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Number of prescriptions							
0	2,091	119,754	397,669	5.26	(5.04, 5.49)	5.26	(5.03, 5.49)
1	0	648	54	0.00	(0.00, 67.88)	0.00	not estimable
2-3	1	443	68	14.73	(0.37, 82.09)	15.10	(0.38, 84.12)
4-5	0	289	48	0.00	(0.00, 77.49)	0.00	not estimable
6-9	1	214	67	14.90	(0.38, 83.04)	19.33	(0.49, 107.68)
10+	0	145	211	0.00	(0.00, 17.50)	0.00	not estimable
Cumulative duration							
0 days	2,091	119,754	397,669	5.26	(5.04, 5.49)	5.26	(5.03, 5.49)
1 - 45 days	1	648	74	13.55	(0.34, 75.48)	12.68	(0.32, 70.64)
46 - 180 days	0	450	111	0.00	(0.00, 33.23)	0.00	not estimable
181 - 365 days	1	211	80	12.54	(0.32, 69.86)	16.93	(0.43, 94.35)
> 365 days	0	122	183	0.00	(0.00, 20.15)	0.00	not estimable
Time since first exposure							
0 days	2,091	119,754	397,669	5.26	(5.04, 5.49)	5.26	(5.03, 5.49)
1 - 45 days	1	648	71	14.07	(0.36, 78.41)	13.09	(0.33, 72.92)
46 - 180 days	0	436	97	0.00	(0.00, 38.19)	0.00	not estimable
181 - 365 days	1	235	77	13.02	(0.33, 72.53)	16.67	(0.42, 92.91)
> 365 days	0	154	203	0.00	(0.00, 18.15)	0.00	not estimable

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Number of prescriptions							
0	1,680	86,623	272,485	6.17	(5.87, 6.47)	5.92	(5.64, 6.21)
1	11	48,790	4,432	2.48	(1.24, 4.44)	3.04	(1.50, 5.47)
2-3	18	32,746	5,705	3.16	(1.87, 4.99)	3.60	(2.12, 5.72)
4-5	12	23,124	4,307	2.79	(1.44, 4.87)	3.15	(1.61, 5.53)
6-9	7	18,596	6,478	1.08	(0.43, 2.23)	1.15	(0.45, 2.38)
10+	52	13,689	21,117	2.46	(1.84, 3.23)	2.32	(1.73, 3.05)
Cumulative duration							
0 days	1,680	86,623	272,485	6.17	(5.87, 6.47)	5.92	(5.64, 6.21)
1 - 45 days	19	48,790	5,611	3.39	(2.04, 5.29)	3.94	(2.36, 6.17)
46 - 180 days	25	33,712	9,234	2.71	(1.75, 4.00)	2.87	(1.85, 4.25)
181 - 365 days	15	19,216	7,889	1.90	(1.06, 3.14)	1.97	(1.09, 3.25)
> 365 days	41	12,696	19,306	2.12	(1.52, 2.88)	2.07	(1.48, 2.81)
Time since first exposure							
0 days	1,680	86,623	272,485	6.17	(5.87, 6.47)	5.92	(5.64, 6.21)
1 - 45 days	18	48,790	5,411	3.33	(1.97, 5.26)	3.89	(2.29, 6.16)
46 - 180 days	20	31,378	7,444	2.69	(1.64, 4.15)	2.82	(1.72, 4.37)
181 - 365 days	12	20,471	6,950	1.73	(0.89, 3.02)	1.75	(0.90, 3.06)
> 365 days	50	17,031	22,234	2.25	(1.67, 2.96)	2.23	(1.65, 2.94)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Number of prescriptions							
0	1,842	113,633	358,729	5.13	(4.90, 5.37)	5.16	(4.93, 5.40)
1	7	11,102	986	7.10	(2.86, 14.63)	7.49	(2.99, 15.48)
2-3	7	6,598	1,064	6.58	(2.64, 13.55)	6.31	(2.51, 13.05)
4-5	6	4,277	728	8.24	(3.03, 17.94)	7.55	(2.73, 16.51)
6-9	9	3,329	1,059	8.50	(3.89, 16.14)	7.36	(3.34, 14.02)
10+	24	2,406	4,144	5.79	(3.71, 8.62)	4.84	(3.07, 7.23)
Cumulative duration							
0 days	1,842	113,633	358,729	5.13	(4.90, 5.37)	5.16	(4.93, 5.40)
1 - 45 days	9	11,102	1,242	7.25	(3.31, 13.75)	7.24	(3.29, 13.77)
46 - 180 days	13	6,754	1,708	7.61	(4.05, 13.02)	6.85	(3.63, 11.74)
181 - 365 days	8	3,313	1,336	5.99	(2.58, 11.80)	4.88	(2.10, 9.64)
> 365 days	23	2,157	3,695	6.22	(3.95, 9.34)	5.33	(3.35, 8.03)
Time since first exposure							
0 days	1,842	113,633	358,729	5.13	(4.90, 5.37)	5.16	(4.93, 5.40)
1 - 45 days	9	11,102	1,191	7.55	(3.45, 14.34)	7.54	(3.43, 14.34)
46 - 180 days	13	6,346	1,377	9.44	(5.03, 16.15)	8.48	(4.49, 14.55)
181 - 365 days	5	3,709	1,172	4.27	(1.39, 9.96)	3.63	(1.16, 8.49)
> 365 days	26	2,948	4,241	6.13	(4.01, 8.98)	5.23	(3.39, 7.69)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Number of prescriptions							
0	2,066	117,556	389,485	5.30	(5.08, 5.54)	5.28	(5.05, 5.51)
1	1	5,893	511	1.96	(0.05, 10.90)	2.29	(0.06, 12.74)
2-3	1	3,872	630	1.59	(0.04, 8.84)	1.56	(0.04, 8.68)
4-5	2	2,575	460	4.35	(0.53, 15.70)	5.35	(0.62, 19.42)
6-9	1	1,971	640	1.56	(0.04, 8.71)	1.64	(0.04, 9.11)
10+	5	1,286	1,262	3.96	(1.29, 9.25)	4.41	(1.40, 10.37)
Cumulative duration							
0 days	2,066	117,556	389,485	5.30	(5.08, 5.54)	5.28	(5.05, 5.51)
1 - 45 days	1	5,893	666	1.50	(0.04, 8.37)	1.72	(0.04, 9.59)
46 - 180 days	3	3,956	1,016	2.95	(0.61, 8.63)	3.45	(0.70, 10.12)
181 - 365 days	3	2,003	766	3.92	(0.81, 11.44)	4.54	(0.90, 13.37)
> 365 days	3	1,143	1,056	2.84	(0.59, 8.31)	2.90	(0.58, 8.51)
Time since first exposure							
0 days	2,066	117,556	389,485	5.30	(5.08, 5.54)	5.28	(5.05, 5.51)
1 - 45 days	1	5,893	642	1.56	(0.04, 8.68)	1.78	(0.05, 9.93)
46 - 180 days	3	3,822	881	3.41	(0.70, 9.96)	3.93	(0.80, 11.52)
181 - 365 days	3	2,249	736	4.08	(0.84, 11.92)	4.79	(0.94, 14.12)
> 365 days	3	1,511	1,245	2.41	(0.50, 7.04)	2.45	(0.49, 7.21)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Number of prescriptions							
0	2,688	78,205	240,316	11.19	(10.77, 11.62)	11.74	(11.30, 12.19)
1	74	50,378	4,425	16.72	(13.13, 20.99)	17.06	(13.39, 21.43)
2-3	69	27,891	4,362	15.82	(12.31, 20.02)	14.82	(11.52, 18.78)
4-5	51	17,706	2,964	17.21	(12.81, 22.62)	14.71	(10.94, 19.35)
6-9	69	13,776	4,264	16.18	(12.59, 20.48)	14.06	(10.90, 17.83)
10+	258	9,897	15,184	16.99	(14.98, 19.20)	13.44	(11.80, 15.22)
Cumulative duration							
0 days	2,688	78,205	240,316	11.19	(10.77, 11.62)	11.74	(11.30, 12.19)
1 - 45 days	97	50,378	5,538	17.52	(14.20, 21.37)	17.21	(13.95, 21.00)
46 - 180 days	132	29,092	7,038	18.76	(15.69, 22.24)	16.56	(13.83, 19.66)
181 - 365 days	84	13,520	5,421	15.49	(12.36, 19.18)	12.78	(10.16, 15.86)
> 365 days	208	8,516	13,201	15.76	(13.69, 18.05)	12.75	(11.04, 14.65)
Time since first exposure							
0 days	2,688	78,205	240,316	11.19	(10.77, 11.62)	11.74	(11.30, 12.19)
1 - 45 days	93	50,378	5,265	17.66	(14.26, 21.64)	17.40	(14.04, 21.32)
46 - 180 days	105	26,257	5,263	19.95	(16.32, 24.15)	17.58	(14.34, 21.32)
181 - 365 days	80	15,290	4,599	17.40	(13.79, 21.65)	14.22	(11.25, 17.72)
> 365 days	243	13,410	16,072	15.12	(13.28, 17.15)	12.45	(10.90, 14.16)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Number of prescriptions							
0	2,471	81,003	205,798	12.01	(11.54, 12.49)	12.36	(11.87, 12.85)
1	62	46,614	4,228	14.67	(11.24, 18.80)	15.72	(12.03, 20.18)
2-3	67	28,015	4,906	13.66	(10.58, 17.34)	13.30	(10.29, 16.91)
4-5	40	19,026	3,594	11.13	(7.95, 15.16)	10.23	(7.29, 13.96)
6-9	77	15,372	5,452	14.12	(11.15, 17.65)	12.58	(9.91, 15.75)
10+	353	11,467	22,833	15.46	(13.89, 17.16)	12.43	(11.14, 13.83)
Cumulative duration							
0 days	2,471	81,003	205,798	12.01	(11.54, 12.49)	12.36	(11.87, 12.85)
1 - 45 days	80	46,614	5,224	15.31	(12.14, 19.06)	15.57	(12.33, 19.39)
46 - 180 days	111	29,826	7,764	14.30	(11.76, 17.22)	13.24	(10.88, 15.95)
181 - 365 days	102	15,862	6,562	15.54	(12.67, 18.87)	13.14	(10.70, 15.96)
> 365 days	306	10,780	21,460	14.26	(12.71, 15.95)	11.73	(10.43, 13.14)
Time since first exposure							
0 days	2,471	81,003	205,798	12.01	(11.54, 12.49)	12.36	(11.87, 12.85)
1 - 45 days	78	46,614	5,000	15.60	(12.33, 19.47)	15.93	(12.58, 19.90)
46 - 180 days	87	27,414	6,127	14.20	(11.37, 17.52)	13.11	(10.48, 16.19)
181 - 365 days	95	16,906	5,654	16.80	(13.59, 20.54)	14.40	(11.63, 17.62)
> 365 days	339	14,937	24,230	13.99	(12.54, 15.56)	11.61	(10.39, 12.93)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Number of prescriptions							
0	4,705	119,754	392,126	12.00	(11.66, 12.35)	12.14	(11.80, 12.50)
1	1	643	54	18.51	(0.47, 103.13)	15.48	(0.39, 86.24)
2-3	1	438	67	14.87	(0.38, 82.83)	15.34	(0.39, 85.49)
4-5	0	285	47	0.00	(0.00, 78.17)	0.00	not estimable
6-9	1	210	66	15.06	(0.38, 83.90)	19.34	(0.49, 107.76)
10+	3	142	208	14.42	(2.97, 42.15)	8.60	(1.63, 25.48)
Cumulative duration							
0 days	4,705	119,754	392,126	12.00	(11.66, 12.35)	12.14	(11.80, 12.50)
1 - 45 days	2	643	73	27.35	(3.31, 98.78)	24.78	(2.97, 89.63)
46 - 180 days	0	445	110	0.00	(0.00, 33.59)	0.00	not estimable
181 - 365 days	1	209	79	12.63	(0.32, 70.36)	17.40	(0.44, 96.96)
> 365 days	3	122	181	16.60	(3.42, 48.51)	9.92	(1.87, 29.39)
Time since first exposure							
0 days	4,705	119,754	392,126	12.00	(11.66, 12.35)	12.14	(11.80, 12.50)
1 - 45 days	2	643	70	28.41	(3.44, 102.61)	25.68	(3.08, 92.84)
46 - 180 days	0	431	96	0.00	(0.00, 38.57)	0.00	not estimable
181 - 365 days	1	233	76	13.13	(0.33, 73.18)	16.67	(0.42, 92.91)
> 365 days	3	152	201	14.95	(3.08, 43.69)	9.20	(1.77, 27.18)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Number of prescriptions							
0	3,513	86,623	268,553	13.08	(12.65, 13.52)	12.82	(12.40, 13.25)
1	41	48,633	4,417	9.28	(6.66, 12.59)	11.16	(7.97, 15.20)
2-3	69	32,591	5,677	12.15	(9.46, 15.38)	13.64	(10.57, 17.32)
4-5	43	22,965	4,277	10.05	(7.28, 13.54)	10.86	(7.81, 14.69)
6-9	50	18,433	6,420	7.79	(5.78, 10.27)	8.05	(5.95, 10.64)
10+	197	13,528	20,750	9.49	(8.21, 10.92)	9.16	(7.91, 10.56)
Cumulative duration							
0 days	3,513	86,623	268,553	13.08	(12.65, 13.52)	12.82	(12.40, 13.25)
1 - 45 days	61	48,633	5,589	10.91	(8.35, 14.02)	12.45	(9.50, 16.02)
46 - 180 days	100	33,549	9,172	10.90	(8.87, 13.26)	11.44	(9.29, 13.94)
181 - 365 days	71	19,049	7,808	9.09	(7.10, 11.47)	9.32	(7.26, 11.77)
> 365 days	168	12,546	18,972	8.86	(7.57, 10.30)	8.78	(7.48, 10.23)
Time since first exposure							
0 days	3,513	86,623	268,553	13.08	(12.65, 13.52)	12.82	(12.40, 13.25)
1 - 45 days	58	48,633	5,391	10.76	(8.17, 13.91)	12.28	(9.30, 15.90)
46 - 180 days	87	31,239	7,403	11.75	(9.41, 14.50)	12.36	(9.88, 15.27)
181 - 365 days	60	20,319	6,892	8.71	(6.64, 11.21)	8.89	(6.77, 11.45)
> 365 days	195	16,844	21,856	8.92	(7.71, 10.27)	8.88	(7.66, 10.24)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Number of prescriptions							
0	4,185	113,633	353,904	11.83	(11.47, 12.19)	12.02	(11.66, 12.39)
1	17	11,058	982	17.31	(10.08, 27.72)	17.95	(10.41, 28.79)
2-3	25	6,559	1,057	23.64	(15.30, 34.90)	22.82	(14.71, 33.77)
4-5	11	4,234	721	15.26	(7.62, 27.31)	13.70	(6.80, 24.59)
6-9	16	3,297	1,049	15.26	(8.72, 24.78)	14.14	(8.02, 23.05)
10+	57	2,379	4,040	14.11	(10.69, 18.28)	12.06	(9.10, 15.66)
Cumulative duration							
0 days	4,185	113,633	353,904	11.83	(11.47, 12.19)	12.02	(11.66, 12.39)
1 - 45 days	21	11,058	1,237	16.98	(10.51, 25.96)	16.85	(10.41, 25.78)
46 - 180 days	37	6,710	1,692	21.86	(15.39, 30.13)	20.11	(14.12, 27.76)
181 - 365 days	16	3,279	1,322	12.11	(6.92, 19.66)	10.91	(6.18, 17.81)
> 365 days	52	2,130	3,598	14.45	(10.79, 18.95)	12.51	(9.31, 16.44)
Time since first exposure							
0 days	4,185	113,633	353,904	11.83	(11.47, 12.19)	12.02	(11.66, 12.39)
1 - 45 days	21	11,058	1,186	17.70	(10.96, 27.06)	17.56	(10.85, 26.88)
46 - 180 days	31	6,308	1,365	22.70	(15.43, 32.23)	20.70	(14.01, 29.44)
181 - 365 days	17	3,677	1,161	14.65	(8.53, 23.45)	13.45	(7.81, 21.58)
> 365 days	57	2,911	4,136	13.78	(10.44, 17.86)	12.05	(9.09, 15.66)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Number of prescriptions							
0	4,632	117,556	384,034	12.06	(11.72, 12.41)	12.17	(11.82, 12.52)
1	2	5,860	508	3.93	(0.48, 14.21)	4.70	(0.57, 16.99)
2-3	3	3,845	626	4.79	(0.99, 14.00)	4.52	(0.93, 13.21)
4-5	3	2,558	457	6.57	(1.35, 19.19)	7.45	(1.47, 21.95)
6-9	4	1,953	632	6.33	(1.72, 16.21)	6.77	(1.84, 17.33)
10+	15	1,271	1,247	12.03	(6.73, 19.84)	12.66	(7.02, 20.97)
Cumulative duration							
0 days	4,632	117,556	384,034	12.06	(11.72, 12.41)	12.17	(11.82, 12.52)
1 - 45 days	3	5,860	662	4.53	(0.93, 13.25)	4.88	(0.99, 14.31)
46 - 180 days	7	3,929	1,009	6.94	(2.79, 14.30)	7.64	(3.05, 15.78)
181 - 365 days	6	1,982	757	7.92	(2.91, 17.24)	8.72	(3.16, 19.05)
> 365 days	11	1,131	1,043	10.55	(5.27, 18.88)	10.95	(5.39, 19.72)
Time since first exposure							
0 days	4,632	117,556	384,034	12.06	(11.72, 12.41)	12.17	(11.82, 12.52)
1 - 45 days	3	5,860	638	4.70	(0.97, 13.74)	5.05	(1.02, 14.82)
46 - 180 days	7	3,797	874	8.00	(3.22, 16.49)	8.72	(3.48, 18.01)
181 - 365 days	6	2,230	728	8.24	(3.02, 17.93)	9.19	(3.32, 20.09)
> 365 days	11	1,493	1,230	8.95	(4.47, 16.01)	9.33	(4.59, 16.80)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Number of prescriptions							
0	5,196	78,205	243,482	21.34	(20.76, 21.93)	22.39	(21.78, 23.00)
1	95	50,473	4,435	21.42	(17.33, 26.19)	21.77	(17.60, 26.62)
2-3	110	28,015	4,384	25.09	(20.62, 30.24)	23.03	(18.91, 27.78)
4-5	97	17,829	2,985	32.50	(26.35, 39.65)	27.74	(22.46, 33.88)
6-9	115	13,894	4,303	26.73	(22.07, 32.08)	22.68	(18.68, 27.27)
10+	552	10,023	15,485	35.65	(32.74, 38.75)	27.81	(25.45, 30.31)
Cumulative duration							
0 days	5,196	78,205	243,482	21.34	(20.76, 21.93)	22.39	(21.78, 23.00)
1 - 45 days	135	50,473	5,554	24.31	(20.38, 28.77)	23.59	(19.78, 27.93)
46 - 180 days	230	29,225	7,087	32.46	(28.40, 36.93)	28.14	(24.59, 32.05)
181 - 365 days	180	13,644	5,483	32.83	(28.21, 37.99)	26.68	(22.87, 30.93)
> 365 days	424	8,630	13,467	31.48	(28.56, 34.63)	24.93	(22.54, 27.50)
Time since first exposure							
0 days	5,196	78,205	243,482	21.34	(20.76, 21.93)	22.39	(21.78, 23.00)
1 - 45 days	132	50,473	5,279	25.01	(20.92, 29.65)	24.27	(20.30, 28.78)
46 - 180 days	180	26,345	5,288	34.04	(29.25, 39.39)	29.30	(25.13, 33.96)
181 - 365 days	173	15,400	4,641	37.28	(31.93, 43.27)	30.51	(26.07, 35.47)
> 365 days	484	13,585	16,383	29.54	(26.97, 32.30)	23.70	(21.58, 25.97)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Number of prescriptions							
0	5,043	81,003	208,308	24.21	(23.55, 24.89)	24.58	(23.90, 25.27)
1	77	46,655	4,233	18.19	(14.36, 22.73)	20.07	(15.81, 25.12)
2-3	84	28,095	4,923	17.06	(13.61, 21.13)	16.99	(13.53, 21.06)
4-5	55	19,125	3,614	15.22	(11.46, 19.81)	14.40	(10.83, 18.77)
6-9	122	15,479	5,494	22.21	(18.44, 26.51)	19.94	(16.53, 23.84)
10+	602	11,570	23,277	25.86	(23.84, 28.01)	20.02	(18.41, 21.74)
Cumulative duration							
0 days	5,043	81,003	208,308	24.21	(23.55, 24.89)	24.58	(23.90, 25.27)
1 - 45 days	102	46,655	5,233	19.49	(15.89, 23.66)	20.04	(16.32, 24.34)
46 - 180 days	160	29,916	7,803	20.51	(17.45, 23.94)	19.09	(16.23, 22.29)
181 - 365 days	153	15,972	6,620	23.11	(19.59, 27.08)	19.88	(16.83, 23.31)
> 365 days	525	10,892	21,885	23.99	(21.98, 26.13)	18.99	(17.35, 20.73)
Time since first exposure							
0 days	5,043	81,003	208,308	24.21	(23.55, 24.89)	24.58	(23.90, 25.27)
1 - 45 days	98	46,655	5,008	19.57	(15.89, 23.85)	20.16	(16.35, 24.59)
46 - 180 days	134	27,482	6,148	21.79	(18.26, 25.81)	20.24	(16.94, 23.99)
181 - 365 days	140	16,997	5,694	24.59	(20.68, 29.01)	21.23	(17.84, 25.09)
> 365 days	568	15,072	24,691	23.00	(21.15, 24.98)	18.45	(16.93, 20.06)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Number of prescriptions							
0	9,452	119,754	397,669	23.77	(23.29, 24.25)	23.76	(23.29, 24.25)
1	0	648	54	0.00	(0.00, 67.88)	0.00	not estimable
2-3	2	443	68	29.47	(3.57, 106.45)	31.10	(3.76, 112.39)
4-5	2	289	48	42.01	(5.09, 151.76)	38.07	(4.16, 138.86)
6-9	2	214	67	29.81	(3.61, 107.67)	31.05	(2.96, 114.57)
10+	1	145	211	4.74	(0.12, 26.44)	5.31	(0.13, 29.57)
Cumulative duration							
0 days	9,452	119,754	397,669	23.77	(23.29, 24.25)	23.76	(23.29, 24.25)
1 - 45 days	1	648	74	13.55	(0.34, 75.48)	12.68	(0.32, 70.64)
46 - 180 days	3	450	111	27.02	(5.57, 78.97)	25.53	(5.25, 74.66)
181 - 365 days	3	211	80	37.62	(7.76, 109.93)	38.73	(7.25, 114.96)
> 365 days	0	122	183	0.00	(0.00, 20.15)	0.00	not estimable
Time since first exposure							
0 days	9,452	119,754	397,669	23.77	(23.29, 24.25)	23.76	(23.29, 24.25)
1 - 45 days	1	648	71	14.07	(0.36, 78.41)	13.09	(0.33, 72.92)
46 - 180 days	3	436	97	31.06	(6.40, 90.76)	29.83	(6.14, 87.19)
181 - 365 days	1	235	77	13.02	(0.33, 72.53)	16.67	(0.42, 92.91)
> 365 days	2	154	203	9.84	(1.19, 35.55)	7.39	(0.68, 27.35)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Number of prescriptions							
0	7,196	86,623	272,485	26.41	(25.80, 27.03)	25.38	(24.80, 25.97)
1	62	48,790	4,432	13.99	(10.73, 17.93)	17.69	(13.51, 22.74)
2-3	64	32,746	5,705	11.22	(8.64, 14.33)	13.36	(10.24, 17.11)
4-5	65	23,124	4,307	15.09	(11.65, 19.24)	17.42	(13.38, 22.29)
6-9	77	18,596	6,478	11.89	(9.38, 14.86)	12.88	(10.13, 16.14)
10+	352	13,689	21,117	16.67	(14.97, 18.50)	16.00	(14.35, 17.79)
Cumulative duration							
0 days	7,196	86,623	272,485	26.41	(25.80, 27.03)	25.38	(24.80, 25.97)
1 - 45 days	84	48,790	5,611	14.97	(11.94, 18.54)	17.65	(14.05, 21.87)
46 - 180 days	141	33,712	9,234	15.27	(12.85, 18.01)	16.73	(14.07, 19.76)
181 - 365 days	104	19,216	7,889	13.18	(10.77, 15.97)	13.69	(11.17, 16.61)
> 365 days	291	12,696	19,306	15.07	(13.39, 16.91)	15.04	(13.34, 16.91)
Time since first exposure							
0 days	7,196	86,623	272,485	26.41	(25.80, 27.03)	25.38	(24.80, 25.97)
1 - 45 days	83	48,790	5,411	15.34	(12.22, 19.02)	18.09	(14.39, 22.46)
46 - 180 days	114	31,378	7,444	15.31	(12.63, 18.40)	16.84	(13.87, 20.26)
181 - 365 days	89	20,471	6,950	12.81	(10.28, 15.76)	13.27	(10.64, 16.34)
> 365 days	334	17,031	22,234	15.02	(13.45, 16.72)	15.07	(13.48, 16.80)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Number of prescriptions							
0	8,475	113,633	358,729	23.63	(23.12, 24.13)	23.74	(23.24, 24.25)
1	15	11,102	986	15.22	(8.52, 25.10)	15.84	(8.83, 26.19)
2-3	27	6,598	1,064	25.36	(16.72, 36.90)	23.94	(15.73, 34.90)
4-5	16	4,277	728	21.99	(12.57, 35.70)	20.12	(11.44, 32.76)
6-9	31	3,329	1,059	29.28	(19.90, 41.56)	25.53	(17.29, 36.30)
10+	123	2,406	4,144	29.68	(24.67, 35.41)	24.99	(20.70, 29.90)
Cumulative duration							
0 days	8,475	113,633	358,729	23.63	(23.12, 24.13)	23.74	(23.24, 24.25)
1 - 45 days	21	11,102	1,242	16.91	(10.46, 25.84)	16.87	(10.42, 25.83)
46 - 180 days	46	6,754	1,708	26.94	(19.72, 35.93)	24.12	(17.63, 32.21)
181 - 365 days	34	3,313	1,336	25.45	(17.62, 35.56)	22.28	(15.39, 31.18)
> 365 days	111	2,157	3,695	30.04	(24.71, 36.18)	25.74	(21.10, 31.08)
Time since first exposure							
0 days	8,475	113,633	358,729	23.63	(23.12, 24.13)	23.74	(23.24, 24.25)
1 - 45 days	21	11,102	1,191	17.63	(10.91, 26.94)	17.60	(10.86, 26.94)
46 - 180 days	43	6,346	1,377	31.23	(22.60, 42.07)	28.07	(20.28, 37.87)
181 - 365 days	27	3,709	1,172	23.04	(15.18, 33.52)	20.46	(13.45, 29.81)
> 365 days	121	2,948	4,241	28.53	(23.68, 34.09)	24.49	(20.26, 29.33)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV3g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Number of prescriptions							
0	9,337	117,556	389,485	23.97	(23.49, 24.46)	23.87	(23.38, 24.35)
1	3	5,893	511	5.87	(1.21, 17.15)	8.89	(1.74, 26.21)
2-3	5	3,872	630	7.93	(2.57, 18.51)	8.53	(2.67, 20.10)
4-5	7	2,575	460	15.21	(6.11, 31.34)	18.97	(7.43, 39.43)
6-9	5	1,971	640	7.82	(2.54, 18.24)	9.17	(2.92, 21.51)
10+	15	1,286	1,262	11.89	(6.65, 19.61)	13.29	(7.37, 22.02)
Cumulative duration							
0 days	9,337	117,556	389,485	23.97	(23.49, 24.46)	23.87	(23.38, 24.35)
1 - 45 days	6	5,893	666	9.01	(3.31, 19.62)	12.00	(4.20, 26.51)
46 - 180 days	9	3,956	1,016	8.86	(4.05, 16.82)	10.51	(4.72, 20.11)
181 - 365 days	9	2,003	766	11.75	(5.37, 22.30)	14.28	(6.45, 27.23)
> 365 days	11	1,143	1,056	10.42	(5.20, 18.65)	11.21	(5.54, 20.13)
Time since first exposure							
0 days	9,337	117,556	389,485	23.97	(23.49, 24.46)	23.87	(23.38, 24.35)
1 - 45 days	6	5,893	642	9.35	(3.43, 20.35)	12.42	(4.35, 27.43)
46 - 180 days	9	3,822	881	10.22	(4.67, 19.40)	11.94	(5.35, 22.85)
181 - 365 days	9	2,249	736	12.23	(5.59, 23.22)	15.14	(6.83, 28.88)
> 365 days	11	1,511	1,245	8.83	(4.41, 15.80)	9.59	(4.74, 17.22)

CI = confidence interval.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with recent exposure to							
Any OAB drug	214	113,060	35,867	5.97	(5.19, 6.82)	6.07	(5.28, 6.94)
Oxybutynin	100	47,840	13,361	7.48	(6.09, 9.10)	7.29	(5.93, 8.87)
Tolterodine	74	44,980	12,246	6.04	(4.74, 7.59)	5.97	(4.69, 7.50)
Darifenacin	1	598	131	7.64	(0.19, 42.55)	6.72	(0.17, 37.46)
Solifenacin	52	45,154	11,306	4.60	(3.44, 6.03)	5.21	(3.88, 6.85)
Trospium	12	10,405	2,837	4.23	(2.19, 7.39)	4.04	(2.08, 7.07)
Fesoterodine	2	5,284	1,053	1.90	(0.23, 6.86)	1.93	(0.21, 7.02)
Overall, aged ≥ 65 years with recent exposure to							
Any OAB drug	179	58,665	18,251	9.81	(8.42, 11.35)	9.92	(8.52, 11.49)
Oxybutynin	81	25,322	7,026	11.53	(9.16, 14.33)	11.36	(9.02, 14.13)
Tolterodine	61	23,834	6,414	9.51	(7.27, 12.22)	9.58	(7.33, 12.31)
Darifenacin	1	319	67	14.89	(0.38, 82.97)	13.13	(0.33, 73.14)
Solifenacin	47	22,579	5,522	8.51	(6.25, 11.32)	9.32	(6.83, 12.42)
Trospium	12	5,839	1,567	7.66	(3.96, 13.38)	7.89	(4.06, 13.80)
Fesoterodine	2	2,534	487	4.10	(0.50, 14.82)	3.76	(0.42, 13.70)
Overall, with high CV risk and with recent exposure to							
Any OAB drug	156	48,561	15,016	10.39	(8.82, 12.15)	8.39	(7.07, 9.87)
Oxybutynin	80	20,823	5,758	13.89	(11.02, 17.29)	11.41	(8.88, 14.40)
Tolterodine	49	19,205	5,143	9.53	(7.05, 12.60)	7.54	(5.49, 10.09)
Darifenacin	1	251	55	18.18	(0.46, 101.3)	12.22	(0.31, 68.07)
Solifenacin	33	18,960	4,667	7.07	(4.87, 9.93)	5.84	(3.98, 8.25)
Trospium	9	4,615	1,231	7.31	(3.34, 13.88)	5.39	(2.43, 10.30)
Fesoterodine	1	2,124	414	2.41	(0.06, 13.44)	1.80	(0.05, 10.05)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with recent exposure to							
Any OAB drug	123	79,374	25,920	4.75	(3.94, 5.66)	4.81	(4.00, 5.74)
Oxybutynin	60	33,208	9,418	6.37	(4.86, 8.20)	6.10	(4.65, 7.85)
Tolterodine	41	31,446	8,704	4.71	(3.38, 6.39)	4.70	(3.37, 6.38)
Darifenacin	1	454	101	9.88	(0.25, 55.05)	9.39	(0.24, 52.30)
Solifenacin	31	33,827	8,610	3.60	(2.45, 5.11)	4.07	(2.75, 5.79)
Trospium	6	7,465	2,078	2.89	(1.06, 6.28)	2.79	(1.01, 6.09)
Fesoterodine	1	3,978	807	1.24	(0.03, 6.91)	1.14	(0.03, 6.36)
Female, aged ≥ 65 with recent exposure to							
Any OAB drug	103	38,911	12,555	8.20	(6.70, 9.95)	8.29	(6.76, 10.05)
Oxybutynin	48	16,918	4,806	9.99	(7.36, 13.24)	9.74	(7.18, 12.91)
Tolterodine	34	15,800	4,335	7.84	(5.43, 10.96)	7.99	(5.53, 11.17)
Darifenacin	1	230	49	20.46	(0.52, 114.0)	19.28	(0.49, 107.4)
Solifenacin	28	15,880	3,959	7.07	(4.70, 10.22)	7.70	(5.10, 11.16)
Trospium	6	3,936	1,089	5.51	(2.02, 11.99)	5.73	(2.08, 12.51)
Fesoterodine	1	1,777	349	2.86	(0.07, 15.96)	2.34	(0.06, 13.06)
Female, with high CV risk and with recent exposure to							
Any OAB drug	79	31,471	10,008	7.89	(6.25, 9.84)	6.39	(5.01, 8.03)
Oxybutynin	44	13,507	3,783	11.63	(8.45, 15.62)	9.67	(6.80, 13.26)
Tolterodine	24	12,391	3,352	7.16	(4.59, 10.65)	5.60	(3.55, 8.39)
Darifenacin	1	176	39	25.63	(0.65, 142.8)	17.06	(0.43, 95.03)
Solifenacin	15	13,120	3,295	4.55	(2.55, 7.51)	3.62	(2.02, 5.99)
Trospium	5	3,047	826	6.05	(1.97, 14.13)	4.52	(1.43, 10.61)
Fesoterodine	1	1,487	291	3.44	(0.09, 19.15)	2.52	(0.06, 14.04)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4a. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Acute Myocardial Infarction, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with recent exposure to							
Any OAB drug	91	33,686	9,947	9.15	(7.37, 11.23)	9.23	(7.43, 11.33)
Oxybutynin	40	14,632	3,944	10.14	(7.25, 13.81)	10.31	(7.36, 14.04)
Tolterodine	33	13,534	3,542	9.32	(6.41, 13.08)	9.17	(6.31, 12.88)
Darifenacin	0	144	30	0.00	(0.00, 124.1)	0.00	not estimable
Solifenacin	21	11,327	2,696	7.79	(4.82, 11.91)	8.11	(5.01, 12.41)
Trospium	6	2,940	759	7.91	(2.90, 17.21)	7.20	(2.64, 15.66)
Fesoterodine	1	1,306	246	4.07	(0.10, 22.65)	3.91	(0.10, 21.78)
Male, aged ≥ 65 years with recent exposure to							
Any OAB drug	76	19,754	5,696	13.34	(10.51, 16.70)	13.42	(10.57, 16.79)
Oxybutynin	33	8,404	2,220	14.87	(10.23, 20.88)	14.83	(10.21, 20.84)
Tolterodine	27	8,034	2,079	12.99	(8.56, 18.89)	12.97	(8.55, 18.88)
Darifenacin	0	89	18	0.00	(0.00, 201.9)	0.00	not estimable
Solifenacin	19	6,699	1,562	12.16	(7.32, 18.99)	12.78	(7.67, 19.98)
Trospium	6	1,903	478	12.56	(4.61, 27.33)	12.49	(4.58, 27.20)
Fesoterodine	1	757	138	7.23	(0.18, 40.27)	6.79	(0.17, 37.82)
Male, with high CV risk and with recent exposure to							
Any OAB drug	77	17,090	5,008	15.37	(12.13, 19.22)	13.42	(10.48, 16.91)
Oxybutynin	36	7,316	1,976	18.22	(12.76, 25.23)	15.83	(11.00, 22.02)
Tolterodine	25	6,814	1,791	13.96	(9.03, 20.61)	12.44	(7.71, 18.83)
Darifenacin	0	75	16	0.00	(0.00, 230.6)	0.00	not estimable
Solifenacin	18	5,840	1,372	13.12	(7.77, 20.73)	11.44	(6.63, 18.29)
Trospium	4	1,568	405	9.87	(2.69, 25.28)	7.61	(2.04, 19.54)
Fesoterodine	0	637	123	0.00	(0.00, 29.88)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with recent exposure to							
Any OAB drug	226	113,001	35,818	6.31	(5.51, 7.19)	6.42	(5.61, 7.32)
Oxybutynin	91	47,792	13,342	6.82	(5.49, 8.37)	6.63	(5.34, 8.15)
Tolterodine	83	44,947	12,230	6.79	(5.41, 8.41)	6.70	(5.33, 8.31)
Darifenacin	1	594	130	7.67	(0.19, 42.74)	6.83	(0.17, 38.07)
Solifenacin	59	45,112	11,292	5.22	(3.98, 6.74)	5.67	(4.30, 7.33)
Trospium	16	10,389	2,827	5.66	(3.23, 9.19)	5.55	(3.16, 9.02)
Fesoterodine	7	5,274	1,050	6.66	(2.68, 13.73)	8.34	(3.26, 17.35)
Overall, aged ≥ 65 years with recent exposure to							
Any OAB drug	198	58,603	18,205	10.88	(9.41, 12.50)	11.01	(9.53, 12.66)
Oxybutynin	80	25,284	7,010	11.41	(9.05, 14.20)	11.25	(8.92, 14.00)
Tolterodine	73	23,797	6,398	11.41	(8.94, 14.35)	11.47	(8.98, 14.42)
Darifenacin	1	314	66	15.07	(0.38, 83.94)	13.34	(0.34, 74.34)
Solifenacin	51	22,541	5,508	9.26	(6.89, 12.17)	9.78	(7.26, 12.89)
Trospium	12	5,824	1,559	7.70	(3.98, 13.45)	7.98	(4.11, 13.96)
Fesoterodine	7	2,524	485	14.43	(5.80, 29.72)	16.28	(6.36, 33.88)
Overall, with high CV risk and with recent exposure to							
Any OAB drug	171	48,519	14,984	11.41	(9.77, 13.26)	9.47	(8.02, 11.09)
Oxybutynin	69	20,786	5,740	12.02	(9.35, 15.21)	9.67	(7.42, 12.36)
Tolterodine	63	19,189	5,136	12.27	(9.43, 15.69)	9.66	(7.31, 12.50)
Darifenacin	1	248	55	18.26	(0.46, 101.8)	12.39	(0.31, 69.06)
Solifenacin	44	18,936	4,658	9.45	(6.86, 12.68)	8.62	(6.09, 11.79)
Trospium	15	4,606	1,225	12.25	(6.85, 20.20)	10.87	(5.78, 18.37)
Fesoterodine	4	2,120	414	9.66	(2.63, 24.74)	8.38	(2.13, 21.76)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with recent exposure to							
Any OAB drug	150	79,339	25,884	5.80	(4.90, 6.80)	5.88	(4.98, 6.90)
Oxybutynin	59	33,177	9,406	6.27	(4.78, 8.09)	5.98	(4.55, 7.72)
Tolterodine	51	31,422	8,690	5.87	(4.37, 7.72)	5.79	(4.31, 7.61)
Darifenacin	1	453	101	9.91	(0.25, 55.22)	9.54	(0.24, 53.15)
Solifenacin	44	33,798	8,598	5.12	(3.72, 6.87)	5.65	(4.09, 7.60)
Trospium	8	7,449	2,074	3.86	(1.67, 7.60)	3.85	(1.65, 7.61)
Fesoterodine	5	3,972	805	6.21	(2.02, 14.49)	8.44	(2.59, 19.99)
Female, aged ≥ 65 with recent exposure to							
Any OAB drug	128	38,864	12,526	10.22	(8.53, 12.15)	10.32	(8.61, 12.27)
Oxybutynin	51	16,890	4,796	10.63	(7.92, 13.98)	10.41	(7.75, 13.69)
Tolterodine	44	15,769	4,322	10.18	(7.40, 13.67)	10.21	(7.41, 13.71)
Darifenacin	1	228	48	20.67	(0.52, 115.1)	19.59	(0.50, 109.2)
Solifenacin	37	15,852	3,950	9.37	(6.60, 12.91)	10.01	(7.03, 13.83)
Trospium	5	3,921	1,087	4.60	(1.49, 10.74)	4.88	(1.56, 11.42)
Fesoterodine	5	1,771	348	14.37	(4.67, 33.54)	17.33	(5.32, 41.05)
Female, with high CV risk and with recent exposure to							
Any OAB drug	115	31,451	9,979	11.52	(9.51, 13.83)	9.48	(7.73, 11.49)
Oxybutynin	46	13,482	3,769	12.20	(8.93, 16.28)	9.55	(6.87, 12.90)
Tolterodine	39	12,378	3,343	11.67	(8.30, 15.95)	8.94	(6.28, 12.31)
Darifenacin	1	176	39	25.61	(0.65, 142.7)	17.30	(0.44, 96.40)
Solifenacin	33	13,106	3,285	10.05	(6.92, 14.11)	9.28	(6.16, 13.34)
Trospium	8	3,037	823	9.72	(4.20, 19.15)	9.58	(3.87, 19.33)
Fesoterodine	3	1,486	291	10.30	(2.12, 30.10)	9.35	(1.77, 27.70)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4b. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Stroke, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with recent exposure to							
Any OAB drug	76	33,662	9,934	7.65	(6.03, 9.58)	7.79	(6.14, 9.75)
Oxybutynin	32	14,615	3,937	8.13	(5.56, 11.48)	8.28	(5.66, 11.69)
Tolterodine	32	13,525	3,540	9.04	(6.18, 12.76)	9.00	(6.16, 12.71)
Darifenacin	0	141	29	0.00	(0.00, 125.3)	0.00	not estimable
Solifenacin	15	11,314	2,694	5.57	(3.12, 9.18)	5.72	(3.19, 9.44)
Trospium	8	2,940	753	10.62	(4.59, 20.93)	9.83	(4.23, 19.38)
Fesoterodine	2	1,302	245	8.17	(0.99, 29.50)	8.09	(0.98, 29.21)
Male, aged ≥ 65 years with recent exposure to							
Any OAB drug	70	19,739	5,679	12.33	(9.61, 15.57)	12.49	(9.73, 15.78)
Oxybutynin	29	8,394	2,214	13.10	(8.77, 18.81)	13.04	(8.73, 18.73)
Tolterodine	29	8,028	2,076	13.97	(9.36, 20.07)	14.15	(9.47, 20.33)
Darifenacin	0	86	18	0.00	(0.00, 205.1)	0.00	not estimable
Solifenacin	14	6,689	1,558	8.99	(4.91, 15.08)	9.28	(5.06, 15.59)
Trospium	7	1,903	472	14.83	(5.96, 30.55)	14.61	(5.87, 30.10)
Fesoterodine	2	753	137	14.56	(1.76, 52.59)	14.04	(1.70, 50.72)
Male, with high CV risk and with recent exposure to							
Any OAB drug	56	17,068	5,004	11.19	(8.45, 14.53)	9.44	(7.02, 12.40)
Oxybutynin	23	7,304	1,970	11.67	(7.40, 17.52)	9.96	(6.19, 15.11)
Tolterodine	24	6,811	1,793	13.39	(8.58, 19.92)	11.48	(7.00, 17.57)
Darifenacin	0	72	16	0.00	(0.00, 234.8)	0.00	not estimable
Solifenacin	11	5,830	1,373	8.01	(4.00, 14.33)	6.95	(3.31, 12.68)
Trospium	7	1,569	402	17.42	(7.00, 35.89)	14.12	(5.43, 29.53)
Fesoterodine	1	634	123	8.15	(0.21, 45.39)	5.92	(0.15, 32.97)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with recent exposure to							
Any OAB drug	152	113,155	36,024	4.22	(3.58, 4.95)	4.31	(3.65, 5.05)
Oxybutynin	65	47,904	13,417	4.84	(3.74, 6.17)	4.67	(3.61, 5.96)
Tolterodine	61	45,033	12,299	4.96	(3.79, 6.37)	4.92	(3.77, 6.33)
Darifenacin	2	599	131	15.24	(1.85, 55.07)	18.44	(1.64, 68.40)
Solifenacin	31	45,249	11,355	2.73	(1.85, 3.88)	3.23	(2.18, 4.60)
Trospium	11	10,428	2,849	3.86	(1.93, 6.91)	3.78	(1.88, 6.77)
Fesoterodine	0	5,298	1,056	0.00	(0.00, 3.49)	0.00	not estimable
Overall, aged ≥ 65 years with recent exposure to							
Any OAB drug	143	58,765	18,379	7.78	(6.56, 9.17)	7.92	(6.67, 9.33)
Oxybutynin	60	25,383	7,073	8.48	(6.47, 10.92)	8.38	(6.39, 10.79)
Tolterodine	56	23,883	6,456	8.67	(6.55, 11.26)	8.81	(6.65, 11.44)
Darifenacin	2	319	67	29.75	(3.60, 107.5)	36.01	(3.20, 133.5)
Solifenacin	31	22,663	5,562	5.57	(3.79, 7.91)	6.31	(4.27, 8.97)
Trospium	11	5,859	1,578	6.97	(3.48, 12.47)	7.37	(3.67, 13.22)
Fesoterodine	0	2,545	490	0.00	(0.00, 7.52)	0.00	not estimable
Overall, with high CV risk and with recent exposure to							
Any OAB drug	119	48,630	15,122	7.87	(6.52, 9.42)	5.99	(4.93, 7.20)
Oxybutynin	54	20,871	5,792	9.32	(7.00, 12.16)	6.97	(5.19, 9.15)
Tolterodine	43	19,245	5,184	8.29	(6.00, 11.17)	6.42	(4.51, 8.80)
Darifenacin	2	252	55	36.18	(4.38, 130.7)	26.82	(3.14, 97.18)
Solifenacin	24	19,023	4,697	5.11	(3.27, 7.60)	4.13	(2.64, 6.15)
Trospium	7	4,632	1,240	5.64	(2.27, 11.63)	4.37	(1.71, 9.07)
Fesoterodine	0	2,134	417	0.00	(0.00, 8.84)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with recent exposure to							
Any OAB drug	91	79,431	26,014	3.50	(2.82, 4.29)	3.56	(2.86, 4.37)
Oxybutynin	37	33,248	9,453	3.91	(2.76, 5.40)	3.69	(2.60, 5.09)
Tolterodine	37	31,478	8,733	4.24	(2.98, 5.84)	4.23	(2.98, 5.84)
Darifenacin	1	455	101	9.86	(0.25, 54.91)	9.35	(0.24, 52.12)
Solifenacin	18	33,886	8,640	2.08	(1.23, 3.29)	2.42	(1.42, 3.83)
Trospium	7	7,478	2,087	3.35	(1.35, 6.91)	3.41	(1.36, 7.04)
Fesoterodine	0	3,988	810	0.00	(0.00, 4.56)	0.00	not estimable
Female, aged ≥ 65 with recent exposure to							
Any OAB drug	84	38,965	12,632	6.65	(5.30, 8.23)	6.74	(5.38, 8.35)
Oxybutynin	34	16,952	4,834	7.03	(4.87, 9.83)	6.90	(4.78, 9.64)
Tolterodine	33	15,829	4,357	7.57	(5.21, 10.64)	7.73	(5.32, 10.86)
Darifenacin	1	230	49	20.43	(0.52, 113.8)	19.21	(0.49, 107.0)
Solifenacin	18	15,930	3,985	4.52	(2.68, 7.14)	4.96	(2.93, 7.86)
Trospium	7	3,946	1,097	6.38	(2.56, 13.14)	6.99	(2.79, 14.45)
Fesoterodine	0	1,785	352	0.00	(0.00, 10.49)	0.00	not estimable
Female, with high CV risk and with recent exposure to							
Any OAB drug	68	31,512	10,062	6.76	(5.25, 8.57)	5.27	(4.05, 6.72)
Oxybutynin	30	13,534	3,801	7.89	(5.33, 11.27)	5.94	(3.96, 8.54)
Tolterodine	25	12,413	3,371	7.42	(4.80, 10.95)	5.92	(3.67, 8.96)
Darifenacin	1	177	39	25.46	(0.64, 141.9)	16.95	(0.43, 94.43)
Solifenacin	12	13,156	3,310	3.63	(1.87, 6.33)	2.95	(1.52, 5.16)
Trospium	5	3,055	832	6.01	(1.95, 14.02)	4.75	(1.52, 11.13)
Fesoterodine	0	1,494	293	0.00	(0.00, 12.57)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4c. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Coronary Heart Disease Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with recent exposure to							
Any OAB drug	61	33,724	10,010	6.09	(4.66, 7.83)	6.20	(4.74, 7.97)
Oxybutynin	28	14,656	3,965	7.06	(4.69, 10.21)	7.15	(4.75, 10.34)
Tolterodine	24	13,555	3,567	6.73	(4.31, 10.01)	6.67	(4.27, 9.93)
Darifenacin	1	144	30	33.64	(0.85, 187.4)	41.40	(1.05, 230.7)
Solifenacin	13	11,363	2,715	4.79	(2.55, 8.19)	5.28	(2.81, 9.05)
Trospium	4	2,950	762	5.25	(1.43, 13.44)	4.71	(1.28, 12.07)
Fesoterodine	0	1,310	246	0.00	(0.00, 14.97)	0.00	not estimable
Male, aged ≥ 65 years with recent exposure to							
Any OAB drug	59	19,800	5,748	10.26	(7.81, 13.24)	10.43	(7.94, 13.45)
Oxybutynin	26	8,431	2,239	11.61	(7.59, 17.01)	11.55	(7.54, 16.92)
Tolterodine	23	8,054	2,099	10.96	(6.95, 16.44)	11.11	(7.04, 16.68)
Darifenacin	1	89	18	54.73	(1.39, 304.9)	71.88	(1.82, 400.5)
Solifenacin	13	6,733	1,577	8.24	(4.39, 14.10)	9.18	(4.87, 15.71)
Trospium	4	1,913	481	8.32	(2.27, 21.31)	8.19	(2.23, 20.96)
Fesoterodine	0	760	139	0.00	(0.00, 26.56)	0.00	not estimable
Male, with high CV risk and with recent exposure to							
Any OAB drug	51	17,118	5,059	10.08	(7.51, 13.25)	7.82	(5.81, 10.30)
Oxybutynin	24	7,337	1,991	12.05	(7.72, 17.94)	9.58	(6.09, 14.31)
Tolterodine	18	6,832	1,813	9.93	(5.88, 15.69)	7.65	(4.51, 12.13)
Darifenacin	1	75	16	62.52	(1.58, 348.3)	51.73	(1.31, 288.2)
Solifenacin	12	5,867	1,387	8.65	(4.47, 15.11)	7.11	(3.67, 12.43)
Trospium	2	1,577	408	4.90	(0.59, 17.70)	3.40	(0.41, 12.27)
Fesoterodine	0	640	124	0.00	(0.00, 29.76)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with recent exposure to							
Any OAB drug	168	113,155	36,024	4.66	(3.99, 5.42)	4.77	(4.08, 5.55)
Oxybutynin	53	47,904	13,417	3.95	(2.96, 5.17)	3.78	(2.83, 4.94)
Tolterodine	67	45,033	12,299	5.45	(4.22, 6.92)	5.40	(4.19, 6.86)
Darifenacin	0	599	131	0.00	(0.00, 28.12)	0.00	not estimable
Solifenacin	39	45,249	11,355	3.43	(2.44, 4.70)	3.87	(2.74, 5.30)
Trospium	16	10,428	2,849	5.62	(3.21, 9.12)	5.58	(3.18, 9.08)
Fesoterodine	5	5,298	1,056	4.73	(1.54, 11.05)	5.79	(1.81, 13.64)
Overall, aged ≥ 65 years with recent exposure to							
Any OAB drug	164	58,765	18,379	8.92	(7.61, 10.40)	9.10	(7.76, 10.61)
Oxybutynin	52	25,383	7,073	7.35	(5.49, 9.64)	7.22	(5.39, 9.47)
Tolterodine	66	23,883	6,456	10.22	(7.91, 13.01)	10.39	(8.03, 13.22)
Darifenacin	0	319	67	0.00	(0.00, 54.88)	0.00	not estimable
Solifenacin	38	22,663	5,562	6.83	(4.83, 9.38)	7.39	(5.21, 10.17)
Trospium	14	5,859	1,578	8.87	(4.85, 14.89)	9.47	(5.16, 15.92)
Fesoterodine	5	2,545	490	10.19	(3.31, 23.79)	11.30	(3.54, 26.63)
Overall, with high CV risk and with recent exposure to							
Any OAB drug	123	48,630	15,122	8.13	(6.76, 9.70)	5.96	(4.94, 7.12)
Oxybutynin	46	20,871	5,792	7.94	(5.81, 10.59)	5.48	(3.99, 7.34)
Tolterodine	43	19,245	5,184	8.29	(6.00, 11.17)	6.01	(4.32, 8.13)
Darifenacin	0	252	55	0.00	(0.00, 66.74)	0.00	not estimable
Solifenacin	25	19,023	4,697	5.32	(3.44, 7.86)	4.22	(2.73, 6.24)
Trospium	12	4,632	1,240	9.68	(5.00, 16.90)	8.07	(4.04, 14.30)
Fesoterodine	5	2,134	417	11.98	(3.89, 27.96)	9.56	(2.93, 22.64)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with recent exposure to							
Any OAB drug	100	79,431	26,014	3.84	(3.13, 4.68)	3.92	(3.19, 4.77)
Oxybutynin	27	33,248	9,453	2.86	(1.88, 4.16)	2.63	(1.73, 3.83)
Tolterodine	45	31,478	8,733	5.15	(3.76, 6.90)	5.12	(3.73, 6.85)
Darifenacin	0	455	101	0.00	(0.00, 36.36)	0.00	not estimable
Solifenacin	25	33,886	8,640	2.89	(1.87, 4.27)	3.27	(2.11, 4.84)
Trospium	10	7,478	2,087	4.79	(2.30, 8.81)	4.92	(2.34, 9.07)
Fesoterodine	2	3,988	810	2.47	(0.30, 8.92)	3.22	(0.27, 11.98)
Female, aged ≥ 65 with recent exposure to							
Any OAB drug	97	38,965	12,632	7.68	(6.23, 9.37)	7.80	(6.33, 9.52)
Oxybutynin	26	16,952	4,834	5.38	(3.51, 7.88)	5.18	(3.38, 7.59)
Tolterodine	44	15,829	4,357	10.10	(7.34, 13.56)	10.27	(7.46, 13.79)
Darifenacin	0	230	49	0.00	(0.00, 75.36)	0.00	not estimable
Solifenacin	24	15,930	3,985	6.02	(3.86, 8.96)	6.48	(4.13, 9.66)
Trospium	9	3,946	1,097	8.20	(3.75, 15.57)	9.15	(4.16, 17.42)
Fesoterodine	2	1,785	352	5.69	(0.69, 20.55)	6.61	(0.56, 24.60)
Female, with high CV risk and with recent exposure to							
Any OAB drug	67	31,512	10,062	6.66	(5.16, 8.46)	4.94	(3.82, 6.29)
Oxybutynin	25	13,534	3,801	6.58	(4.26, 9.71)	4.51	(2.89, 6.68)
Tolterodine	25	12,413	3,371	7.42	(4.80, 10.95)	5.43	(3.50, 8.05)
Darifenacin	0	177	39	0.00	(0.00, 93.92)	0.00	not estimable
Solifenacin	14	13,156	3,310	4.23	(2.31, 7.10)	3.38	(1.84, 5.68)
Trospium	7	3,055	832	8.41	(3.38, 17.34)	7.32	(2.87, 15.20)
Fesoterodine	2	1,494	293	6.82	(0.83, 24.63)	6.41	(0.64, 23.55)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4d. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cerebrovascular Disease Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with recent exposure to							
Any OAB drug	68	33,724	10,010	6.79	(5.28, 8.61)	6.93	(5.38, 8.79)
Oxybutynin	26	14,656	3,965	6.56	(4.28, 9.61)	6.67	(4.36, 9.77)
Tolterodine	22	13,555	3,567	6.17	(3.87, 9.34)	6.12	(3.83, 9.27)
Darifenacin	0	144	30	0.00	(0.00, 124.1)	0.00	not estimable
Solifenacin	14	11,363	2,715	5.16	(2.82, 8.65)	5.38	(2.93, 9.04)
Trospium	6	2,950	762	7.88	(2.89, 17.14)	7.26	(2.65, 15.83)
Fesoterodine	3	1,310	246	12.17	(2.51, 35.57)	12.28	(2.53, 35.88)
Male, aged ≥ 65 years with recent exposure to							
Any OAB drug	67	19,800	5,748	11.66	(9.03, 14.80)	11.87	(9.20, 15.07)
Oxybutynin	26	8,431	2,239	11.61	(7.59, 17.01)	11.58	(7.56, 16.97)
Tolterodine	22	8,054	2,099	10.48	(6.57, 15.87)	10.63	(6.66, 16.10)
Darifenacin	0	89	18	0.00	(0.00, 201.9)	0.00	not estimable
Solifenacin	14	6,733	1,577	8.88	(4.85, 14.90)	9.34	(5.09, 15.70)
Trospium	5	1,913	481	10.40	(3.38, 24.28)	10.15	(3.30, 23.69)
Fesoterodine	3	760	139	21.60	(4.45, 63.13)	21.31	(4.40, 62.29)
Male, with high CV risk and with recent exposure to							
Any OAB drug	56	17,118	5,059	11.07	(8.36, 14.37)	8.51	(6.42, 11.07)
Oxybutynin	21	7,337	1,991	10.55	(6.53, 16.12)	7.95	(4.91, 12.15)
Tolterodine	18	6,832	1,813	9.93	(5.88, 15.69)	7.45	(4.41, 11.79)
Darifenacin	0	75	16	0.00	(0.00, 230.6)	0.00	not estimable
Solifenacin	11	5,867	1,387	7.93	(3.96, 14.19)	6.36	(3.17, 11.38)
Trospium	5	1,577	408	12.25	(3.98, 28.59)	9.98	(2.95, 23.87)
Fesoterodine	3	640	124	24.20	(4.99, 70.73)	17.50	(3.61, 51.14)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with recent exposure to							
Any OAB drug	315	113,155	36,024	8.74	(7.81, 9.77)	8.94	(7.98, 9.98)
Oxybutynin	116	47,904	13,417	8.65	(7.14, 10.37)	8.31	(6.87, 9.97)
Tolterodine	126	45,033	12,299	10.24	(8.53, 12.20)	10.17	(8.47, 12.11)
Darifenacin	2	599	131	15.24	(1.85, 55.07)	18.44	(1.64, 68.40)
Solifenacin	69	45,249	11,355	6.08	(4.73, 7.69)	6.99	(5.43, 8.87)
Trospium	26	10,428	2,849	9.13	(5.96, 13.37)	9.03	(5.89, 13.25)
Fesoterodine	5	5,298	1,056	4.73	(1.54, 11.05)	5.79	(1.81, 13.64)
Overall, aged ≥ 65 years with recent exposure to							
Any OAB drug	302	58,765	18,379	16.43	(14.63, 18.39)	16.75	(14.91, 18.75)
Oxybutynin	110	25,383	7,073	15.55	(12.78, 18.74)	15.33	(12.60, 18.48)
Tolterodine	120	23,883	6,456	18.59	(15.41, 22.23)	18.89	(15.66, 22.59)
Darifenacin	2	319	67	29.75	(3.60, 107.5)	36.01	(3.20, 133.5)
Solifenacin	68	22,663	5,562	12.23	(9.49, 15.50)	13.49	(10.45, 17.13)
Trospium	24	5,859	1,578	15.21	(9.75, 22.63)	16.21	(10.36, 24.15)
Fesoterodine	5	2,545	490	10.19	(3.31, 23.79)	11.30	(3.54, 26.63)
Overall, with high CV risk and with recent exposure to							
Any OAB drug	240	48,630	15,122	15.87	(13.93, 18.01)	11.84	(10.36, 13.48)
Oxybutynin	99	20,871	5,792	17.09	(13.89, 20.81)	12.33	(9.97, 15.07)
Tolterodine	86	19,245	5,184	16.59	(13.27, 20.49)	12.42	(9.82, 15.48)
Darifenacin	2	252	55	36.18	(4.38, 130.7)	26.82	(3.14, 97.18)
Solifenacin	48	19,023	4,697	10.22	(7.54, 13.55)	8.16	(6.01, 10.83)
Trospium	19	4,632	1,240	15.32	(9.22, 23.93)	12.44	(7.35, 19.62)
Fesoterodine	5	2,134	417	11.98	(3.89, 27.96)	9.56	(2.93, 22.64)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with recent exposure to							
Any OAB drug	187	79,431	26,014	7.19	(6.20, 8.30)	7.32	(6.30, 8.44)
Oxybutynin	63	33,248	9,453	6.66	(5.12, 8.53)	6.23	(4.79, 7.97)
Tolterodine	80	31,478	8,733	9.16	(7.26, 11.40)	9.13	(7.24, 11.36)
Darifenacin	1	455	101	9.86	(0.25, 54.91)	9.35	(0.24, 52.12)
Solifenacin	42	33,886	8,640	4.86	(3.50, 6.57)	5.54	(3.98, 7.50)
Trospium	17	7,478	2,087	8.14	(4.74, 13.04)	8.32	(4.83, 13.36)
Fesoterodine	2	3,988	810	2.47	(0.30, 8.92)	3.22	(0.27, 11.98)
Female, aged ≥ 65 with recent exposure to							
Any OAB drug	177	38,965	12,632	14.01	(12.02, 16.24)	14.23	(12.21, 16.48)
Oxybutynin	59	16,952	4,834	12.20	(9.29, 15.74)	11.88	(9.04, 15.33)
Tolterodine	75	15,829	4,357	17.21	(13.54, 21.58)	17.56	(13.81, 22.01)
Darifenacin	1	230	49	20.43	(0.52, 113.8)	19.21	(0.49, 107.0)
Solifenacin	41	15,930	3,985	10.29	(7.38, 13.96)	11.13	(7.97, 15.13)
Trospium	16	3,946	1,097	14.58	(8.34, 23.68)	16.15	(9.19, 26.28)
Fesoterodine	2	1,785	352	5.69	(0.69, 20.55)	6.61	(0.56, 24.60)
Female, with high CV risk and with recent exposure to							
Any OAB drug	133	31,512	10,062	13.22	(11.07, 15.66)	10.06	(8.39, 11.97)
Oxybutynin	54	13,534	3,801	14.21	(10.67, 18.54)	10.27	(7.66, 13.47)
Tolterodine	50	12,413	3,371	14.83	(11.01, 19.55)	11.36	(8.29, 15.15)
Darifenacin	1	177	39	25.46	(0.64, 141.9)	16.95	(0.43, 94.43)
Solifenacin	25	13,156	3,310	7.55	(4.89, 11.15)	6.06	(3.91, 8.95)
Trospium	12	3,055	832	14.42	(7.45, 25.19)	12.07	(6.16, 21.21)
Fesoterodine	2	1,494	293	6.82	(0.83, 24.63)	6.41	(0.64, 23.55)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4e. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Cardiovascular Death, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with recent exposure to							
Any OAB drug	128	33,724	10,010	12.79	(10.67, 15.20)	13.04	(10.88, 15.51)
Oxybutynin	53	14,656	3,965	13.37	(10.01, 17.49)	13.57	(10.17, 17.76)
Tolterodine	46	13,555	3,567	12.90	(9.44, 17.20)	12.79	(9.36, 17.07)
Darifenacin	1	144	30	33.64	(0.85, 187.4)	41.40	(1.05, 230.7)
Solifenacin	27	11,363	2,715	9.95	(6.55, 14.47)	10.67	(7.01, 15.54)
Trospium	9	2,950	762	11.81	(5.40, 22.42)	10.82	(4.94, 20.57)
Fesoterodine	3	1,310	246	12.17	(2.51, 35.57)	12.28	(2.53, 35.88)
Male, aged ≥ 65 years with recent exposure to							
Any OAB drug	125	19,800	5,748	21.75	(18.10, 25.91)	22.12	(18.41, 26.36)
Oxybutynin	51	8,431	2,239	22.78	(16.96, 29.95)	22.70	(16.90, 29.84)
Tolterodine	45	8,054	2,099	21.44	(15.64, 28.69)	21.74	(15.85, 29.10)
Darifenacin	1	89	18	54.73	(1.39, 304.9)	71.88	(1.82, 400.5)
Solifenacin	27	6,733	1,577	17.12	(11.28, 24.91)	18.52	(12.18, 26.98)
Trospium	8	1,913	481	16.65	(7.19, 32.80)	16.34	(7.05, 32.20)
Fesoterodine	3	760	139	21.60	(4.45, 63.13)	21.31	(4.40, 62.29)
Male, with high CV risk and with recent exposure to							
Any OAB drug	107	17,118	5,059	21.15	(17.33, 25.56)	16.34	(13.37, 19.76)
Oxybutynin	45	7,337	1,991	22.60	(16.49, 30.24)	17.52	(12.74, 23.50)
Tolterodine	36	6,832	1,813	19.86	(13.91, 27.49)	15.11	(10.56, 20.95)
Darifenacin	1	75	16	62.52	(1.58, 348.3)	51.73	(1.31, 288.2)
Solifenacin	23	5,867	1,387	16.58	(10.51, 24.88)	13.47	(8.53, 20.22)
Trospium	7	1,577	408	17.15	(6.90, 35.34)	13.38	(5.08, 28.08)
Fesoterodine	3	640	124	24.20	(4.99, 70.73)	17.50	(3.61, 51.14)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with recent exposure to							
Any OAB drug	543	112,906	35,665	15.23	(13.97, 16.56)	15.59	(14.31, 16.96)
Oxybutynin	232	47,729	13,287	17.46	(15.29, 19.86)	17.04	(14.92, 19.39)
Tolterodine	201	44,894	12,178	16.50	(14.30, 18.95)	16.40	(14.21, 18.83)
Darifenacin	3	593	130	23.06	(4.76, 67.39)	25.46	(4.52, 76.18)
Solifenacin	129	45,020	11,244	11.47	(9.58, 13.63)	12.72	(10.60, 15.14)
Trospium	38	10,367	2,815	13.50	(9.55, 18.53)	13.31	(9.40, 18.28)
Fesoterodine	11	5,260	1,047	10.51	(5.25, 18.81)	12.35	(6.03, 22.31)
Overall, aged ≥ 65 years with recent exposure to							
Any OAB drug	477	58,503	18,079	26.38	(24.07, 28.86)	26.83	(24.47, 29.35)
Oxybutynin	201	25,224	6,964	28.86	(25.01, 33.14)	28.54	(24.73, 32.77)
Tolterodine	175	23,748	6,358	27.52	(23.60, 31.92)	27.84	(23.87, 32.29)
Darifenacin	3	314	66	45.25	(9.33, 132.2)	49.71	(8.82, 148.7)
Solifenacin	116	22,458	5,468	21.21	(17.53, 25.44)	22.69	(18.71, 27.26)
Trospium	34	5,804	1,548	21.96	(15.21, 30.69)	23.13	(15.99, 32.35)
Fesoterodine	11	2,513	482	22.81	(11.39, 40.82)	24.11	(11.77, 43.57)
Overall, with high CV risk and with recent exposure to							
Any OAB drug	407	48,450	14,880	27.35	(24.76, 30.14)	22.08	(19.88, 24.44)
Oxybutynin	182	20,739	5,706	31.89	(27.43, 36.88)	25.37	(21.62, 29.55)
Tolterodine	144	19,149	5,096	28.26	(23.83, 33.27)	22.26	(18.58, 26.43)
Darifenacin	3	247	54	55.05	(11.35, 160.9)	39.62	(8.07, 116.0)
Solifenacin	91	18,876	4,629	19.66	(15.83, 24.13)	16.99	(13.52, 21.05)
Trospium	33	4,590	1,216	27.13	(18.67, 38.10)	22.46	(15.16, 31.93)
Fesoterodine	7	2,110	411	17.03	(6.85, 35.08)	13.80	(5.39, 28.73)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with recent exposure to							
Any OAB drug	334	79,282	25,792	12.95	(11.60, 14.42)	13.21	(11.83, 14.71)
Oxybutynin	138	33,138	9,371	14.73	(12.37, 17.40)	14.07	(11.82, 16.63)
Tolterodine	118	31,390	8,662	13.62	(11.28, 16.31)	13.59	(11.25, 16.28)
Darifenacin	2	452	101	19.87	(2.41, 71.78)	19.15	(2.32, 69.17)
Solifenacin	90	33,741	8,568	10.50	(8.45, 12.91)	11.73	(9.41, 14.44)
Trospium	23	7,437	2,065	11.14	(7.06, 16.71)	11.26	(7.11, 16.94)
Fesoterodine	7	3,962	802	8.73	(3.51, 17.98)	10.81	(4.12, 22.67)
Female, aged ≥ 65 with recent exposure to							
Any OAB drug	289	38,810	12,450	23.21	(20.61, 26.05)	23.54	(20.90, 26.42)
Oxybutynin	117	16,857	4,768	24.54	(20.29, 29.41)	24.01	(19.85, 28.78)
Tolterodine	102	15,740	4,302	23.71	(19.33, 28.79)	24.08	(19.63, 29.24)
Darifenacin	2	228	48	41.39	(5.01, 149.5)	39.32	(4.76, 142.1)
Solifenacin	80	15,802	3,924	20.39	(16.16, 25.37)	21.85	(17.29, 27.24)
Trospium	20	3,911	1,078	18.55	(11.33, 28.64)	20.09	(12.22, 31.11)
Fesoterodine	7	1,763	345	20.27	(8.15, 41.76)	22.19	(8.45, 46.55)
Female, with high CV risk and with recent exposure to							
Any OAB drug	238	31,410	9,926	23.98	(21.03, 27.22)	19.45	(16.94, 22.21)
Oxybutynin	104	13,456	3,751	27.72	(22.65, 33.59)	22.16	(17.85, 27.14)
Tolterodine	80	12,356	3,325	24.06	(19.08, 29.94)	18.84	(14.78, 23.64)
Darifenacin	2	175	39	51.56	(6.24, 186.3)	34.83	(4.22, 125.8)
Solifenacin	59	13,072	3,270	18.04	(13.73, 23.27)	15.61	(11.68, 20.40)
Trospium	20	3,030	817	24.47	(14.95, 37.79)	21.40	(12.79, 33.44)
Fesoterodine	5	1,479	289	17.31	(5.62, 40.40)	14.52	(4.52, 34.29)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4f. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for Major Adverse Cardiovascular Event, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with recent exposure to							
Any OAB drug	209	33,624	9,872	21.17	(18.40, 24.24)	21.60	(18.77, 24.74)
Oxybutynin	94	14,591	3,916	24.01	(19.40, 29.38)	24.55	(19.84, 30.04)
Tolterodine	83	13,504	3,516	23.61	(18.80, 29.26)	23.49	(18.70, 29.12)
Darifenacin	1	141	29	33.96	(0.86, 189.2)	41.40	(1.05, 230.7)
Solifenacin	39	11,279	2,676	14.57	(10.36, 19.92)	15.23	(10.81, 20.84)
Trospium	15	2,930	750	19.99	(11.19, 32.98)	18.47	(10.33, 30.47)
Fesoterodine	4	1,298	244	16.37	(4.46, 41.91)	16.25	(4.42, 41.61)
Male, aged ≥ 65 years with recent exposure to							
Any OAB drug	188	19,693	5,629	33.40	(28.80, 38.53)	33.85	(29.18, 39.05)
Oxybutynin	84	8,367	2,195	38.27	(30.52, 47.38)	38.21	(30.48, 47.31)
Tolterodine	73	8,008	2,057	35.50	(27.82, 44.63)	35.86	(28.11, 45.10)
Darifenacin	1	86	18	55.59	(1.41, 309.7)	71.88	(1.82, 400.5)
Solifenacin	36	6,656	1,544	23.32	(16.33, 32.29)	24.49	(17.12, 33.94)
Trospium	14	1,893	470	29.81	(16.30, 50.02)	29.60	(16.18, 49.66)
Fesoterodine	4	750	137	29.23	(7.96, 74.85)	28.21	(7.68, 72.25)
Male, with high CV risk and with recent exposure to							
Any OAB drug	169	17,040	4,954	34.11	(29.16, 39.66)	28.71	(24.40, 33.55)
Oxybutynin	78	7,283	1,955	39.90	(31.54, 49.79)	33.47	(26.31, 41.94)
Tolterodine	64	6,793	1,771	36.13	(27.83, 46.14)	30.90	(23.32, 40.04)
Darifenacin	1	72	16	63.65	(1.61, 354.7)	51.73	(1.31, 288.2)
Solifenacin	32	5,804	1,359	23.55	(16.11, 33.24)	20.46	(13.79, 29.17)
Trospium	13	1,560	399	32.57	(17.34, 55.70)	25.13	(13.15, 43.33)
Fesoterodine	2	631	122	16.36	(1.98, 59.10)	11.98	(1.45, 43.29)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, with recent exposure to							
Any OAB drug	1,434	113,155	36,024	39.81	(37.77, 41.92)	40.60	(38.53, 42.76)
Oxybutynin	504	47,904	13,417	37.56	(34.36, 40.99)	36.08	(32.99, 39.37)
Tolterodine	531	45,033	12,299	43.17	(39.58, 47.01)	42.82	(39.25, 46.62)
Darifenacin	5	599	131	38.11	(12.37, 88.94)	43.80	(13.69, 103.3)
Solifenacin	361	45,249	11,355	31.79	(28.60, 35.25)	35.92	(32.28, 39.86)
Trospium	116	10,428	2,849	40.71	(33.64, 48.83)	39.56	(32.65, 47.49)
Fesoterodine	30	5,298	1,056	28.40	(19.16, 40.54)	37.96	(25.37, 54.51)
Overall, aged ≥ 65 years with recent exposure to							
Any OAB drug	1,326	58,765	18,379	72.15	(68.31, 76.14)	73.39	(69.49, 77.45)
Oxybutynin	459	25,383	7,073	64.89	(59.09, 71.11)	63.68	(57.98, 69.79)
Tolterodine	492	23,883	6,456	76.21	(69.62, 83.25)	77.34	(70.65, 84.49)
Darifenacin	5	319	67	74.38	(24.15, 173.6)	85.52	(26.73, 201.6)
Solifenacin	334	22,663	5,562	60.05	(53.78, 66.85)	65.64	(58.74, 73.13)
Trospium	107	5,859	1,578	67.82	(55.58, 81.95)	70.49	(57.71, 85.24)
Fesoterodine	26	2,545	490	53.01	(34.63, 77.67)	66.70	(43.22, 98.20)
Overall, with high CV risk and with recent exposure to							
Any OAB drug	1,015	48,630	15,122	67.12	(63.06, 71.38)	50.33	(47.21, 53.59)
Oxybutynin	361	20,871	5,792	62.33	(56.06, 69.10)	45.67	(40.91, 50.82)
Tolterodine	373	19,245	5,184	71.95	(64.83, 79.64)	53.70	(48.20, 59.65)
Darifenacin	5	252	55	90.46	(29.37, 211.1)	69.57	(21.87, 163.8)
Solifenacin	256	19,023	4,697	54.50	(48.03, 61.61)	44.25	(38.94, 50.08)
Trospium	85	4,632	1,240	68.54	(54.75, 84.75)	51.37	(40.79, 63.79)
Fesoterodine	22	2,134	417	52.72	(33.04, 79.82)	47.71	(29.47, 72.83)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, with recent exposure to							
Any OAB drug	863	79,431	26,014	33.17	(31.00, 35.46)	33.78	(31.56, 36.11)
Oxybutynin	293	33,248	9,453	31.00	(27.55, 34.76)	28.98	(25.75, 32.50)
Tolterodine	330	31,478	8,733	37.79	(33.82, 42.09)	37.67	(33.71, 41.96)
Darifenacin	2	455	101	19.71	(2.39, 71.20)	21.93	(2.45, 79.83)
Solifenacin	223	33,886	8,640	25.81	(22.53, 29.43)	29.16	(25.43, 33.28)
Trospium	74	7,478	2,087	35.45	(27.84, 44.51)	35.25	(27.62, 44.31)
Fesoterodine	15	3,988	810	18.52	(10.37, 30.55)	26.28	(14.38, 43.83)
Female, aged ≥ 65 with recent exposure to							
Any OAB drug	787	38,965	12,632	62.30	(58.03, 66.81)	63.31	(58.96, 67.90)
Oxybutynin	265	16,952	4,834	54.82	(48.41, 61.83)	53.06	(46.86, 59.85)
Tolterodine	298	15,829	4,357	68.39	(60.85, 76.62)	69.75	(62.05, 78.14)
Darifenacin	2	230	49	40.86	(4.95, 147.6)	45.04	(5.03, 164.0)
Solifenacin	202	15,930	3,985	50.69	(43.94, 58.18)	55.11	(47.72, 63.31)
Trospium	68	3,946	1,097	61.97	(48.13, 78.57)	65.91	(51.09, 83.67)
Fesoterodine	13	1,785	352	36.97	(19.69, 63.22)	49.27	(25.78, 84.94)
Female, with high CV risk and with recent exposure to							
Any OAB drug	575	31,512	10,062	57.14	(52.57, 62.01)	43.30	(39.75, 47.06)
Oxybutynin	200	13,534	3,801	52.62	(45.58, 60.44)	38.24	(32.90, 44.17)
Tolterodine	219	12,413	3,371	64.96	(56.64, 74.16)	49.08	(42.58, 56.27)
Darifenacin	2	177	39	50.92	(6.17, 183.9)	42.64	(4.38, 156.4)
Solifenacin	148	13,156	3,310	44.71	(37.80, 52.53)	37.03	(31.23, 43.59)
Trospium	50	3,055	832	60.10	(44.61, 79.23)	45.87	(33.85, 60.72)
Fesoterodine	11	1,494	293	37.50	(18.72, 67.09)	38.66	(19.02, 69.62)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV4g. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) for All-Cause Mortality, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, with recent exposure to							
Any OAB drug	571	33,724	10,010	57.05	(52.46, 61.92)	57.84	(53.19, 62.78)
Oxybutynin	211	14,656	3,965	53.22	(46.28, 60.91)	54.01	(46.96, 61.81)
Tolterodine	201	13,555	3,567	56.36	(48.83, 64.71)	55.81	(48.36, 64.09)
Darifenacin	3	144	30	100.92	(20.81, 294.9)	99.03	(19.16, 292.5)
Solifenacin	138	11,363	2,715	50.83	(42.71, 60.06)	52.99	(44.49, 62.63)
Trospium	42	2,950	762	55.13	(39.73, 74.52)	50.46	(36.35, 68.23)
Fesoterodine	15	1,310	246	60.86	(34.06, 100.4)	67.44	(37.40, 111.7)
Male, aged ≥ 65 years with recent exposure to							
Any OAB drug	539	19,800	5,748	93.78	(86.03, 102.0)	94.89	(87.05, 103.3)
Oxybutynin	194	8,431	2,239	86.64	(74.88, 99.73)	86.36	(74.63, 99.41)
Tolterodine	194	8,054	2,099	92.44	(79.89, 106.4)	93.54	(80.83, 107.7)
Darifenacin	3	89	18	164.18	(33.86, 479.8)	171.94	(33.27, 507.8)
Solifenacin	132	6,733	1,577	83.71	(70.04, 99.27)	88.12	(73.68, 104.6)
Trospium	39	1,913	481	81.15	(57.71, 110.9)	80.25	(57.06, 109.7)
Fesoterodine	13	760	139	93.61	(49.84, 160.1)	103.89	(54.80, 178.5)
Male, with high CV risk and with recent exposure to							
Any OAB drug	440	17,118	5,059	86.97	(79.03, 95.49)	68.08	(61.82, 74.79)
Oxybutynin	161	7,337	1,991	80.86	(68.85, 94.36)	64.46	(54.75, 75.37)
Tolterodine	154	6,832	1,813	84.95	(72.07, 99.48)	65.38	(55.42, 76.62)
Darifenacin	3	75	16	187.56	(38.68, 548.1)	137.55	(27.92, 403.1)
Solifenacin	108	5,867	1,387	77.87	(63.88, 94.02)	62.49	(51.22, 75.50)
Trospium	35	1,577	408	85.76	(59.73, 119.3)	65.25	(45.08, 91.23)
Fesoterodine	11	640	124	88.74	(44.30, 158.8)	70.56	(35.04, 126.5)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with current exposure to				
Any OAB drug	0.91	(0.78, 1.06)	0.98	(0.84, 1.13)
Oxybutynin	1.17	(0.97, 1.41)	1.19	(0.98, 1.43)
Darifenacin	0.38	(0.10, 2.15)	0.49	(0.07, 3.49)
Solifenacin	0.68	(0.55, 0.83)	0.80	(0.66, 0.98)
Trospium	1.06	(0.79, 1.44)	1.11	(0.82, 1.52)
Fesoterodine	0.64	(0.39, 1.11)	0.79	(0.45, 1.39)
Overall, aged ≥ 65 years with current exposure to				
Any OAB drug	0.94	(0.80, 1.11)	0.96	(0.82, 1.12)
Oxybutynin	1.22	(1.00, 1.49)	1.19	(0.98, 1.45)
Darifenacin	0.00	(0.00, 1.63)	0.00	not estimable
Solifenacin	0.69	(0.55, 0.86)	0.74	(0.60, 0.93)
Trospium	1.05	(0.76, 1.47)	1.07	(0.77, 1.49)
Fesoterodine	0.80	(0.48, 1.43)	0.87	(0.48, 1.56)
Overall, with high CV risk and with current exposure to				
Any OAB drug	0.89	(0.75, 1.07)	0.96	(0.80, 1.16)
Oxybutynin	1.11	(0.89, 1.38)	1.18	(0.92, 1.50)
Darifenacin	0.50	(0.13, 2.84)	0.79	(0.11, 5.67)
Solifenacin	0.67	(0.53, 0.85)	0.78	(0.61, 0.99)
Trospium	0.92	(0.64, 1.33)	0.92	(0.63, 1.35)
Fesoterodine	0.79	(0.46, 1.44)	0.86	(0.46, 1.60)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with current exposure to				
Any OAB drug	0.91	(0.74, 1.12)	0.96	(0.79, 1.17)
Oxybutynin	1.22	(0.95, 1.57)	1.18	(0.92, 1.52)
Darifenacin	0.70	(0.19, 3.99)	0.87	(0.12, 6.21)
Solifenacin	0.63	(0.48, 0.82)	0.72	(0.55, 0.95)
Trospium	1.16	(0.79, 1.73)	1.24	(0.83, 1.86)
Fesoterodine	0.67	(0.36, 1.35)	0.83	(0.40, 1.73)
Female, aged ≥ 65 with current exposure to				
Any OAB drug	0.96	(0.76, 1.20)	0.98	(0.79, 1.21)
Oxybutynin	1.30	(0.99, 1.70)	1.24	(0.95, 1.61)
Darifenacin	0.00	(0.00, 3.31)	0.00	not estimable
Solifenacin	0.68	(0.51, 0.92)	0.73	(0.55, 0.98)
Trospium	1.14	(0.75, 1.77)	1.20	(0.78, 1.85)
Fesoterodine	0.84	(0.43, 1.78)	0.90	(0.42, 1.96)
Female, with high CV risk and with current exposure to				
Any OAB drug	0.90	(0.70, 1.16)	0.94	(0.73, 1.20)
Oxybutynin	1.21	(0.89, 1.64)	1.18	(0.86, 1.61)
Darifenacin	1.08	(0.28, 6.18)	1.41	(0.20, 10.10)
Solifenacin	0.62	(0.45, 0.87)	0.71	(0.51, 1.00)
Trospium	0.97	(0.60, 1.61)	0.99	(0.59, 1.66)
Fesoterodine	0.80	(0.39, 1.81)	0.93	(0.40, 2.15)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with current exposure to				
Any OAB drug	0.95	(0.75, 1.19)	1.00	(0.80, 1.25)
Oxybutynin	1.10	(0.82, 1.46)	1.19	(0.90, 1.57)
Darifenacin	0.00	(0.00, 3.12)	0.00	not estimable
Solifenacin	0.82	(0.61, 1.11)	0.90	(0.67, 1.21)
Trospium	0.96	(0.61, 1.57)	0.94	(0.58, 1.54)
Fesoterodine	0.65	(0.31, 1.57)	0.73	(0.30, 1.79)
Male, aged ≥ 65 years with current exposure to				
Any OAB drug	0.94	(0.73, 1.20)	0.94	(0.75, 1.19)
Oxybutynin	1.15	(0.85, 1.55)	1.13	(0.84, 1.52)
Darifenacin	0.00	(0.00, 3.13)	0.00	not estimable
Solifenacin	0.74	(0.53, 1.03)	0.76	(0.55, 1.05)
Trospium	0.96	(0.59, 1.62)	0.91	(0.55, 1.53)
Fesoterodine	0.79	(0.37, 1.90)	0.82	(0.33, 2.02)
Male, with high CV risk and with current exposure to				
Any OAB drug	0.91	(0.70, 1.17)	1.00	(0.76, 1.31)
Oxybutynin	1.01	(0.73, 1.40)	1.18	(0.81, 1.72)
Darifenacin	0.00	(0.00, 3.37)	0.00	not estimable
Solifenacin	0.77	(0.55, 1.09)	0.87	(0.61, 1.23)
Trospium	0.89	(0.53, 1.54)	0.82	(0.47, 1.44)
Fesoterodine	0.83	(0.39, 2.00)	0.76	(0.31, 1.89)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Stroke, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with current exposure to				
Any OAB drug	0.91	(0.79, 1.04)	0.95	(0.83, 1.08)
Oxybutynin	1.10	(0.93, 1.31)	1.07	(0.90, 1.26)
Darifenacin	0.93	(0.38, 2.76)	0.81	(0.26, 2.55)
Solifenacin	0.70	(0.59, 0.84)	0.81	(0.68, 0.97)
Trospium	1.00	(0.76, 1.32)	1.03	(0.78, 1.37)
Fesoterodine	0.44	(0.26, 0.79)	0.55	(0.30, 1.01)
Overall, aged ≥ 65 years with current exposure to				
Any OAB drug	0.95	(0.82, 1.10)	0.96	(0.84, 1.11)
Oxybutynin	1.16	(0.97, 1.40)	1.11	(0.93, 1.32)
Darifenacin	1.07	(0.44, 3.15)	0.95	(0.30, 2.99)
Solifenacin	0.77	(0.64, 0.93)	0.83	(0.69, 1.01)
Trospium	0.96	(0.71, 1.31)	0.98	(0.72, 1.34)
Fesoterodine	0.43	(0.23, 0.85)	0.49	(0.24, 0.99)
Overall, with high CV risk and with current exposure to				
Any OAB drug	0.94	(0.80, 1.10)	0.90	(0.75, 1.07)
Oxybutynin	1.21	(0.99, 1.47)	1.06	(0.86, 1.32)
Darifenacin	1.32	(0.54, 3.90)	0.90	(0.28, 2.91)
Solifenacin	0.68	(0.54, 0.84)	0.68	(0.54, 0.86)
Trospium	1.00	(0.73, 1.40)	0.98	(0.68, 1.39)
Fesoterodine	0.49	(0.27, 0.99)	0.45	(0.22, 0.93)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Stroke, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with current exposure to				
Any OAB drug	0.89	(0.75, 1.06)	0.93	(0.78, 1.10)
Oxybutynin	1.13	(0.91, 1.40)	1.04	(0.84, 1.29)
Darifenacin	0.49	(0.13, 2.76)	0.47	(0.07, 3.37)
Solifenacin	0.67	(0.54, 0.84)	0.79	(0.63, 0.98)
Trospium	1.02	(0.73, 1.45)	1.07	(0.75, 1.52)
Fesoterodine	0.23	(0.10, 0.60)	0.30	(0.11, 0.83)
Female, aged ≥ 65 with current exposure to				
Any OAB drug	0.94	(0.78, 1.13)	0.95	(0.79, 1.13)
Oxybutynin	1.19	(0.95, 1.49)	1.10	(0.88, 1.38)
Darifenacin	0.60	(0.16, 3.38)	0.56	(0.08, 4.00)
Solifenacin	0.75	(0.59, 0.95)	0.83	(0.65, 1.04)
Trospium	0.96	(0.67, 1.42)	1.00	(0.68, 1.47)
Fesoterodine	0.16	(0.06, 0.59)	0.21	(0.05, 0.87)
Female, with high CV risk and with current exposure to				
Any OAB drug	0.93	(0.75, 1.15)	0.89	(0.71, 1.12)
Oxybutynin	1.23	(0.95, 1.59)	1.04	(0.79, 1.38)
Darifenacin	0.78	(0.21, 4.46)	0.62	(0.09, 4.43)
Solifenacin	0.67	(0.51, 0.89)	0.69	(0.52, 0.93)
Trospium	1.02	(0.68, 1.56)	1.05	(0.67, 1.65)
Fesoterodine	0.19	(0.07, 0.71)	0.22	(0.05, 0.91)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Stroke, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with current exposure to				
Any OAB drug	0.96	(0.76, 1.20)	0.99	(0.79, 1.23)
Oxybutynin	1.06	(0.80, 1.42)	1.11	(0.84, 1.48)
Darifenacin	1.71	(0.59, 6.32)	1.43	(0.35, 5.90)
Solifenacin	0.80	(0.59, 1.09)	0.84	(0.63, 1.14)
Trospium	0.96	(0.61, 1.57)	0.96	(0.59, 1.57)
Fesoterodine	0.92	(0.47, 1.96)	1.01	(0.47, 2.18)
Male, aged ≥ 65 years with current exposure to				
Any OAB drug	0.99	(0.77, 1.26)	0.99	(0.79, 1.25)
Oxybutynin	1.14	(0.84, 1.54)	1.12	(0.83, 1.50)
Darifenacin	1.73	(0.60, 6.40)	1.64	(0.40, 6.77)
Solifenacin	0.84	(0.61, 1.16)	0.85	(0.62, 1.16)
Trospium	0.97	(0.60, 1.63)	0.95	(0.57, 1.59)
Fesoterodine	0.95	(0.47, 2.14)	0.99	(0.44, 2.27)
Male, with high CV risk and with current exposure to				
Any OAB drug	0.97	(0.74, 1.25)	0.91	(0.68, 1.21)
Oxybutynin	1.18	(0.86, 1.63)	1.10	(0.78, 1.55)
Darifenacin	1.96	(0.68, 7.29)	1.43	(0.35, 5.86)
Solifenacin	0.70	(0.49, 1.00)	0.67	(0.46, 0.97)
Trospium	0.99	(0.60, 1.70)	0.83	(0.48, 1.45)
Fesoterodine	1.05	(0.51, 2.37)	0.89	(0.38, 2.05)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5c. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with current exposure to				
Any OAB drug	0.91	(0.74, 1.12)	0.99	(0.81, 1.21)
Oxybutynin	1.34	(1.05, 1.72)	1.36	(1.07, 1.73)
Darifenacin	1.40	(0.49, 5.14)	1.77	(0.43, 7.31)
Solifenacin	0.46	(0.34, 0.63)	0.56	(0.41, 0.76)
Trospium	1.21	(0.83, 1.80)	1.25	(0.85, 1.86)
Fesoterodine	0.80	(0.44, 1.57)	1.10	(0.56, 2.17)
Overall, aged ≥ 65 years with current exposure to				
Any OAB drug	0.92	(0.75, 1.14)	0.95	(0.77, 1.16)
Oxybutynin	1.32	(1.03, 1.70)	1.26	(0.99, 1.62)
Darifenacin	1.44	(0.51, 5.32)	1.82	(0.44, 7.51)
Solifenacin	0.49	(0.36, 0.67)	0.54	(0.40, 0.74)
Trospium	1.14	(0.77, 1.72)	1.13	(0.75, 1.71)
Fesoterodine	0.87	(0.47, 1.77)	1.01	(0.49, 2.07)
Overall, with high CV risk and with current exposure to				
Any OAB drug	0.94	(0.74, 1.19)	1.05	(0.83, 1.35)
Oxybutynin	1.36	(1.03, 1.81)	1.54	(1.12, 2.11)
Darifenacin	0.91	(0.24, 5.21)	1.35	(0.19, 9.67)
Solifenacin	0.52	(0.37, 0.74)	0.63	(0.45, 0.89)
Trospium	1.10	(0.71, 1.75)	1.18	(0.74, 1.90)
Fesoterodine	0.91	(0.47, 1.94)	1.18	(0.54, 2.59)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5c. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with current exposure to				
Any OAB drug	0.88	(0.66, 1.17)	0.94	(0.72, 1.24)
Oxybutynin	1.34	(0.95, 1.89)	1.28	(0.92, 1.78)
Darifenacin	2.63	(0.90, 9.86)	3.21	(0.77, 13.40)
Solifenacin	0.47	(0.31, 0.71)	0.57	(0.38, 0.85)
Trospium	0.93	(0.54, 1.70)	1.00	(0.55, 1.81)
Fesoterodine	0.78	(0.36, 1.90)	1.11	(0.44, 2.77)
Female, aged ≥ 65 with current exposure to				
Any OAB drug	0.89	(0.66, 1.19)	0.91	(0.69, 1.20)
Oxybutynin	1.28	(0.90, 1.82)	1.18	(0.84, 1.66)
Darifenacin	2.91	(0.99, 10.90)	3.33	(0.80, 13.88)
Solifenacin	0.49	(0.32, 0.75)	0.54	(0.36, 0.82)
Trospium	0.90	(0.51, 1.67)	0.95	(0.51, 1.76)
Fesoterodine	0.98	(0.45, 2.39)	1.14	(0.46, 2.87)
Female, with high CV risk and with current exposure to				
Any OAB drug	0.89	(0.62, 1.25)	0.97	(0.70, 1.34)
Oxybutynin	1.30	(0.87, 1.95)	1.37	(0.90, 2.08)
Darifenacin	1.92	(0.49, 11.20)	2.34	(0.32, 16.94)
Solifenacin	0.52	(0.33, 0.84)	0.63	(0.39, 1.01)
Trospium	0.85	(0.44, 1.75)	0.98	(0.48, 1.99)
Fesoterodine	0.71	(0.27, 2.19)	0.94	(0.29, 3.05)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5c. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with current exposure to				
Any OAB drug	0.98	(0.72, 1.34)	1.05	(0.78, 1.40)
Oxybutynin	1.34	(0.93, 1.93)	1.45	(1.02, 2.06)
Darifenacin	0.00	(0.00, 5.61)	0.00	not estimable
Solifenacin	0.50	(0.32, 0.80)	0.56	(0.35, 0.88)
Trospium	1.59	(0.96, 2.73)	1.56	(0.92, 2.65)
Fesoterodine	0.93	(0.40, 2.49)	1.09	(0.40, 3.00)
Male, aged ≥ 65 years with current exposure to				
Any OAB drug	0.99	(0.72, 1.35)	1.00	(0.74, 1.34)
Oxybutynin	1.40	(0.96, 2.03)	1.36	(0.95, 1.95)
Darifenacin	0.00	(0.00, 5.20)	0.00	not estimable
Solifenacin	0.52	(0.33, 0.84)	0.54	(0.34, 0.87)
Trospium	1.47	(0.86, 2.57)	1.35	(0.78, 2.35)
Fesoterodine	0.77	(0.30, 2.37)	0.84	(0.26, 2.68)
Male, with high CV risk and with current exposure to				
Any OAB drug	1.02	(0.71, 1.44)	1.18	(0.82, 1.69)
Oxybutynin	1.44	(0.96, 2.16)	1.77	(1.10, 2.83)
Darifenacin	0.00	(0.00, 6.40)	0.00	not estimable
Solifenacin	0.56	(0.34, 0.94)	0.63	(0.38, 1.03)
Trospium	1.40	(0.78, 2.63)	1.47	(0.78, 2.75)
Fesoterodine	1.23	(0.52, 3.35)	1.50	(0.52, 4.34)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5d. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Disease Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with current exposure to				
Any OAB drug	0.89	(0.70, 1.12)	0.94	(0.75, 1.18)
Oxybutynin	1.42	(1.07, 1.87)	1.36	(1.04, 1.78)
Darifenacin	0.00	(0.00, 3.35)	0.00	not estimable
Solifenacin	0.40	(0.28, 0.58)	0.49	(0.34, 0.70)
Trospium	1.10	(0.71, 1.76)	1.16	(0.73, 1.85)
Fesoterodine	0.23	(0.08, 0.84)	0.30	(0.07, 1.21)
Overall, aged ≥ 65 years with current exposure to				
Any OAB drug	0.91	(0.71, 1.16)	0.92	(0.73, 1.16)
Oxybutynin	1.43	(1.08, 1.90)	1.32	(1.00, 1.73)
Darifenacin	0.00	(0.00, 3.53)	0.00	not estimable
Solifenacin	0.44	(0.31, 0.64)	0.49	(0.34, 0.71)
Trospium	1.00	(0.63, 1.65)	1.05	(0.64, 1.71)
Fesoterodine	0.14	(0.04, 0.81)	0.16	(0.02, 1.13)
Overall, with high CV risk and with current exposure to				
Any OAB drug	0.87	(0.66, 1.13)	0.89	(0.68, 1.16)
Oxybutynin	1.30	(0.95, 1.79)	1.24	(0.89, 1.72)
Darifenacin	0.00	(0.00, 4.26)	0.00	not estimable
Solifenacin	0.41	(0.27, 0.62)	0.45	(0.30, 0.69)
Trospium	0.99	(0.59, 1.70)	1.14	(0.65, 1.99)
Fesoterodine	0.32	(0.11, 1.19)	0.42	(0.10, 1.84)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5d. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Disease Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with current exposure to				
Any OAB drug	0.85	(0.63, 1.13)	0.90	(0.69, 1.19)
Oxybutynin	1.36	(0.97, 1.91)	1.27	(0.92, 1.77)
Darifenacin	0.00	(0.00, 4.91)	0.00	not estimable
Solifenacin	0.34	(0.22, 0.54)	0.43	(0.28, 0.68)
Trospium	1.13	(0.68, 1.96)	1.26	(0.73, 2.17)
Fesoterodine	0.00	(0.00, 0.58)	0.00	not estimable
Female, aged ≥ 65 with current exposure to				
Any OAB drug	0.84	(0.63, 1.13)	0.86	(0.65, 1.13)
Oxybutynin	1.26	(0.89, 1.79)	1.14	(0.82, 1.59)
Darifenacin	0.00	(0.00, 5.35)	0.00	not estimable
Solifenacin	0.38	(0.24, 0.60)	0.43	(0.27, 0.67)
Trospium	0.94	(0.54, 1.72)	1.04	(0.58, 1.88)
Fesoterodine	0.00	(0.00, 0.72)	0.00	not estimable
Female, with high CV risk and with current exposure to				
Any OAB drug	0.82	(0.58, 1.15)	0.87	(0.63, 1.22)
Oxybutynin	1.21	(0.80, 1.81)	1.20	(0.79, 1.82)
Darifenacin	0.00	(0.00, 7.20)	0.00	not estimable
Solifenacin	0.35	(0.21, 0.60)	0.41	(0.24, 0.70)
Trospium	1.11	(0.62, 2.11)	1.39	(0.73, 2.64)
Fesoterodine	0.00	(0.00, 0.88)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5d. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Disease Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with current exposure to				
Any OAB drug	1.00	(0.64, 1.54)	1.03	(0.68, 1.54)
Oxybutynin	1.54	(0.93, 2.55)	1.57	(0.98, 2.52)
Darifenacin	0.00	(0.00, 11.18)	0.00	not estimable
Solifenacin	0.56	(0.30, 1.07)	0.61	(0.33, 1.13)
Trospium	1.03	(0.46, 2.49)	0.93	(0.39, 2.23)
Fesoterodine	0.90	(0.29, 3.52)	1.00	(0.24, 4.18)
Male, aged ≥ 65 years with current exposure to				
Any OAB drug	1.08	(0.67, 1.72)	1.09	(0.72, 1.67)
Oxybutynin	1.86	(1.10, 3.13)	1.79	(1.10, 2.90)
Darifenacin	0.00	(0.00, 11.31)	0.00	not estimable
Solifenacin	0.61	(0.32, 1.20)	0.65	(0.34, 1.22)
Trospium	1.16	(0.51, 2.83)	1.06	(0.44, 2.55)
Fesoterodine	0.54	(0.13, 3.27)	0.57	(0.08, 4.15)
Male, with high CV risk and with current exposure to				
Any OAB drug	0.95	(0.59, 1.52)	0.92	(0.58, 1.44)
Oxybutynin	1.48	(0.87, 2.53)	1.31	(0.78, 2.21)
Darifenacin	0.00	(0.00, 11.09)	0.00	not estimable
Solifenacin	0.54	(0.28, 1.07)	0.55	(0.28, 1.08)
Trospium	0.73	(0.29, 2.08)	0.61	(0.21, 1.75)
Fesoterodine	1.04	(0.33, 4.10)	1.33	(0.30, 5.97)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5e. Crude and Standardized Incidence Rate Ratios for Cardiovascular Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with current exposure to				
Any OAB drug	0.90	(0.77, 1.04)	0.96	(0.83, 1.12)
Oxybutynin	1.37	(1.14, 1.64)	1.35	(1.13, 1.62)
Darifenacin	0.79	(0.28, 2.90)	1.00	(0.24, 4.10)
Solifenacin	0.42	(0.33, 0.54)	0.52	(0.41, 0.65)
Trospium	1.18	(0.88, 1.59)	1.23	(0.91, 1.66)
Fesoterodine	0.51	(0.29, 0.95)	0.69	(0.36, 1.30)
Overall, aged ≥ 65 years with current exposure to				
Any OAB drug	0.91	(0.78, 1.07)	0.93	(0.80, 1.08)
Oxybutynin	1.36	(1.12, 1.64)	1.28	(1.06, 1.54)
Darifenacin	0.83	(0.29, 3.02)	1.04	(0.25, 4.26)
Solifenacin	0.45	(0.36, 0.58)	0.51	(0.40, 0.64)
Trospium	1.09	(0.81, 1.50)	1.11	(0.81, 1.52)
Fesoterodine	0.50	(0.27, 1.00)	0.57	(0.28, 1.17)
Overall, with high CV risk and with current exposure to				
Any OAB drug	0.90	(0.75, 1.07)	0.97	(0.81, 1.16)
Oxybutynin	1.32	(1.07, 1.63)	1.39	(1.10, 1.75)
Darifenacin	0.51	(0.14, 2.87)	0.72	(0.10, 5.15)
Solifenacin	0.46	(0.35, 0.60)	0.53	(0.40, 0.69)
Trospium	1.05	(0.75, 1.50)	1.17	(0.81, 1.68)
Fesoterodine	0.58	(0.31, 1.16)	0.76	(0.37, 1.58)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5e. Crude and Standardized Incidence Rate Ratios for Cardiovascular Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with current exposure to				
Any OAB drug	0.86	(0.70, 1.05)	0.92	(0.75, 1.11)
Oxybutynin	1.35	(1.06, 1.71)	1.28	(1.01, 1.62)
Darifenacin	1.32	(0.46, 4.87)	1.62	(0.39, 6.68)
Solifenacin	0.38	(0.28, 0.52)	0.48	(0.35, 0.65)
Trospium	1.05	(0.71, 1.57)	1.15	(0.77, 1.72)
Fesoterodine	0.39	(0.19, 0.93)	0.56	(0.23, 1.37)
Female, aged ≥ 65 with current exposure to				
Any OAB drug	0.86	(0.70, 1.06)	0.88	(0.72, 1.07)
Oxybutynin	1.27	(1.00, 1.63)	1.16	(0.91, 1.48)
Darifenacin	1.45	(0.51, 5.35)	1.66	(0.40, 6.88)
Solifenacin	0.41	(0.30, 0.56)	0.46	(0.34, 0.63)
Trospium	0.93	(0.62, 1.44)	1.01	(0.66, 1.55)
Fesoterodine	0.49	(0.23, 1.17)	0.57	(0.23, 1.41)
Female, with high CV risk and with current exposure to				
Any OAB drug	0.84	(0.66, 1.07)	0.91	(0.72, 1.15)
Oxybutynin	1.24	(0.94, 1.65)	1.27	(0.95, 1.71)
Darifenacin	0.95	(0.25, 5.42)	1.15	(0.16, 8.24)
Solifenacin	0.41	(0.29, 0.58)	0.49	(0.34, 0.70)
Trospium	0.98	(0.63, 1.58)	1.18	(0.73, 1.91)
Fesoterodine	0.35	(0.14, 1.05)	0.46	(0.15, 1.47)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5e. Crude and Standardized Incidence Rate Ratios for Cardiovascular Death, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with current exposure to				
Any OAB drug	0.98	(0.76, 1.26)	1.03	(0.81, 1.31)
Oxybutynin	1.38	(1.03, 1.86)	1.47	(1.11, 1.95)
Darifenacin	0.00	(0.00, 3.70)	0.00	not estimable
Solifenacin	0.53	(0.37, 0.77)	0.58	(0.40, 0.84)
Trospium	1.41	(0.92, 2.24)	1.36	(0.86, 2.13)
Fesoterodine	0.77	(0.36, 1.87)	0.89	(0.36, 2.20)
Male, aged ≥ 65 years with current exposure to				
Any OAB drug	1.01	(0.78, 1.30)	1.02	(0.80, 1.30)
Oxybutynin	1.52	(1.12, 2.05)	1.47	(1.10, 1.97)
Darifenacin	0.00	(0.00, 3.53)	0.00	not estimable
Solifenacin	0.56	(0.38, 0.82)	0.58	(0.40, 0.85)
Trospium	1.38	(0.88, 2.22)	1.27	(0.80, 2.03)
Fesoterodine	0.53	(0.21, 1.60)	0.57	(0.18, 1.82)
Male, with high CV risk and with current exposure to				
Any OAB drug	0.99	(0.75, 1.30)	1.07	(0.80, 1.42)
Oxybutynin	1.44	(1.04, 1.99)	1.58	(1.09, 2.27)
Darifenacin	0.00	(0.00, 4.01)	0.00	not estimable
Solifenacin	0.56	(0.38, 0.85)	0.60	(0.40, 0.90)
Trospium	1.17	(0.71, 2.00)	1.14	(0.66, 1.95)
Fesoterodine	0.98	(0.45, 2.38)	1.26	(0.49, 3.26)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5f. Crude and Standardized Incidence Rate Ratios for Major Adverse Cardiovascular Event, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with current exposure to				
Any OAB drug	0.91	(0.83, 1.00)	0.97	(0.88, 1.06)
Oxybutynin	1.14	(1.02, 1.29)	1.13	(1.01, 1.28)
Darifenacin	0.93	(0.47, 2.03)	0.97	(0.43, 2.22)
Solifenacin	0.66	(0.58, 0.75)	0.78	(0.68, 0.88)
Trospium	1.10	(0.91, 1.33)	1.15	(0.95, 1.39)
Fesoterodine	0.53	(0.37, 0.78)	0.67	(0.45, 0.99)
Overall, aged ≥ 65 years with current exposure to				
Any OAB drug	0.95	(0.85, 1.05)	0.96	(0.87, 1.06)
Oxybutynin	1.19	(1.05, 1.35)	1.14	(1.01, 1.30)
Darifenacin	0.87	(0.42, 2.05)	0.90	(0.36, 2.22)
Solifenacin	0.70	(0.61, 0.81)	0.77	(0.67, 0.88)
Trospium	1.07	(0.88, 1.32)	1.09	(0.89, 1.35)
Fesoterodine	0.55	(0.37, 0.85)	0.62	(0.40, 0.96)
Overall, with high CV risk and with current exposure to				
Any OAB drug	0.92	(0.82, 1.03)	0.93	(0.83, 1.05)
Oxybutynin	1.18	(1.03, 1.35)	1.14	(0.98, 1.33)
Darifenacin	1.04	(0.51, 2.46)	1.03	(0.40, 2.62)
Solifenacin	0.65	(0.56, 0.76)	0.71	(0.60, 0.83)
Trospium	1.00	(0.80, 1.26)	1.01	(0.79, 1.28)
Fesoterodine	0.65	(0.44, 0.99)	0.69	(0.44, 1.07)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5f. Crude and Standardized Incidence Rate Ratios for Major Adverse Cardiovascular Event, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with current exposure to				
Any OAB drug	0.89	(0.78, 1.00)	0.93	(0.82, 1.05)
Oxybutynin	1.16	(0.99, 1.35)	1.10	(0.94, 1.28)
Darifenacin	1.04	(0.47, 2.68)	1.18	(0.44, 3.20)
Solifenacin	0.61	(0.52, 0.72)	0.72	(0.61, 0.85)
Trospium	1.10	(0.87, 1.41)	1.17	(0.91, 1.50)
Fesoterodine	0.37	(0.22, 0.65)	0.47	(0.26, 0.85)
Female, aged ≥ 65 with current exposure to				
Any OAB drug	0.93	(0.81, 1.06)	0.94	(0.83, 1.07)
Oxybutynin	1.19	(1.01, 1.41)	1.12	(0.96, 1.32)
Darifenacin	0.94	(0.39, 2.79)	1.01	(0.32, 3.21)
Solifenacin	0.67	(0.56, 0.80)	0.74	(0.62, 0.88)
Trospium	1.07	(0.82, 1.40)	1.12	(0.86, 1.46)
Fesoterodine	0.38	(0.22, 0.74)	0.44	(0.22, 0.86)
Female, with high CV risk and with current exposure to				
Any OAB drug	0.89	(0.77, 1.04)	0.90	(0.77, 1.06)
Oxybutynin	1.19	(0.99, 1.43)	1.11	(0.91, 1.35)
Darifenacin	1.20	(0.49, 3.55)	1.26	(0.40, 3.99)
Solifenacin	0.60	(0.49, 0.74)	0.66	(0.53, 0.81)
Trospium	1.00	(0.75, 1.36)	1.05	(0.76, 1.44)
Fesoterodine	0.40	(0.22, 0.79)	0.46	(0.22, 0.93)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5f. Crude and Standardized Incidence Rate Ratios for Major Adverse Cardiovascular Event, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with current exposure to				
Any OAB drug	0.98	(0.84, 1.13)	1.02	(0.88, 1.18)
Oxybutynin	1.12	(0.93, 1.35)	1.19	(0.99, 1.43)
Darifenacin	0.76	(0.27, 2.78)	0.65	(0.16, 2.64)
Solifenacin	0.80	(0.66, 0.98)	0.86	(0.71, 1.06)
Trospium	1.12	(0.83, 1.53)	1.12	(0.82, 1.52)
Fesoterodine	0.88	(0.55, 1.48)	0.99	(0.59, 1.67)
Male, aged ≥ 65 years with current exposure to				
Any OAB drug	0.99	(0.84, 1.16)	0.99	(0.85, 1.16)
Oxybutynin	1.20	(0.98, 1.46)	1.18	(0.97, 1.43)
Darifenacin	0.76	(0.27, 2.79)	0.73	(0.18, 2.97)
Solifenacin	0.79	(0.64, 0.98)	0.81	(0.65, 1.00)
Trospium	1.10	(0.80, 1.53)	1.06	(0.76, 1.47)
Fesoterodine	0.84	(0.50, 1.50)	0.89	(0.50, 1.59)
Male, with high CV risk and with current exposure to				
Any OAB drug	0.97	(0.82, 1.15)	0.99	(0.82, 1.19)
Oxybutynin	1.17	(0.95, 1.44)	1.20	(0.95, 1.51)
Darifenacin	0.85	(0.30, 3.12)	0.65	(0.16, 2.65)
Solifenacin	0.76	(0.60, 0.95)	0.79	(0.62, 1.01)
Trospium	1.02	(0.73, 1.45)	0.93	(0.65, 1.34)
Fesoterodine	1.06	(0.65, 1.83)	1.07	(0.61, 1.87)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5g. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with current exposure to				
Any OAB drug	0.97	(0.90, 1.05)	1.03	(0.96, 1.11)
Oxybutynin	1.36	(1.24, 1.48)	1.33	(1.22, 1.46)
Darifenacin	0.69	(0.37, 1.43)	0.85	(0.39, 1.85)
Solifenacin	0.65	(0.59, 0.72)	0.80	(0.72, 0.89)
Trospium	1.17	(1.01, 1.36)	1.22	(1.05, 1.42)
Fesoterodine	0.44	(0.32, 0.62)	0.62	(0.44, 0.87)
Overall, aged ≥ 65 years with current exposure to				
Any OAB drug	0.98	(0.91, 1.06)	1.00	(0.93, 1.08)
Oxybutynin	1.32	(1.20, 1.45)	1.24	(1.13, 1.36)
Darifenacin	0.74	(0.40, 1.53)	0.92	(0.42, 2.00)
Solifenacin	0.69	(0.62, 0.77)	0.78	(0.70, 0.87)
Trospium	1.14	(0.98, 1.33)	1.16	(1.00, 1.36)
Fesoterodine	0.50	(0.36, 0.71)	0.60	(0.42, 0.86)
Overall, with high CV risk and with current exposure to				
Any OAB drug	0.98	(0.89, 1.07)	1.05	(0.96, 1.15)
Oxybutynin	1.33	(1.19, 1.48)	1.34	(1.19, 1.50)
Darifenacin	0.82	(0.42, 1.79)	1.12	(0.48, 2.57)
Solifenacin	0.69	(0.61, 0.78)	0.83	(0.73, 0.94)
Trospium	1.06	(0.89, 1.27)	1.15	(0.95, 1.39)
Fesoterodine	0.48	(0.34, 0.72)	0.61	(0.40, 0.92)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5g. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with current exposure to				
Any OAB drug	0.94	(0.85, 1.04)	1.01	(0.91, 1.11)
Oxybutynin	1.35	(1.20, 1.52)	1.29	(1.14, 1.45)
Darifenacin	0.82	(0.40, 1.92)	0.91	(0.37, 2.22)
Solifenacin	0.61	(0.54, 0.70)	0.76	(0.67, 0.87)
Trospium	1.11	(0.92, 1.35)	1.20	(0.99, 1.46)
Fesoterodine	0.35	(0.23, 0.55)	0.53	(0.33, 0.86)
Female, aged ≥ 65 with current exposure to				
Any OAB drug	0.94	(0.85, 1.04)	0.96	(0.87, 1.06)
Oxybutynin	1.26	(1.11, 1.42)	1.15	(1.02, 1.30)
Darifenacin	0.92	(0.44, 2.16)	0.97	(0.40, 2.35)
Solifenacin	0.64	(0.56, 0.73)	0.73	(0.64, 0.84)
Trospium	1.05	(0.86, 1.29)	1.12	(0.92, 1.38)
Fesoterodine	0.42	(0.27, 0.68)	0.54	(0.33, 0.88)
Female, with high CV risk and with current exposure to				
Any OAB drug	0.94	(0.83, 1.05)	1.02	(0.91, 1.16)
Oxybutynin	1.28	(1.11, 1.48)	1.28	(1.10, 1.48)
Darifenacin	1.00	(0.45, 2.58)	1.26	(0.46, 3.42)
Solifenacin	0.65	(0.55, 0.76)	0.82	(0.70, 0.97)
Trospium	0.97	(0.77, 1.24)	1.15	(0.90, 1.48)
Fesoterodine	0.28	(0.16, 0.53)	0.41	(0.21, 0.80)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5g. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Current Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with current exposure to				
Any OAB drug	1.04	(0.92, 1.18)	1.08	(0.96, 1.22)
Oxybutynin	1.36	(1.17, 1.57)	1.41	(1.22, 1.63)
Darifenacin	0.49	(0.18, 1.80)	0.75	(0.17, 3.34)
Solifenacin	0.78	(0.66, 0.92)	0.86	(0.73, 1.01)
Trospium	1.30	(1.04, 1.65)	1.25	(0.99, 1.58)
Fesoterodine	0.66	(0.42, 1.07)	0.75	(0.46, 1.23)
Male, aged ≥ 65 years with current exposure to				
Any OAB drug	1.08	(0.95, 1.22)	1.08	(0.95, 1.22)
Oxybutynin	1.44	(1.23, 1.67)	1.38	(1.19, 1.61)
Darifenacin	0.49	(0.17, 1.78)	0.84	(0.19, 3.76)
Solifenacin	0.82	(0.69, 0.98)	0.87	(0.73, 1.03)
Trospium	1.31	(1.04, 1.68)	1.23	(0.96, 1.57)
Fesoterodine	0.65	(0.40, 1.10)	0.70	(0.41, 1.20)
Male, with high CV risk and with current exposure to				
Any OAB drug	1.05	(0.92, 1.21)	1.10	(0.95, 1.26)
Oxybutynin	1.40	(1.18, 1.65)	1.45	(1.21, 1.73)
Darifenacin	0.59	(0.21, 2.15)	0.86	(0.19, 3.94)
Solifenacin	0.78	(0.65, 0.95)	0.85	(0.70, 1.03)
Trospium	1.20	(0.92, 1.58)	1.16	(0.87, 1.53)
Fesoterodine	0.86	(0.55, 1.43)	0.96	(0.57, 1.61)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5h. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with recent exposure to				
Any OAB drug	1.02	(0.85, 1.23)	1.21	(1.01, 1.46)
Oxybutynin	1.28	(1.02, 1.63)	1.46	(1.15, 1.84)
Tolterodine	1.04	(0.80, 1.35)	1.19	(0.92, 1.55)
Darifenacin	1.31	(0.35, 7.36)	1.34	(0.19, 9.57)
Solifenacin	0.79	(0.59, 1.07)	1.04	(0.77, 1.41)
Trospium	0.72	(0.43, 1.29)	0.81	(0.45, 1.44)
Fesoterodine	0.33	(0.12, 1.19)	0.38	(0.09, 1.57)
Overall, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.15	(0.94, 1.41)	1.19	(0.97, 1.45)
Oxybutynin	1.35	(1.05, 1.75)	1.36	(1.05, 1.76)
Tolterodine	1.11	(0.84, 1.49)	1.15	(0.86, 1.53)
Darifenacin	1.74	(0.47, 9.81)	1.57	(0.22, 11.21)
Solifenacin	1.00	(0.73, 1.37)	1.12	(0.81, 1.53)
Trospium	0.90	(0.53, 1.60)	0.94	(0.53, 1.69)
Fesoterodine	0.48	(0.17, 1.76)	0.45	(0.11, 1.84)
Overall, with high CV risk and with recent exposure to				
Any OAB drug	1.11	(0.89, 1.38)	1.25	(1.00, 1.56)
Oxybutynin	1.49	(1.14, 1.94)	1.70	(1.29, 2.25)
Tolterodine	1.02	(0.75, 1.40)	1.12	(0.81, 1.57)
Darifenacin	1.94	(0.52, 10.97)	1.82	(0.25, 13.00)
Solifenacin	0.76	(0.53, 1.10)	0.87	(0.59, 1.27)
Trospium	0.78	(0.43, 1.52)	0.80	(0.41, 1.59)
Fesoterodine	0.26	(0.07, 1.46)	0.27	(0.04, 1.92)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5h. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with recent exposure to				
Any OAB drug	1.03	(0.80, 1.33)	1.22	(0.95, 1.56)
Oxybutynin	1.39	(1.02, 1.90)	1.54	(1.14, 2.10)
Tolterodine	1.03	(0.73, 1.47)	1.19	(0.84, 1.69)
Darifenacin	2.15	(0.57, 12.21)	2.38	(0.33, 17.00)
Solifenacin	0.78	(0.54, 1.17)	1.03	(0.69, 1.53)
Trospium	0.63	(0.31, 1.41)	0.71	(0.31, 1.61)
Fesoterodine	0.27	(0.07, 1.53)	0.29	(0.04, 2.07)
Female, aged ≥ 65 with recent exposure to				
Any OAB drug	1.20	(0.91, 1.58)	1.24	(0.95, 1.61)
Oxybutynin	1.46	(1.04, 2.06)	1.45	(1.04, 2.03)
Tolterodine	1.14	(0.79, 1.69)	1.19	(0.81, 1.75)
Darifenacin	2.98	(0.79, 16.96)	2.87	(0.40, 20.57)
Solifenacin	1.03	(0.69, 1.57)	1.15	(0.76, 1.74)
Trospium	0.80	(0.40, 1.80)	0.85	(0.37, 1.95)
Fesoterodine	0.42	(0.11, 2.37)	0.35	(0.05, 2.50)
Female, with high CV risk and with recent exposure to				
Any OAB drug	1.08	(0.79, 1.47)	1.21	(0.88, 1.65)
Oxybutynin	1.59	(1.11, 2.30)	1.83	(1.24, 2.69)
Tolterodine	0.98	(0.63, 1.55)	1.06	(0.67, 1.68)
Darifenacin	3.50	(0.92, 19.98)	3.22	(0.45, 23.15)
Solifenacin	0.62	(0.37, 1.08)	0.68	(0.39, 1.19)
Trospium	0.83	(0.39, 2.00)	0.85	(0.34, 2.13)
Fesoterodine	0.47	(0.12, 2.68)	0.48	(0.07, 3.42)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5h. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with recent exposure to				
Any OAB drug	1.05	(0.79, 1.40)	1.20	(0.91, 1.59)
Oxybutynin	1.16	(0.81, 1.69)	1.34	(0.93, 1.93)
Tolterodine	1.07	(0.73, 1.59)	1.19	(0.81, 1.76)
Darifenacin	0.00	(0.00, 14.49)	0.00	not estimable
Solifenacin	0.89	(0.57, 1.44)	1.06	(0.66, 1.69)
Trospium	0.91	(0.45, 2.04)	0.94	(0.41, 2.13)
Fesoterodine	0.47	(0.12, 2.66)	0.51	(0.07, 3.65)
Male, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.12	(0.83, 1.53)	1.13	(0.84, 1.53)
Oxybutynin	1.25	(0.85, 1.87)	1.25	(0.84, 1.86)
Tolterodine	1.09	(0.72, 1.69)	1.09	(0.71, 1.68)
Darifenacin	0.00	(0.00, 17.31)	0.00	not estimable
Solifenacin	1.02	(0.64, 1.68)	1.08	(0.66, 1.76)
Trospium	1.06	(0.52, 2.38)	1.05	(0.46, 2.40)
Fesoterodine	0.61	(0.16, 3.47)	0.57	(0.08, 4.11)
Male, with high CV risk and with recent exposure to				
Any OAB drug	1.19	(0.87, 1.63)	1.30	(0.95, 1.79)
Oxybutynin	1.41	(0.96, 2.10)	1.54	(1.03, 2.28)
Tolterodine	1.08	(0.70, 1.70)	1.21	(0.75, 1.94)
Darifenacin	0.00	(0.00, 18.25)	0.00	not estimable
Solifenacin	1.02	(0.63, 1.70)	1.11	(0.66, 1.87)
Trospium	0.77	(0.33, 2.03)	0.74	(0.27, 2.02)
Fesoterodine	0.00	(0.00, 2.36)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5i. Crude and Standardized Incidence Rate Ratios for Stroke, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with recent exposure to				
Any OAB drug	0.87	(0.73, 1.04)	1.01	(0.85, 1.21)
Oxybutynin	0.94	(0.75, 1.19)	1.05	(0.83, 1.32)
Tolterodine	0.94	(0.74, 1.20)	1.06	(0.83, 1.35)
Darifenacin	1.06	(0.28, 5.94)	1.08	(0.15, 7.68)
Solifenacin	0.72	(0.55, 0.96)	0.89	(0.67, 1.19)
Trospium	0.78	(0.50, 1.29)	0.88	(0.53, 1.45)
Fesoterodine	0.92	(0.49, 1.92)	1.32	(0.61, 2.83)
Overall, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.01	(0.84, 1.22)	1.04	(0.87, 1.25)
Oxybutynin	1.06	(0.83, 1.37)	1.07	(0.83, 1.37)
Tolterodine	1.06	(0.82, 1.38)	1.09	(0.84, 1.41)
Darifenacin	1.40	(0.38, 7.89)	1.26	(0.18, 9.01)
Solifenacin	0.86	(0.65, 1.17)	0.93	(0.69, 1.25)
Trospium	0.72	(0.43, 1.27)	0.76	(0.42, 1.35)
Fesoterodine	1.34	(0.71, 2.81)	1.54	(0.72, 3.32)
Overall, with high CV risk and with recent exposure to				
Any OAB drug	1.05	(0.85, 1.29)	1.08	(0.86, 1.35)
Oxybutynin	1.10	(0.84, 1.45)	1.10	(0.82, 1.48)
Tolterodine	1.13	(0.85, 1.50)	1.10	(0.81, 1.49)
Darifenacin	1.68	(0.45, 9.44)	1.41	(0.20, 10.09)
Solifenacin	0.87	(0.63, 1.20)	0.98	(0.69, 1.40)
Trospium	1.12	(0.70, 1.90)	1.24	(0.71, 2.17)
Fesoterodine	0.89	(0.40, 2.30)	0.95	(0.35, 2.64)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5i. Crude and Standardized Incidence Rate Ratios for Stroke, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with recent exposure to				
Any OAB drug	0.88	(0.70, 1.09)	1.02	(0.82, 1.26)
Oxybutynin	0.95	(0.71, 1.28)	1.04	(0.77, 1.39)
Tolterodine	0.89	(0.66, 1.21)	1.00	(0.74, 1.37)
Darifenacin	1.50	(0.40, 8.45)	1.65	(0.23, 11.80)
Solifenacin	0.77	(0.56, 1.08)	0.98	(0.70, 1.36)
Trospium	0.58	(0.32, 1.17)	0.67	(0.33, 1.36)
Fesoterodine	0.94	(0.45, 2.23)	1.46	(0.59, 3.64)
Female, aged ≥ 65 with recent exposure to				
Any OAB drug	1.00	(0.79, 1.27)	1.03	(0.82, 1.30)
Oxybutynin	1.05	(0.77, 1.44)	1.04	(0.76, 1.43)
Tolterodine	1.00	(0.72, 1.40)	1.02	(0.73, 1.43)
Darifenacin	2.03	(0.54, 11.48)	1.96	(0.27, 14.02)
Solifenacin	0.92	(0.65, 1.32)	1.00	(0.70, 1.44)
Trospium	0.45	(0.22, 1.08)	0.49	(0.20, 1.20)
Fesoterodine	1.41	(0.67, 3.36)	1.74	(0.70, 4.32)
Female, with high CV risk and with recent exposure to				
Any OAB drug	1.14	(0.88, 1.48)	1.18	(0.89, 1.56)
Oxybutynin	1.21	(0.86, 1.71)	1.19	(0.83, 1.72)
Tolterodine	1.15	(0.81, 1.67)	1.11	(0.76, 1.63)
Darifenacin	2.53	(0.67, 14.37)	2.16	(0.30, 15.47)
Solifenacin	0.99	(0.68, 1.47)	1.16	(0.76, 1.76)
Trospium	0.96	(0.51, 1.95)	1.19	(0.56, 2.54)
Fesoterodine	1.02	(0.41, 3.05)	1.17	(0.36, 3.77)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5i. Crude and Standardized Incidence Rate Ratios for Stroke, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with recent exposure to				
Any OAB drug	0.88	(0.65, 1.19)	1.00	(0.75, 1.35)
Oxybutynin	0.93	(0.64, 1.40)	1.07	(0.72, 1.58)
Tolterodine	1.04	(0.71, 1.55)	1.16	(0.78, 1.72)
Darifenacin	0.00	(0.00, 14.66)	0.00	not estimable
Solifenacin	0.64	(0.39, 1.10)	0.74	(0.43, 1.27)
Trospium	1.22	(0.65, 2.49)	1.26	(0.62, 2.60)
Fesoterodine	0.94	(0.33, 3.47)	1.04	(0.26, 4.22)
Male, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.04	(0.76, 1.43)	1.06	(0.78, 1.44)
Oxybutynin	1.11	(0.74, 1.69)	1.11	(0.73, 1.68)
Tolterodine	1.18	(0.79, 1.80)	1.20	(0.79, 1.82)
Darifenacin	0.00	(0.00, 17.64)	0.00	not estimable
Solifenacin	0.76	(0.45, 1.33)	0.79	(0.45, 1.38)
Trospium	1.25	(0.64, 2.68)	1.24	(0.58, 2.67)
Fesoterodine	1.23	(0.43, 4.56)	1.19	(0.29, 4.84)
Male, with high CV risk and with recent exposure to				
Any OAB drug	0.91	(0.65, 1.29)	0.89	(0.61, 1.28)
Oxybutynin	0.95	(0.61, 1.52)	0.93	(0.57, 1.53)
Tolterodine	1.09	(0.70, 1.73)	1.08	(0.65, 1.78)
Darifenacin	0.00	(0.00, 19.54)	0.00	not estimable
Solifenacin	0.65	(0.37, 1.23)	0.65	(0.33, 1.27)
Trospium	1.42	(0.72, 3.05)	1.32	(0.59, 2.95)
Fesoterodine	0.66	(0.17, 3.80)	0.55	(0.08, 4.00)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5j. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with recent exposure to				
Any OAB drug	1.32	(1.04, 1.68)	1.62	(1.28, 2.05)
Oxybutynin	1.51	(1.12, 2.05)	1.76	(1.31, 2.37)
Tolterodine	1.55	(1.14, 2.11)	1.85	(1.37, 2.51)
Darifenacin	4.76	(1.67, 17.54)	6.94	(1.63, 29.51)
Solifenacin	0.85	(0.59, 1.27)	1.22	(0.82, 1.80)
Trospium	1.21	(0.69, 2.23)	1.42	(0.77, 2.64)
Fesoterodine	0.00	(0.00, 1.11)	0.00	not estimable
Overall, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.50	(1.17, 1.91)	1.57	(1.24, 1.99)
Oxybutynin	1.63	(1.20, 2.23)	1.66	(1.22, 2.26)
Tolterodine	1.67	(1.22, 2.30)	1.75	(1.28, 2.39)
Darifenacin	5.72	(2.00, 21.09)	7.14	(1.68, 30.34)
Solifenacin	1.07	(0.73, 1.60)	1.25	(0.84, 1.85)
Trospium	1.34	(0.77, 2.48)	1.46	(0.79, 2.71)
Fesoterodine	0.00	(0.00, 1.47)	0.00	not estimable
Overall, with high CV risk and with recent exposure to				
Any OAB drug	1.53	(1.16, 2.02)	1.79	(1.36, 2.35)
Oxybutynin	1.81	(1.30, 2.55)	2.08	(1.48, 2.93)
Tolterodine	1.61	(1.13, 2.33)	1.92	(1.31, 2.80)
Darifenacin	7.04	(2.45, 26.09)	8.02	(1.97, 32.73)
Solifenacin	0.99	(0.65, 1.56)	1.23	(0.79, 1.93)
Trospium	1.10	(0.56, 2.35)	1.31	(0.60, 2.85)
Fesoterodine	0.00	(0.00, 1.75)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5j. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with recent exposure to				
Any OAB drug	1.42	(1.03, 1.97)	1.74	(1.28, 2.38)
Oxybutynin	1.59	(1.07, 2.40)	1.81	(1.22, 2.70)
Tolterodine	1.73	(1.16, 2.60)	2.08	(1.39, 3.09)
Darifenacin	4.01	(1.05, 23.10)	4.59	(0.64, 33.01)
Solifenacin	0.85	(0.52, 1.44)	1.18	(0.70, 1.99)
Trospium	1.37	(0.69, 2.96)	1.67	(0.76, 3.65)
Fesoterodine	0.00	(0.00, 1.90)	0.00	not estimable
Female, aged ≥ 65 with recent exposure to				
Any OAB drug	1.60	(1.14, 2.23)	1.67	(1.21, 2.29)
Oxybutynin	1.69	(1.12, 2.58)	1.70	(1.13, 2.57)
Tolterodine	1.82	(1.20, 2.79)	1.91	(1.26, 2.89)
Darifenacin	4.91	(1.28, 28.27)	4.75	(0.66, 34.18)
Solifenacin	1.09	(0.66, 1.84)	1.23	(0.73, 2.07)
Trospium	1.53	(0.77, 3.33)	1.73	(0.79, 3.78)
Fesoterodine	0.00	(0.00, 2.59)	0.00	not estimable
Female, with high CV risk and with recent exposure to				
Any OAB drug	1.64	(1.11, 2.41)	1.96	(1.35, 2.84)
Oxybutynin	1.91	(1.21, 3.06)	2.21	(1.39, 3.50)
Tolterodine	1.80	(1.11, 2.96)	2.20	(1.33, 3.65)
Darifenacin	6.18	(1.58, 36.00)	6.30	(0.87, 45.60)
Solifenacin	0.88	(0.49, 1.67)	1.10	(0.58, 2.06)
Trospium	1.46	(0.66, 3.63)	1.77	(0.70, 4.45)
Fesoterodine	0.00	(0.00, 3.16)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5j. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with recent exposure to				
Any OAB drug	1.24	(0.86, 1.80)	1.47	(1.03, 2.10)
Oxybutynin	1.44	(0.92, 2.28)	1.70	(1.09, 2.65)
Tolterodine	1.37	(0.86, 2.23)	1.58	(0.99, 2.54)
Darifenacin	6.85	(1.77, 39.61)	9.82	(1.36, 70.84)
Solifenacin	0.98	(0.56, 1.79)	1.25	(0.69, 2.28)
Trospium	1.07	(0.46, 2.88)	1.12	(0.41, 3.08)
Fesoterodine	0.00	(0.00, 3.14)	0.00	not estimable
Male, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.42	(0.98, 2.06)	1.45	(1.02, 2.08)
Oxybutynin	1.60	(1.02, 2.58)	1.61	(1.02, 2.55)
Tolterodine	1.51	(0.94, 2.48)	1.55	(0.96, 2.50)
Darifenacin	7.56	(1.96, 43.74)	10.02	(1.39, 72.26)
Solifenacin	1.14	(0.65, 2.10)	1.28	(0.70, 2.33)
Trospium	1.15	(0.49, 3.10)	1.14	(0.41, 3.14)
Fesoterodine	0.00	(0.00, 3.78)	0.00	not estimable
Male, with high CV risk and with recent exposure to				
Any OAB drug	1.46	(0.96, 2.20)	1.57	(1.06, 2.32)
Oxybutynin	1.74	(1.07, 2.89)	1.92	(1.17, 3.14)
Tolterodine	1.43	(0.84, 2.51)	1.53	(0.89, 2.64)
Darifenacin	9.03	(2.31, 52.71)	10.37	(1.43, 75.08)
Solifenacin	1.25	(0.69, 2.38)	1.43	(0.76, 2.68)
Trospium	0.71	(0.24, 2.70)	0.68	(0.17, 2.80)
Fesoterodine	0.00	(0.00, 4.46)	0.00	not estimable

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5k. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Disease Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with recent exposure to				
Any OAB drug	1.86	(1.44, 2.40)	2.25	(1.76, 2.88)
Oxybutynin	1.58	(1.13, 2.22)	1.78	(1.28, 2.48)
Tolterodine	2.18	(1.59, 2.99)	2.55	(1.88, 3.47)
Darifenacin	0.00	(0.00, 11.43)	0.00	not estimable
Solifenacin	1.37	(0.95, 2.00)	1.83	(1.26, 2.65)
Trospium	2.24	(1.37, 3.82)	2.64	(1.55, 4.47)
Fesoterodine	1.89	(0.89, 4.56)	2.73	(1.10, 6.80)
Overall, aged ≥ 65 years with recent exposure to				
Any OAB drug	2.23	(1.72, 2.89)	2.32	(1.81, 2.97)
Oxybutynin	1.84	(1.31, 2.60)	1.84	(1.32, 2.57)
Tolterodine	2.56	(1.86, 3.52)	2.65	(1.94, 3.61)
Darifenacin	0.00	(0.00, 13.98)	0.00	not estimable
Solifenacin	1.71	(1.18, 2.51)	1.88	(1.29, 2.74)
Trospium	2.22	(1.32, 3.90)	2.41	(1.38, 4.23)
Fesoterodine	2.55	(1.19, 6.15)	2.88	(1.16, 7.17)
Overall, with high CV risk and with recent exposure to				
Any OAB drug	1.95	(1.45, 2.62)	2.03	(1.52, 2.72)
Oxybutynin	1.91	(1.32, 2.77)	1.87	(1.29, 2.71)
Tolterodine	1.99	(1.37, 2.92)	2.05	(1.40, 3.00)
Darifenacin	0.00	(0.00, 16.39)	0.00	not estimable
Solifenacin	1.28	(0.83, 2.02)	1.44	(0.91, 2.27)
Trospium	2.32	(1.33, 4.28)	2.75	(1.47, 5.16)
Fesoterodine	2.88	(1.34, 6.99)	3.26	(1.29, 8.25)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5k. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Disease Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with recent exposure to				
Any OAB drug	1.54	(1.12, 2.12)	1.89	(1.40, 2.56)
Oxybutynin	1.15	(0.74, 1.81)	1.27	(0.82, 1.98)
Tolterodine	2.07	(1.42, 3.04)	2.47	(1.70, 3.59)
Darifenacin	0.00	(0.00, 14.98)	0.00	not estimable
Solifenacin	1.16	(0.74, 1.85)	1.58	(1.00, 2.50)
Trospium	1.92	(1.05, 3.75)	2.37	(1.22, 4.62)
Fesoterodine	0.99	(0.34, 3.72)	1.55	(0.36, 6.71)
Female, aged ≥ 65 with recent exposure to				
Any OAB drug	1.79	(1.30, 2.47)	1.87	(1.38, 2.55)
Oxybutynin	1.26	(0.81, 1.99)	1.24	(0.79, 1.95)
Tolterodine	2.36	(1.61, 3.48)	2.47	(1.69, 3.59)
Darifenacin	0.00	(0.00, 18.06)	0.00	not estimable
Solifenacin	1.41	(0.89, 2.26)	1.56	(0.98, 2.48)
Trospium	1.92	(1.02, 3.84)	2.20	(1.09, 4.41)
Fesoterodine	1.33	(0.46, 4.98)	1.59	(0.37, 6.85)
Female, with high CV risk and with recent exposure to				
Any OAB drug	1.58	(1.08, 2.32)	1.77	(1.22, 2.57)
Oxybutynin	1.56	(0.97, 2.57)	1.62	(0.99, 2.63)
Tolterodine	1.76	(1.09, 2.90)	1.95	(1.20, 3.17)
Darifenacin	0.00	(0.00, 23.16)	0.00	not estimable
Solifenacin	1.01	(0.57, 1.84)	1.21	(0.67, 2.20)
Trospium	2.00	(0.99, 4.42)	2.62	(1.17, 5.87)
Fesoterodine	1.62	(0.55, 6.16)	2.30	(0.54, 9.77)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5k. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Disease Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with recent exposure to				
Any OAB drug	2.68	(1.68, 4.22)	3.10	(2.03, 4.73)
Oxybutynin	2.59	(1.51, 4.48)	2.98	(1.77, 5.01)
Tolterodine	2.43	(1.39, 4.32)	2.74	(1.59, 4.72)
Darifenacin	0.00	(0.00, 51.90)	0.00	not estimable
Solifenacin	2.03	(1.09, 3.92)	2.40	(1.28, 4.52)
Trospium	3.11	(1.40, 7.53)	3.24	(1.35, 7.78)
Fesoterodine	4.80	(1.79, 15.35)	5.49	(1.68, 17.93)
Male, aged ≥ 65 years with recent exposure to				
Any OAB drug	3.39	(2.08, 5.43)	3.48	(2.25, 5.38)
Oxybutynin	3.37	(1.93, 5.94)	3.39	(2.00, 5.76)
Tolterodine	3.05	(1.71, 5.49)	3.11	(1.79, 5.42)
Darifenacin	0.00	(0.00, 62.57)	0.00	not estimable
Solifenacin	2.58	(1.36, 5.04)	2.74	(1.44, 5.19)
Trospium	3.02	(1.29, 7.90)	2.97	(1.15, 7.69)
Fesoterodine	6.28	(2.31, 20.26)	6.24	(1.90, 20.50)
Male, with high CV risk and with recent exposure to				
Any OAB drug	2.70	(1.64, 4.39)	2.58	(1.61, 4.14)
Oxybutynin	2.57	(1.44, 4.67)	2.41	(1.35, 4.31)
Tolterodine	2.42	(1.32, 4.51)	2.26	(1.23, 4.14)
Darifenacin	0.00	(0.00, 60.01)	0.00	not estimable
Solifenacin	1.94	(0.98, 3.99)	1.93	(0.95, 3.92)
Trospium	2.99	(1.27, 7.81)	3.03	(1.12, 8.19)
Fesoterodine	5.91	(2.17, 19.05)	5.31	(1.60, 17.58)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5l. Crude and Standardized Incidence Rate Ratios for Cardiovascular Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with recent exposure to				
Any OAB drug	1.55	(1.30, 1.85)	1.90	(1.60, 2.25)
Oxybutynin	1.53	(1.23, 1.93)	1.76	(1.41, 2.20)
Tolterodine	1.82	(1.46, 2.27)	2.16	(1.74, 2.68)
Darifenacin	2.71	(0.96, 9.89)	3.91	(0.92, 16.56)
Solifenacin	1.08	(0.83, 1.42)	1.48	(1.13, 1.94)
Trospium	1.62	(1.11, 2.43)	1.92	(1.28, 2.88)
Fesoterodine	0.84	(0.40, 1.99)	1.23	(0.50, 3.02)
Overall, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.81	(1.52, 2.16)	1.89	(1.59, 2.25)
Oxybutynin	1.71	(1.36, 2.16)	1.73	(1.38, 2.18)
Tolterodine	2.05	(1.64, 2.57)	2.13	(1.71, 2.66)
Darifenacin	3.28	(1.16, 11.98)	4.07	(0.96, 17.22)
Solifenacin	1.35	(1.03, 1.77)	1.52	(1.16, 2.00)
Trospium	1.68	(1.13, 2.56)	1.83	(1.20, 2.79)
Fesoterodine	1.12	(0.54, 2.66)	1.28	(0.52, 3.14)
Overall, with high CV risk and with recent exposure to				
Any OAB drug	1.71	(1.40, 2.09)	1.90	(1.55, 2.31)
Oxybutynin	1.85	(1.44, 2.37)	1.97	(1.53, 2.54)
Tolterodine	1.79	(1.39, 2.33)	1.99	(1.52, 2.60)
Darifenacin	3.91	(1.38, 14.33)	4.29	(1.06, 17.41)
Solifenacin	1.10	(0.81, 1.53)	1.31	(0.95, 1.80)
Trospium	1.66	(1.07, 2.66)	1.99	(1.22, 3.24)
Fesoterodine	1.29	(0.62, 3.08)	1.53	(0.61, 3.81)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5l. Crude and Standardized Incidence Rate Ratios for Cardiovascular Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with recent exposure to				
Any OAB drug	1.47	(1.17, 1.85)	1.81	(1.45, 2.25)
Oxybutynin	1.37	(1.02, 1.85)	1.54	(1.14, 2.07)
Tolterodine	1.88	(1.42, 2.49)	2.25	(1.71, 2.97)
Darifenacin	2.02	(0.54, 11.44)	2.31	(0.32, 16.51)
Solifenacin	1.00	(0.71, 1.42)	1.37	(0.97, 1.93)
Trospium	1.67	(1.05, 2.77)	2.05	(1.24, 3.41)
Fesoterodine	0.51	(0.18, 1.86)	0.79	(0.19, 3.40)
Female, aged ≥ 65 with recent exposure to				
Any OAB drug	1.68	(1.34, 2.12)	1.76	(1.41, 2.20)
Oxybutynin	1.47	(1.08, 2.00)	1.47	(1.08, 1.99)
Tolterodine	2.07	(1.56, 2.76)	2.17	(1.64, 2.88)
Darifenacin	2.45	(0.65, 13.90)	2.37	(0.33, 16.98)
Solifenacin	1.24	(0.88, 1.76)	1.38	(0.97, 1.95)
Trospium	1.75	(1.09, 2.95)	2.00	(1.19, 3.36)
Fesoterodine	0.68	(0.24, 2.52)	0.82	(0.19, 3.50)
Female, with high CV risk and with recent exposure to				
Any OAB drug	1.59	(1.21, 2.07)	1.84	(1.41, 2.39)
Oxybutynin	1.71	(1.23, 2.39)	1.87	(1.34, 2.63)
Tolterodine	1.78	(1.27, 2.52)	2.07	(1.46, 2.95)
Darifenacin	3.06	(0.81, 17.42)	3.09	(0.43, 22.18)
Solifenacin	0.91	(0.60, 1.42)	1.11	(0.71, 1.72)
Trospium	1.73	(1.00, 3.16)	2.20	(1.20, 4.04)
Fesoterodine	0.82	(0.28, 3.03)	1.17	(0.28, 4.90)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5l. Crude and Standardized Incidence Rate Ratios for Cardiovascular Death, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with recent exposure to				
Any OAB drug	1.74	(1.31, 2.29)	2.04	(1.56, 2.67)
Oxybutynin	1.82	(1.29, 2.57)	2.13	(1.52, 2.98)
Tolterodine	1.75	(1.23, 2.52)	2.00	(1.41, 2.85)
Darifenacin	4.57	(1.20, 26.08)	6.48	(0.90, 46.50)
Solifenacin	1.35	(0.89, 2.09)	1.67	(1.09, 2.57)
Trospium	1.60	(0.87, 3.18)	1.69	(0.85, 3.36)
Fesoterodine	1.65	(0.66, 4.98)	1.92	(0.61, 6.07)
Male, aged ≥ 65 years with recent exposure to				
Any OAB drug	2.06	(1.55, 2.73)	2.11	(1.61, 2.77)
Oxybutynin	2.16	(1.52, 3.08)	2.17	(1.54, 3.06)
Tolterodine	2.03	(1.42, 2.94)	2.08	(1.45, 2.97)
Darifenacin	5.18	(1.36, 29.63)	6.86	(0.96, 49.25)
Solifenacin	1.62	(1.07, 2.52)	1.77	(1.15, 2.72)
Trospium	1.58	(0.83, 3.24)	1.56	(0.76, 3.22)
Fesoterodine	2.05	(0.82, 6.18)	2.03	(0.64, 6.43)
Male, with high CV risk and with recent exposure to				
Any OAB drug	1.94	(1.43, 2.64)	1.99	(1.48, 2.69)
Oxybutynin	2.08	(1.43, 3.04)	2.14	(1.47, 3.11)
Tolterodine	1.82	(1.23, 2.74)	1.84	(1.23, 2.76)
Darifenacin	5.75	(1.50, 32.98)	6.32	(0.88, 45.45)
Solifenacin	1.52	(0.97, 2.45)	1.64	(1.03, 2.63)
Trospium	1.58	(0.80, 3.41)	1.63	(0.73, 3.64)
Fesoterodine	2.22	(0.88, 6.75)	2.14	(0.67, 6.78)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5m. Crude and Standardized Incidence Rate Ratios for Major Adverse Cardiovascular Event, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with recent exposure to				
Any OAB drug	1.04	(0.93, 1.17)	1.23	(1.10, 1.39)
Oxybutynin	1.20	(1.03, 1.39)	1.35	(1.16, 1.57)
Tolterodine	1.13	(0.96, 1.33)	1.30	(1.11, 1.52)
Darifenacin	1.58	(0.65, 4.64)	2.02	(0.62, 6.53)
Solifenacin	0.79	(0.65, 0.95)	1.01	(0.83, 1.22)
Trospium	0.92	(0.68, 1.28)	1.05	(0.76, 1.46)
Fesoterodine	0.72	(0.43, 1.30)	0.98	(0.53, 1.80)
Overall, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.21	(1.07, 1.37)	1.25	(1.11, 1.42)
Oxybutynin	1.32	(1.13, 1.56)	1.33	(1.13, 1.57)
Tolterodine	1.26	(1.06, 1.50)	1.30	(1.10, 1.54)
Darifenacin	2.07	(0.85, 6.09)	2.32	(0.72, 7.52)
Solifenacin	0.97	(0.80, 1.19)	1.06	(0.87, 1.30)
Trospium	1.01	(0.73, 1.42)	1.08	(0.76, 1.53)
Fesoterodine	1.04	(0.62, 1.88)	1.13	(0.61, 2.07)
Overall, with high CV risk and with recent exposure to				
Any OAB drug	1.19	(1.04, 1.37)	1.28	(1.11, 1.48)
Oxybutynin	1.39	(1.17, 1.66)	1.47	(1.22, 1.77)
Tolterodine	1.23	(1.02, 1.49)	1.29	(1.06, 1.58)
Darifenacin	2.40	(0.99, 7.07)	2.30	(0.74, 7.19)
Solifenacin	0.86	(0.69, 1.08)	0.99	(0.78, 1.25)
Trospium	1.18	(0.85, 1.69)	1.30	(0.90, 1.89)
Fesoterodine	0.74	(0.39, 1.54)	0.80	(0.37, 1.72)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5m. Crude and Standardized Incidence Rate Ratios for Major Adverse Cardiovascular Event, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with recent exposure to				
Any OAB drug	1.04	(0.89, 1.21)	1.22	(1.05, 1.42)
Oxybutynin	1.18	(0.97, 1.44)	1.30	(1.07, 1.59)
Tolterodine	1.09	(0.89, 1.35)	1.26	(1.02, 1.55)
Darifenacin	1.59	(0.57, 5.79)	1.77	(0.44, 7.11)
Solifenacin	0.84	(0.67, 1.06)	1.09	(0.86, 1.37)
Trospium	0.89	(0.60, 1.36)	1.04	(0.68, 1.59)
Fesoterodine	0.70	(0.37, 1.45)	1.00	(0.46, 2.17)
Female, aged ≥ 65 with recent exposure to				
Any OAB drug	1.20	(1.02, 1.41)	1.24	(1.06, 1.46)
Oxybutynin	1.27	(1.03, 1.57)	1.27	(1.02, 1.56)
Tolterodine	1.23	(0.98, 1.54)	1.27	(1.02, 1.59)
Darifenacin	2.14	(0.76, 7.79)	2.07	(0.52, 8.32)
Solifenacin	1.05	(0.83, 1.35)	1.15	(0.90, 1.47)
Trospium	0.96	(0.63, 1.51)	1.06	(0.67, 1.67)
Fesoterodine	1.05	(0.55, 2.18)	1.17	(0.54, 2.54)
Female, with high CV risk and with recent exposure to				
Any OAB drug	1.21	(1.00, 1.45)	1.31	(1.08, 1.59)
Oxybutynin	1.39	(1.11, 1.76)	1.49	(1.17, 1.91)
Tolterodine	1.21	(0.94, 1.56)	1.27	(0.97, 1.66)
Darifenacin	2.59	(0.92, 9.47)	2.35	(0.58, 9.44)
Solifenacin	0.91	(0.69, 1.21)	1.05	(0.78, 1.42)
Trospium	1.23	(0.81, 1.94)	1.44	(0.90, 2.31)
Fesoterodine	0.87	(0.42, 2.06)	0.98	(0.40, 2.42)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5m. Crude and Standardized Incidence Rate Ratios for Major Adverse Cardiovascular Event, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with recent exposure to				
Any OAB drug	1.09	(0.90, 1.31)	1.25	(1.04, 1.51)
Oxybutynin	1.23	(0.97, 1.57)	1.42	(1.12, 1.81)
Tolterodine	1.21	(0.95, 1.56)	1.36	(1.06, 1.75)
Darifenacin	1.74	(0.47, 9.81)	2.40	(0.34, 17.11)
Solifenacin	0.75	(0.54, 1.05)	0.88	(0.63, 1.24)
Trospium	1.03	(0.64, 1.73)	1.07	(0.63, 1.80)
Fesoterodine	0.84	(0.38, 2.18)	0.94	(0.35, 2.53)
Male, aged ≥ 65 years with recent exposure to				
Any OAB drug	1.25	(1.02, 1.52)	1.27	(1.05, 1.55)
Oxybutynin	1.43	(1.12, 1.85)	1.44	(1.12, 1.85)
Tolterodine	1.33	(1.02, 1.74)	1.35	(1.03, 1.76)
Darifenacin	2.08	(0.56, 11.70)	2.70	(0.38, 19.26)
Solifenacin	0.87	(0.62, 1.24)	0.92	(0.65, 1.31)
Trospium	1.11	(0.68, 1.91)	1.11	(0.65, 1.91)
Fesoterodine	1.09	(0.49, 2.84)	1.06	(0.39, 2.85)
Male, with high CV risk and with recent exposure to				
Any OAB drug	1.21	(0.98, 1.49)	1.24	(0.99, 1.54)
Oxybutynin	1.41	(1.09, 1.85)	1.44	(1.09, 1.90)
Tolterodine	1.28	(0.97, 1.70)	1.33	(0.98, 1.80)
Darifenacin	2.25	(0.60, 12.71)	2.23	(0.31, 15.91)
Solifenacin	0.83	(0.58, 1.22)	0.88	(0.60, 1.30)
Trospium	1.15	(0.70, 2.02)	1.08	(0.61, 1.92)
Fesoterodine	0.58	(0.20, 2.12)	0.52	(0.13, 2.08)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5n. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Overall, with recent exposure to				
Any OAB drug	1.76	(1.62, 1.91)	2.11	(1.95, 2.30)
Oxybutynin	1.66	(1.49, 1.85)	1.88	(1.68, 2.09)
Tolterodine	1.91	(1.71, 2.12)	2.23	(2.00, 2.48)
Darifenacin	1.68	(0.82, 3.94)	2.28	(0.93, 5.58)
Solifenacin	1.40	(1.25, 1.59)	1.87	(1.65, 2.11)
Trospium	1.80	(1.49, 2.18)	2.06	(1.70, 2.50)
Fesoterodine	1.26	(0.90, 1.80)	1.98	(1.36, 2.86)
Overall, aged ≥ 65 years with recent exposure to				
Any OAB drug	2.04	(1.87, 2.22)	2.12	(1.95, 2.31)
Oxybutynin	1.83	(1.64, 2.05)	1.84	(1.64, 2.06)
Tolterodine	2.15	(1.93, 2.40)	2.24	(2.00, 2.50)
Darifenacin	2.10	(1.02, 4.92)	2.47	(1.01, 6.05)
Solifenacin	1.69	(1.50, 1.92)	1.90	(1.67, 2.15)
Trospium	1.91	(1.58, 2.34)	2.04	(1.67, 2.49)
Fesoterodine	1.50	(1.05, 2.21)	1.93	(1.30, 2.86)
Overall, with high CV risk and with recent exposure to				
Any OAB drug	1.95	(1.76, 2.15)	2.13	(1.93, 2.36)
Oxybutynin	1.81	(1.59, 2.06)	1.94	(1.70, 2.21)
Tolterodine	2.09	(1.84, 2.37)	2.28	(2.00, 2.60)
Darifenacin	2.63	(1.27, 6.16)	2.95	(1.21, 7.21)
Solifenacin	1.58	(1.37, 1.83)	1.88	(1.62, 2.17)
Trospium	1.99	(1.60, 2.50)	2.18	(1.73, 2.75)
Fesoterodine	1.53	(1.04, 2.34)	2.02	(1.31, 3.13)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5n. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Female, with recent exposure to				
Any OAB drug	1.68	(1.51, 1.87)	2.05	(1.84, 2.27)
Oxybutynin	1.57	(1.37, 1.81)	1.75	(1.52, 2.02)
Tolterodine	1.92	(1.67, 2.20)	2.28	(1.99, 2.61)
Darifenacin	1.00	(0.36, 3.63)	1.33	(0.33, 5.40)
Solifenacin	1.31	(1.12, 1.53)	1.77	(1.51, 2.06)
Trospium	1.80	(1.42, 2.29)	2.13	(1.67, 2.72)
Fesoterodine	0.94	(0.59, 1.56)	1.59	(0.94, 2.70)
Female, aged ≥ 65 with recent exposure to				
Any OAB drug	1.89	(1.69, 2.11)	1.98	(1.78, 2.21)
Oxybutynin	1.66	(1.44, 1.93)	1.66	(1.43, 1.92)
Tolterodine	2.08	(1.80, 2.40)	2.18	(1.90, 2.52)
Darifenacin	1.24	(0.44, 4.50)	1.41	(0.35, 5.74)
Solifenacin	1.54	(1.31, 1.81)	1.73	(1.47, 2.03)
Trospium	1.88	(1.48, 2.42)	2.06	(1.60, 2.66)
Fesoterodine	1.12	(0.69, 1.94)	1.54	(0.88, 2.70)
Female, with high CV risk and with recent exposure to				
Any OAB drug	1.80	(1.58, 2.06)	2.07	(1.82, 2.37)
Oxybutynin	1.66	(1.40, 1.97)	1.83	(1.53, 2.19)
Tolterodine	2.05	(1.74, 2.43)	2.35	(1.98, 2.79)
Darifenacin	1.61	(0.57, 5.84)	2.04	(0.49, 8.44)
Solifenacin	1.41	(1.17, 1.71)	1.77	(1.46, 2.15)
Trospium	1.90	(1.43, 2.55)	2.20	(1.63, 2.97)
Fesoterodine	1.18	(0.70, 2.14)	1.85	(1.01, 3.40)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV5n. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Current Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)[a]	Standardized Incidence Rate Ratio[b]	(95% CI)[c]
Male, with recent exposure to				
Any OAB drug	1.95	(1.70, 2.22)	2.22	(1.95, 2.53)
Oxybutynin	1.82	(1.53, 2.16)	2.07	(1.75, 2.46)
Tolterodine	1.92	(1.62, 2.29)	2.14	(1.80, 2.55)
Darifenacin	3.44	(1.42, 10.14)	3.80	(1.20, 12.07)
Solifenacin	1.73	(1.43, 2.11)	2.04	(1.67, 2.48)
Trospium	1.88	(1.39, 2.59)	1.94	(1.41, 2.67)
Fesoterodine	2.08	(1.31, 3.47)	2.59	(1.54, 4.37)
Male, aged ≥ 65 years with recent exposure to				
Any OAB drug	2.32	(2.02, 2.67)	2.36	(2.06, 2.70)
Oxybutynin	2.15	(1.80, 2.57)	2.15	(1.80, 2.56)
Tolterodine	2.29	(1.92, 2.74)	2.32	(1.95, 2.77)
Darifenacin	4.07	(1.67, 12.00)	4.27	(1.35, 13.55)
Solifenacin	2.08	(1.70, 2.54)	2.19	(1.79, 2.68)
Trospium	2.01	(1.47, 2.81)	1.99	(1.43, 2.78)
Fesoterodine	2.32	(1.42, 4.02)	2.58	(1.47, 4.52)
Male, with high CV risk and with recent exposure to				
Any OAB drug	2.21	(1.90, 2.58)	2.24	(1.92, 2.61)
Oxybutynin	2.06	(1.69, 2.51)	2.12	(1.74, 2.58)
Tolterodine	2.16	(1.77, 2.64)	2.15	(1.76, 2.63)
Darifenacin	4.77	(1.96, 14.10)	4.52	(1.44, 14.17)
Solifenacin	1.98	(1.59, 2.48)	2.05	(1.64, 2.57)
Trospium	2.18	(1.56, 3.11)	2.14	(1.50, 3.07)
Fesoterodine	2.26	(1.33, 4.10)	2.32	(1.26, 4.25)

CI = confidence interval; CV = cardiovascular; OAB = overactive bladder.

[a] Confidence intervals were calculated using a Poisson model method described in Sahai and Khurshid. *Statistics in Epidemiology Methods, Techniques, and Applications.* CRC Press 1996. Chapter 3 pg. 17.

[b] Standardized to the sex and age distribution of the study cohort person-years.

[c] Confidence intervals were calculated using the normal approximation as described in Newman. *Biostatistical Methods in Epidemiology.* New York: John Wiley and Sons, 2001. Chapter 12 pg. 253.

Table CV6. Adjusted Hazard Rate Ratio of Cardiovascular Endpoints

	Reference is *Current Use* of Tolterodine		Additional Analysis: Reference is *Current Use* of Any Other OAB Drug[a]		Additional Analysis: Reference is Periods of *No or Past Use* of Any OAB Drug	
	Incidence Rate Ratio	(95% CI)	Incidence Rate Ratio	(95% CI)	Incidence Rate Ratio	(95% CI)
Acute myocardial infarction[b]						
Current exposure						
Oxybutynin	1.14	(0.94, 1.37)	1.43	(0.93, 2.21)	1.09	(0.94, 1.27)
Tolterodine	Ref.		1.23	(0.80, 1.89)	0.96	(0.83, 1.11)
Darifenacin	0.44	(0.06, 3.15)	0.46	(0.06, 3.28)	0.42	(0.06, 3.01)
Solifenacin	0.78	(0.64, 0.95)	0.91	(0.59, 1.42)	0.75	(0.63, 0.88)
Trospium	1.10	(0.81, 1.50)	1.37	(0.84, 2.26)	1.05	(0.79, 1.40)
Fesoterodine	0.83	(0.48, 1.46)	0.99	(0.50, 1.94)	0.80	(0.46, 1.38)
Recent exposure						
Oxybutynin	1.41	(1.11, 1.80)	1.67	(1.12, 2.50)	1.35	(1.09, 1.68)
Tolterodine	1.15	(0.89, 1.50)	1.37	(0.90, 2.08)	1.11	(0.87, 1.41)
Darifenacin	1.74	(0.24, 12.38)	2.06	(0.28, 15.08)	1.67	(0.23, 11.83)
Solifenacin	1.00	(0.73, 1.35)	1.18	(0.76, 1.84)	0.96	(0.72, 1.27)
Trospium	0.80	(0.45, 1.44)	0.95	(0.49, 1.85)	0.77	(0.44, 1.36)
Fesoterodine	0.46	(0.11, 1.85)	0.55	(0.13, 2.28)	0.44	(0.11, 1.77)
Stroke						
Current exposure						
Oxybutynin	1.05	(0.88, 1.24)	1.19	(0.89, 1.60)	1.20	(1.04, 1.38)
Tolterodine	Ref.		1.13	(0.85, 1.51)	1.15	(1.01, 1.31)
Darifenacin	1.08	(0.34, 3.35)	1.23	(0.39, 3.86)	1.23	(0.40, 3.83)
Solifenacin	0.82	(0.69, 0.98)	0.89	(0.66, 1.20)	0.94	(0.81, 1.09)
Trospium	1.02	(0.77, 1.36)	1.16	(0.81, 1.68)	1.17	(0.90, 1.53)
Fesoterodine	0.57	(0.31, 1.05)	0.58	(0.31, 1.10)	0.66	(0.36, 1.19)
Recent exposure						
Oxybutynin	1.07	(0.84, 1.36)	1.18	(0.87, 1.61)	1.22	(0.98, 1.52)
Tolterodine	1.08	(0.85, 1.39)	1.20	(0.88, 1.64)	1.24	(0.99, 1.56)
Darifenacin	1.34	(0.19, 9.57)	1.49	(0.21, 10.71)	1.54	(0.22, 10.94)
Solifenacin	0.93	(0.70, 1.24)	1.03	(0.73, 1.45)	1.07	(0.82, 1.39)
Trospium	0.87	(0.53, 1.45)	0.97	(0.56, 1.66)	1.00	(0.61, 1.64)
Fesoterodine	1.31	(0.62, 2.79)	1.46	(0.67, 3.16)	1.51	(0.72, 3.17)

Table CV6. Adjusted Hazard Rate Ratio of Cardiovascular Endpoints

	Reference is *Current Use* of Tolterodine		Additional Analysis: Reference is *Current Use* of Any Other OAB Drug[a]		Additional Analysis: Reference is Periods of *No or Past Use* of Any OAB Drug	
	Incidence Rate Ratio	(95% CI)	Incidence Rate Ratio	(95% CI)	Incidence Rate Ratio	(95% CI)
Coronary heart disease death						
Current exposure						
Oxybutynin	1.27	(0.99, 1.61)	1.18	(0.82, 1.70)	1.15	(0.95, 1.39)
Tolterodine	Ref.		0.89	(0.62, 1.28)	0.91	(0.75, 1.10)
Darifenacin	1.77	(0.44, 7.15)	1.76	(0.44, 7.13)	1.61	(0.40, 6.43)
Solifenacin	0.57	(0.42, 0.77)	0.45	(0.30, 0.68)	0.51	(0.40, 0.67)
Trospium	1.24	(0.84, 1.84)	1.15	(0.72, 1.85)	1.13	(0.79, 1.62)
Fesoterodine	1.13	(0.58, 2.23)	1.04	(0.51, 2.12)	1.03	(0.53, 1.99)
Recent exposure						
Oxybutynin	1.71	(1.26, 2.33)	1.55	(1.07, 2.25)	1.55	(1.19, 2.03)
Tolterodine	1.81	(1.33, 2.46)	1.64	(1.13, 2.39)	1.64	(1.25, 2.15)
Darifenacin	7.02	(1.73, 28.42)	6.37	(1.55, 26.23)	6.37	(1.59, 25.52)
Solifenacin	1.14	(0.76, 1.69)	1.03	(0.66, 1.62)	1.03	(0.72, 1.48)
Trospium	1.37	(0.74, 2.54)	1.24	(0.65, 2.38)	1.24	(0.68, 2.25)
Fesoterodine	0.00	(0.00, > 100)	0.00	(0.00, > 100)	0.00	(0.00, > 100)
Cerebrovascular disease death						
Current exposure						
Oxybutynin	1.32	(1.01, 1.73)	2.01	(1.33, 3.06)	1.06	(0.86, 1.31)
Tolterodine	Ref.		1.42	(0.93, 2.16)	0.80	(0.65, 0.99)
Solifenacin	0.50	(0.35, 0.71)	0.59	(0.37, 0.95)	0.40	(0.29, 0.55)
Trospium	1.13	(0.71, 1.79)	1.64	(0.95, 2.86)	0.90	(0.59, 1.38)
Fesoterodine	0.33	(0.08, 1.36)	0.36	(0.09, 1.45)	0.27	(0.07, 1.08)
Recent exposure						
Oxybutynin	1.79	(1.28, 2.52)	2.37	(1.57, 3.58)	1.44	(1.08, 1.92)
Tolterodine	2.59	(1.89, 3.54)	3.42	(2.31, 5.07)	2.08	(1.60, 2.70)
Solifenacin	1.87	(1.29, 2.73)	2.48	(1.59, 3.85)	1.50	(1.09, 2.09)
Trospium	2.57	(1.51, 4.37)	3.40	(1.90, 6.06)	2.06	(1.25, 3.39)
Fesoterodine	3.09	(1.26, 7.60)	4.08	(1.61, 10.35)	2.48	(1.03, 5.98)

Table CV6. Adjusted Hazard Rate Ratio of Cardiovascular Endpoints

	Reference is *Current Use* of Tolterodine		Additional Analysis: Reference is *Current Use* of Any Other OAB Drug[a]		Additional Analysis: Reference is Periods of *No or Past Use* of Any OAB Drug	
	Incidence Rate Ratio	(95% CI)	Incidence Rate Ratio	(95% CI)	Incidence Rate Ratio	(95% CI)
Cardiovascular death						
Current exposure						
Oxybutynin	1.28	(1.07, 1.53)	1.50	(1.07, 2.10)	1.10	(0.95, 1.26)
Tolterodine	Ref.		1.11	(0.80, 1.56)	0.86	(0.74, 0.99)
Darifenacin	1.00	(0.25, 4.03)	1.11	(0.28, 4.50)	0.86	(0.21, 3.43)
Solifenacin	0.52	(0.41, 0.66)	0.51	(0.35, 0.74)	0.45	(0.36, 0.55)
Trospium	1.20	(0.89, 1.62)	1.39	(0.92, 2.10)	1.03	(0.78, 1.36)
Fesoterodine	0.72	(0.38, 1.36)	0.76	(0.38, 1.50)	0.62	(0.33, 1.16)
Recent exposure						
Oxybutynin	1.74	(1.38, 2.19)	1.90	(1.38, 2.63)	1.49	(1.22, 1.81)
Tolterodine	2.14	(1.72, 2.67)	2.34	(1.70, 3.23)	1.84	(1.52, 2.22)
Darifenacin	3.95	(0.98, 15.91)	4.32	(1.05, 17.76)	3.39	(0.85, 13.56)
Solifenacin	1.45	(1.10, 1.91)	1.59	(1.11, 2.27)	1.24	(0.97, 1.59)
Trospium	1.84	(1.23, 2.77)	2.02	(1.26, 3.22)	1.58	(1.07, 2.33)
Fesoterodine	1.36	(0.56, 3.29)	1.48	(0.59, 3.71)	1.16	(0.48, 2.80)
Major adverse cardiovascular event						
Current exposure						
Oxybutynin	1.09	(0.97, 1.23)	1.18	(0.96, 1.44)	1.10	(1.00, 1.22)
Tolterodine	Ref.		1.06	(0.87, 1.30)	1.01	(0.92, 1.11)
Darifenacin	1.09	(0.49, 2.43)	1.17	(0.52, 2.63)	1.10	(0.49, 2.45)
Solifenacin	0.77	(0.68, 0.88)	0.78	(0.64, 0.96)	0.78	(0.70, 0.87)
Trospium	1.14	(0.94, 1.38)	1.24	(0.96, 1.59)	1.15	(0.96, 1.38)
Fesoterodine	0.71	(0.48, 1.04)	0.70	(0.46, 1.06)	0.72	(0.49, 1.05)
Recent exposure						
Oxybutynin	1.34	(1.14, 1.56)	1.41	(1.15, 1.72)	1.35	(1.18, 1.55)
Tolterodine	1.29	(1.10, 1.52)	1.36	(1.10, 1.67)	1.31	(1.13, 1.51)
Darifenacin	2.09	(0.67, 6.52)	2.20	(0.70, 6.91)	2.12	(0.68, 6.57)
Solifenacin	1.01	(0.84, 1.23)	1.07	(0.84, 1.35)	1.03	(0.86, 1.23)
Trospium	1.04	(0.75, 1.44)	1.09	(0.76, 1.55)	1.05	(0.76, 1.44)
Fesoterodine	1.04	(0.57, 1.90)	1.10	(0.60, 2.02)	1.06	(0.58, 1.91)

Table CV6. Adjusted Hazard Rate Ratio of Cardiovascular Endpoints

	Reference is *Current Use* of Tolterodine		Additional Analysis: Reference is *Current Use* of Any Other OAB Drug[a]		Additional Analysis: Reference is Periods of *No or Past Use* of Any OAB Drug	
	Incidence Rate Ratio	(95% CI)	Incidence Rate Ratio	(95% CI)	Incidence Rate Ratio	(95% CI)
All-cause mortality						
Current exposure						
Oxybutynin	1.29	(1.18, 1.41)	1.49	(1.24, 1.78)	1.00	(0.93, 1.07)
Tolterodine	Ref.		1.10	(0.92, 1.31)	0.77	(0.72, 0.83)
Darifenacin	0.84	(0.40, 1.77)	0.89	(0.42, 1.87)	0.65	(0.31, 1.36)
Solifenacin	0.80	(0.72, 0.88)	0.84	(0.70, 1.01)	0.62	(0.57, 0.67)
Trospium	1.19	(1.03, 1.39)	1.36	(1.10, 1.68)	0.92	(0.81, 1.06)
Fesoterodine	0.61	(0.44, 0.86)	0.61	(0.42, 0.88)	0.47	(0.34, 0.66)
Recent exposure						
Oxybutynin	1.95	(1.74, 2.18)	2.11	(1.78, 2.49)	1.51	(1.37, 1.66)
Tolterodine	2.31	(2.08, 2.58)	2.50	(2.12, 2.95)	1.79	(1.63, 1.96)
Darifenacin	2.39	(0.99, 5.75)	2.58	(1.06, 6.26)	1.84	(0.77, 4.43)
Solifenacin	1.94	(1.72, 2.20)	2.10	(1.76, 2.50)	1.50	(1.35, 1.67)
Trospium	2.09	(1.72, 2.53)	2.25	(1.79, 2.83)	1.61	(1.34, 1.94)
Fesoterodine	1.96	(1.36, 2.82)	2.12	(1.44, 3.11)	1.52	(1.06, 2.17)

CI = confidence interval; Ref = reference; OAB = overactive bladder.

Model adjusts for age at cohort entry and sex.

Note: The reported confidence intervals were created based on the Wald confidence limits for the appropriate linear combination of the model estimates.

[a] The effect of the current exposure for other OAB drugs was averaged across the other study drugs of interest assuming equal probabilities of use.

[b] In the model for acute myocardial infarction, patients who took darifenacin were excluded as there were no observed events in this subgroup.

Table CV7a. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Tolterodine

	Current Use of Oxybutynin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Acute myocardial infarction							
Propensity score stratum							
1	33	4,541	7.27 (5.00, 10.21)	35	10,004	3.50 (2.44, 4.87)	2.08 (1.26, 3.44)
2	21	3,989	5.27 (3.26, 8.05)	43	7,116	6.04 (4.37, 8.14)	0.87 (0.52, 1.50)
3	32	3,861	8.29 (5.67, 11.70)	36	5,944	6.06 (4.24, 8.39)	1.37 (0.83, 2.27)
4	26	3,352	7.76 (5.07, 11.36)	30	4,698	6.39 (4.31, 9.12)	1.21 (0.70, 2.12)
5	17	2,941	5.78 (3.37, 9.25)	33	3,536	9.33 (6.42, 13.11)	0.62 (0.34, 1.14)
6	19	2,598	7.31 (4.40, 11.42)	14	2,193	6.38 (3.49, 10.71)	1.15 (0.53, 2.47)
7	17	2,034	8.36 (4.87, 13.38)	7	1,601	4.37 (1.76, 9.01)	1.91 (0.66, 5.45)
8	13	1,706	7.62 (4.06, 13.03)	9	932	9.66 (4.42, 18.33)	0.79 (0.30, 2.09)
9	7	1,266	5.53 (2.22, 11.39)	2	596	3.36 (0.41, 12.13)	1.65 (0.21, 16.25)
10	3	864	3.47 (0.72, 10.15)	0	325	0.00 (0.00, 11.35)	
Stratified Mantel-Haenszel rate ratio							1.20 (0.98, 1.46)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 77,008 patients who experienced single exposure to either oxybutynin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7a. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Tolterodine

	Current Use of Oxybutynin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Stroke							
Propensity score stratum							
1	33	4,530	7.28 (5.01, 10.23)	42	10,014	4.19 (3.02, 5.67)	1.74 (1.08, 2.81)
2	26	3,992	6.51 (4.25, 9.54)	66	7,108	9.29 (7.18, 11.81)	0.70 (0.45, 1.12)
3	44	3,859	11.40 (8.28, 15.30)	57	5,942	9.59 (7.27, 12.43)	1.19 (0.79, 1.79)
4	29	3,338	8.69 (5.82, 12.48)	45	4,674	9.63 (7.02, 12.88)	0.90 (0.56, 1.47)
5	30	2,932	10.23 (6.90, 14.60)	24	3,538	6.78 (4.35, 10.09)	1.51 (0.84, 2.70)
6	24	2,594	9.25 (5.93, 13.77)	15	2,189	6.85 (3.83, 11.30)	1.35 (0.65, 2.77)
7	21	2,042	10.29 (6.37, 15.72)	14	1,604	8.73 (4.77, 14.64)	1.18 (0.55, 2.51)
8	14	1,700	8.24 (4.50, 13.82)	7	931	7.52 (3.02, 15.50)	1.09 (0.37, 3.21)
9	8	1,263	6.33 (2.73, 12.48)	5	594	8.42 (2.73, 19.65)	0.75 (0.20, 2.92)
10	2	863	2.32 (0.28, 8.37)	1	325	3.08 (0.08, 17.15)	0.75 (0.04, 44.43)
Stratified Mantel-Haenszel rate ratio							1.12 (0.94, 1.34)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 77,008 patients who experienced single exposure to either oxybutynin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7a. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Tolterodine

	Current Use of Oxybutynin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Coronary heart disease death							
Propensity score stratum							
1	18	4,573	3.94 (2.33, 6.22)	15	10,068	1.49 (0.83, 2.46)	2.64 (1.24, 5.63)
2	12	4,020	2.99 (1.54, 5.21)	28	7,174	3.90 (2.59, 5.64)	0.76 (0.39, 1.55)
3	18	3,895	4.62 (2.74, 7.30)	22	5,986	3.68 (2.30, 5.56)	1.26 (0.65, 2.46)
4	20	3,362	5.95 (3.63, 9.19)	19	4,720	4.03 (2.42, 6.29)	1.48 (0.75, 2.93)
5	17	2,959	5.74 (3.35, 9.20)	13	3,553	3.66 (1.95, 6.26)	1.57 (0.70, 3.52)
6	14	2,608	5.37 (2.93, 9.01)	9	2,201	4.09 (1.87, 7.76)	1.31 (0.50, 3.44)
7	9	2,046	4.40 (2.01, 8.35)	6	1,608	3.73 (1.37, 8.12)	1.18 (0.35, 4.02)
8	9	1,709	5.26 (2.41, 9.99)	5	935	5.35 (1.74, 12.49)	0.98 (0.26, 3.74)
9	4	1,268	3.15 (0.86, 8.07)	2	596	3.36 (0.41, 12.12)	0.94 (0.11, 10.39)
10	4	864	4.63 (1.26, 11.85)	0	325	0.00 (0.00, 11.35)	
Stratified Mantel-Haenszel rate ratio							1.36 (1.05, 1.75)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 77,008 patients who experienced single exposure to either oxybutynin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7a. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Tolterodine

	Current Use of Oxybutynin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cerebrovascular disease death							
Propensity score stratum							
1	8	4,573	1.75 (0.76, 3.45)	15	10,068	1.49 (0.83, 2.46)	1.17 (0.49, 2.95)
2	13	4,020	3.23 (1.72, 5.53)	20	7,174	2.79 (1.70, 4.31)	1.16 (0.56, 2.45)
3	17	3,895	4.36 (2.54, 6.99)	21	5,986	3.51 (2.17, 5.36)	1.24 (0.63, 2.48)
4	20	3,362	5.95 (3.63, 9.19)	21	4,720	4.45 (2.75, 6.80)	1.34 (0.69, 2.59)
5	14	2,959	4.73 (2.59, 7.94)	12	3,553	3.38 (1.75, 5.90)	1.40 (0.59, 3.32)
6	12	2,608	4.60 (2.38, 8.04)	6	2,201	2.73 (1.00, 5.93)	1.69 (0.52, 5.48)
7	10	2,046	4.89 (2.34, 8.99)	2	1,608	1.24 (0.15, 4.49)	3.93 (0.51, 36.88)
8	5	1,709	2.92 (0.95, 6.83)	2	935	2.14 (0.26, 7.73)	1.37 (0.17, 14.35)
9	2	1,268	1.58 (0.19, 5.70)	1	596	1.68 (0.04, 9.35)	0.94 (0.05, 55.45)
10	0	864	0.00 (0.00, 4.27)	0	325	0.00 (0.00, 11.35)	
Stratified Mantel-Haenszel rate ratio							1.37 (1.03, 1.82)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 77,008 patients who experienced single exposure to either oxybutynin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7a. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Tolterodine

	Current Use of Oxybutynin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cardiovascular mortality							
Propensity score stratum							
1	25	4,573	5.47 (3.54, 8.07)	29	10,068	2.88 (1.93, 4.14)	1.90 (1.08, 3.36)
2	24	4,020	5.97 (3.83, 8.88)	48	7,174	6.69 (4.93, 8.87)	0.89 (0.55, 1.49)
3	34	3,895	8.73 (6.05, 12.20)	43	5,986	7.18 (5.20, 9.68)	1.22 (0.76, 1.95)
4	40	3,362	11.90 (8.50, 16.20)	40	4,720	8.48 (6.05, 11.54)	1.40 (0.88, 2.23)
5	31	2,959	10.48 (7.12, 14.87)	24	3,553	6.75 (4.33, 10.05)	1.55 (0.87, 2.76)
6	24	2,608	9.20 (5.90, 13.69)	15	2,201	6.82 (3.81, 11.24)	1.35 (0.65, 2.77)
7	19	2,046	9.29 (5.59, 14.50)	8	1,608	4.98 (2.15, 9.80)	1.87 (0.69, 4.93)
8	14	1,709	8.19 (4.48, 13.74)	7	935	7.49 (3.01, 15.43)	1.09 (0.37, 3.20)
9	6	1,268	4.73 (1.74, 10.30)	3	596	5.03 (1.04, 14.71)	0.94 (0.17, 5.81)
10	4	864	4.63 (1.26, 11.85)	0	325	0.00 (0.00, 11.35)	
Stratified Mantel-Haenszel rate ratio							1.34 (1.11, 1.62)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 77,008 patients who experienced single exposure to either oxybutynin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7a. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Tolterodine

	Current Use of Oxybutynin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Major adverse cardiovascular event							
Propensity score stratum							
1	68	4,498	15.12 (11.74, 19.17)	83	9,950	8.34 (6.64, 10.34)	1.81 (1.30, 2.53)
2	50	3,961	12.62 (9.37, 16.64)	121	7,051	17.16 (14.24, 20.51)	0.74 (0.53, 1.03)
3	81	3,828	21.16 (16.81, 26.30)	101	5,905	17.10 (13.93, 20.78)	1.24 (0.92, 1.67)
4	61	3,329	18.33 (14.02, 23.54)	85	4,653	18.27 (14.59, 22.59)	1.00 (0.72, 1.41)
5	58	2,914	19.90 (15.11, 25.73)	61	3,522	17.32 (13.25, 22.25)	1.15 (0.79, 1.67)
6	51	2,584	19.74 (14.70, 25.96)	35	2,182	16.04 (11.18, 22.31)	1.23 (0.77, 1.95)
7	41	2,029	20.21 (14.50, 27.41)	25	1,597	15.66 (10.13, 23.11)	1.29 (0.75, 2.21)
8	32	1,696	18.86 (12.90, 26.63)	19	928	20.47 (12.32, 31.97)	0.92 (0.49, 1.72)
9	17	1,261	13.49 (7.86, 21.59)	8	593	13.48 (5.82, 26.56)	1.00 (0.37, 2.68)
10	8	862	9.28 (4.00, 18.28)	1	325	3.08 (0.08, 17.15)	3.01 (0.17, 133.72)
Stratified Mantel-Haenszel rate ratio							1.14 (1.01, 1.30)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 77,008 patients who experienced single exposure to either oxybutynin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7a. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Tolterodine

	Current Use of Oxybutynin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
All-cause death							
Propensity score stratum							
1	85	4,573	18.59 (14.85, 22.98)	106	10,068	10.53 (8.62, 12.73)	1.77 (1.32, 2.37)
2	107	4,020	26.62 (21.81, 32.16)	174	7,174	24.26 (20.79, 28.14)	1.10 (0.86, 1.40)
3	147	3,895	37.74 (31.89, 44.36)	182	5,986	30.41 (26.15, 35.16)	1.24 (0.99, 1.55)
4	133	3,362	39.56 (33.12, 46.88)	137	4,720	29.03 (24.37, 34.32)	1.36 (1.07, 1.74)
5	114	2,959	38.52 (31.78, 46.28)	116	3,553	32.65 (26.98, 39.16)	1.18 (0.90, 1.54)
6	79	2,608	30.29 (23.98, 37.75)	64	2,201	29.08 (22.40, 37.14)	1.04 (0.74, 1.47)
7	78	2,046	38.12 (30.14, 47.58)	43	1,608	26.74 (19.35, 36.02)	1.43 (0.95, 2.12)
8	62	1,709	36.27 (27.81, 46.49)	29	935	31.03 (20.78, 44.57)	1.17 (0.72, 1.88)
9	31	1,268	24.44 (16.60, 34.69)	13	596	21.81 (11.61, 37.29)	1.12 (0.53, 2.33)
10	22	864	25.47 (15.96, 38.55)	8	325	24.61 (10.62, 48.48)	1.03 (0.39, 2.69)
Stratified Mantel-Haenszel rate ratio							1.26 (1.14, 1.38)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 77,008 patients who experienced single exposure to either oxybutynin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7c. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Tolterodine

	Current Use of Solifenacin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Acute myocardial infarction							
Propensity score stratum							
1	31	8,726	3.55 (2.41, 5.04)	129	21,213	6.08 (5.08, 7.23)	0.58 (0.40, 0.87)
2	14	5,048	2.77 (1.52, 4.65)	35	5,391	6.49 (4.52, 9.03)	0.43 (0.23, 0.81)
3	19	3,970	4.79 (2.88, 7.47)	12	2,648	4.53 (2.34, 7.92)	1.06 (0.46, 2.39)
4	24	3,247	7.39 (4.74, 11.00)	15	1,753	8.55 (4.79, 14.11)	0.86 (0.42, 1.77)
5	10	2,785	3.59 (1.72, 6.60)	3	1,272	2.36 (0.49, 6.89)	1.52 (0.29, 8.61)
6	8	2,436	3.28 (1.42, 6.47)	4	905	4.42 (1.20, 11.31)	0.74 (0.17, 3.37)
7	2	1,951	1.03 (0.12, 3.70)	4	638	6.27 (1.71, 16.05)	0.16 (0.03, 1.14)
8	5	1,520	3.29 (1.07, 7.68)	2	454	4.40 (0.53, 15.91)	0.75 (0.09, 7.85)
9	3	1,353	2.22 (0.46, 6.48)	3	348	8.62 (1.78, 25.19)	0.26 (0.04, 1.92)
10	3	1,029	2.91 (0.60, 8.52)	0	224	0.00 (0.00, 16.44)	
Stratified Mantel-Haenszel rate ratio							0.64 (0.50, 0.82)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 68,976 patients who experienced single exposure to either solifenacin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7c. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Tolterodine

	Current Use of Solifenacin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Stroke							
Propensity score stratum							
1	39	8,686	4.49 (3.19, 6.14)	179	21,219	8.44 (7.25, 9.77)	0.53 (0.38, 0.76)
2	22	5,053	4.35 (2.73, 6.59)	28	5,370	5.21 (3.46, 7.54)	0.84 (0.47, 1.51)
3	23	3,955	5.82 (3.69, 8.73)	19	2,643	7.19 (4.33, 11.23)	0.81 (0.42, 1.57)
4	20	3,244	6.17 (3.77, 9.52)	10	1,758	5.69 (2.73, 10.46)	1.08 (0.45, 2.59)
5	19	2,771	6.86 (4.13, 10.71)	9	1,272	7.08 (3.24, 13.43)	0.97 (0.38, 2.43)
6	18	2,430	7.41 (4.39, 11.71)	6	902	6.65 (2.44, 14.47)	1.11 (0.35, 3.43)
7	5	1,951	2.56 (0.83, 5.98)	4	638	6.27 (1.71, 16.06)	0.41 (0.09, 2.06)
8	5	1,518	3.29 (1.07, 7.68)	2	454	4.40 (0.53, 15.91)	0.75 (0.09, 7.85)
9	4	1,353	2.96 (0.81, 7.57)	1	347	2.88 (0.07, 16.06)	1.03 (0.06, 50.51)
10	4	1,029	3.89 (1.06, 9.96)	0	224	0.00 (0.00, 16.44)	
Stratified Mantel-Haenszel rate ratio							0.70 (0.56, 0.88)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 68,976 patients who experienced single exposure to either solifenacin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7c. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Tolterodine

	Current Use of Solifenacin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Coronary heart disease death							
Propensity score stratum							
1	13	8,774	1.48 (0.79, 2.53)	77	21,372	3.60 (2.84, 4.50)	0.41 (0.24, 0.75)
2	5	5,080	0.98 (0.32, 2.30)	19	5,412	3.51 (2.11, 5.48)	0.28 (0.11, 0.78)
3	6	3,986	1.51 (0.55, 3.28)	3	2,659	1.13 (0.23, 3.30)	1.33 (0.24, 8.24)
4	8	3,265	2.45 (1.06, 4.83)	10	1,762	5.68 (2.72, 10.44)	0.43 (0.16, 1.21)
5	5	2,792	1.79 (0.58, 4.18)	3	1,276	2.35 (0.48, 6.87)	0.76 (0.13, 4.91)
6	5	2,438	2.05 (0.67, 4.79)	1	907	1.10 (0.03, 6.14)	1.86 (0.11, 87.97)
7	4	1,954	2.05 (0.56, 5.24)	1	639	1.56 (0.04, 8.72)	1.31 (0.07, 64.43)
8	0	1,522	0.00 (0.00, 2.42)	0	454	0.00 (0.00, 8.12)	
9	0	1,354	0.00 (0.00, 2.72)	0	348	0.00 (0.00, 10.59)	
10	1	1,030	0.97 (0.02, 5.41)	0	224	0.00 (0.00, 16.44)	
Stratified Mantel-Haenszel rate ratio							0.49 (0.33, 0.71)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 68,976 patients who experienced single exposure to either solifenacin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7c. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Tolterodine

	Current Use of Solifenacin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cerebrovascular disease death							
Propensity score stratum							
1	6	8,774	0.68 (0.25, 1.49)	76	21,372	3.56 (2.80, 4.45)	0.19 (0.09, 0.44)
2	8	5,080	1.57 (0.68, 3.10)	9	5,412	1.66 (0.76, 3.16)	0.95 (0.33, 2.77)
3	3	3,986	0.75 (0.16, 2.20)	4	2,659	1.50 (0.41, 3.85)	0.50 (0.10, 2.96)
4	5	3,265	1.53 (0.50, 3.57)	1	1,762	0.57 (0.01, 3.16)	2.70 (0.15, 127.62)
5	5	2,792	1.79 (0.58, 4.18)	1	1,276	0.78 (0.02, 4.37)	2.29 (0.13, 108.12)
6	4	2,438	1.64 (0.45, 4.20)	1	907	1.10 (0.03, 6.14)	1.49 (0.08, 73.28)
7	0	1,954	0.00 (0.00, 1.89)	1	639	1.56 (0.04, 8.72)	0.00 (0.00, 12.76)
8	1	1,522	0.66 (0.02, 3.66)	0	454	0.00 (0.00, 8.12)	
9	1	1,354	0.74 (0.02, 4.12)	0	348	0.00 (0.00, 10.59)	
10	0	1,030	0.00 (0.00, 3.58)	0	224	0.00 (0.00, 16.44)	
Stratified Mantel-Haenszel rate ratio							0.45 (0.28, 0.73)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 68,976 patients who experienced single exposure to either solifenacin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7c. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Tolterodine

	Current Use of Solifenacin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cardiovascular mortality							
Propensity score stratum							
1	18	8,774	2.05 (1.22, 3.24)	152	21,372	7.11 (6.03, 8.34)	0.29 (0.18, 0.47)
2	13	5,080	2.56 (1.36, 4.38)	28	5,412	5.17 (3.44, 7.48)	0.49 (0.26, 0.99)
3	9	3,986	2.26 (1.03, 4.29)	7	2,659	2.63 (1.06, 5.42)	0.86 (0.28, 2.71)
4	12	3,265	3.68 (1.90, 6.42)	11	1,762	6.24 (3.12, 11.17)	0.59 (0.24, 1.47)
5	10	2,792	3.58 (1.72, 6.59)	4	1,276	3.13 (0.85, 8.02)	1.14 (0.27, 4.99)
6	8	2,438	3.28 (1.42, 6.46)	2	907	2.21 (0.27, 7.97)	1.49 (0.19, 14.38)
7	4	1,954	2.05 (0.56, 5.24)	2	639	3.13 (0.38, 11.31)	0.65 (0.08, 7.23)
8	1	1,522	0.66 (0.02, 3.66)	0	454	0.00 (0.00, 8.12)	
9	1	1,354	0.74 (0.02, 4.12)	0	348	0.00 (0.00, 10.59)	
10	1	1,030	0.97 (0.02, 5.41)	0	224	0.00 (0.00, 16.44)	
Stratified Mantel-Haenszel rate ratio							0.46 (0.34, 0.62)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 68,976 patients who experienced single exposure to either solifenacin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7c. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Tolterodine

	Current Use of Solifenacin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Major adverse cardiovascular event							
Propensity score stratum							
1	73	8,638	8.45 (6.62, 10.63)	344	21,066	16.33 (14.65, 18.15)	0.52 (0.40, 0.67)
2	42	5,025	8.36 (6.02, 11.30)	69	5,350	12.90 (10.03, 16.32)	0.65 (0.44, 0.96)
3	43	3,939	10.92 (7.90, 14.70)	34	2,632	12.92 (8.95, 18.05)	0.84 (0.52, 1.37)
4	43	3,226	13.33 (9.65, 17.95)	28	1,750	16.00 (10.63, 23.13)	0.83 (0.49, 1.39)
5	34	2,765	12.30 (8.52, 17.19)	14	1,267	11.05 (6.04, 18.53)	1.11 (0.54, 2.25)
6	28	2,428	11.53 (7.66, 16.67)	11	901	12.21 (6.10, 21.86)	0.94 (0.41, 2.10)
7	10	1,948	5.13 (2.46, 9.44)	8	637	12.56 (5.42, 24.75)	0.41 (0.14, 1.19)
8	10	1,516	6.60 (3.16, 12.13)	4	454	8.81 (2.40, 22.56)	0.75 (0.18, 3.27)
9	7	1,352	5.18 (2.08, 10.66)	4	347	11.54 (3.14, 29.54)	0.45 (0.10, 2.09)
10	7	1,028	6.81 (2.74, 14.03)	0	224	0.00 (0.00, 16.44)	
Stratified Mantel-Haenszel rate ratio							0.65 (0.56, 0.76)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 68,976 patients who experienced single exposure to either solifenacin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7c. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Tolterodine

	Current Use of Solifenacin			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
All-cause death							
Propensity score stratum							
1	122	8,774	13.90 (11.55, 16.60)	528	21,372	24.71 (22.64, 26.91)	0.56 (0.46, 0.69)
2	72	5,080	14.17 (11.09, 17.85)	128	5,412	23.65 (19.73, 28.12)	0.60 (0.45, 0.81)
3	73	3,986	18.31 (14.35, 23.03)	59	2,659	22.19 (16.89, 28.62)	0.83 (0.57, 1.18)
4	63	3,265	19.30 (14.83, 24.69)	46	1,762	26.11 (19.11, 34.83)	0.74 (0.49, 1.11)
5	43	2,792	15.40 (11.15, 20.75)	20	1,276	15.67 (9.57, 24.20)	0.98 (0.54, 1.76)
6	38	2,438	15.58 (11.03, 21.39)	7	907	7.72 (3.10, 15.90)	2.02 (0.73, 5.36)
7	27	1,954	13.82 (9.11, 20.11)	14	639	21.91 (11.98, 36.76)	0.63 (0.30, 1.30)
8	16	1,522	10.51 (6.01, 17.07)	4	454	8.80 (2.40, 22.54)	1.19 (0.29, 4.91)
9	16	1,354	11.82 (6.75, 19.19)	1	348	2.87 (0.07, 15.99)	4.12 (0.24, 172.64)
10	9	1,030	8.74 (4.00, 16.59)	1	224	4.46 (0.11, 24.84)	1.96 (0.11, 85.96)
Stratified Mantel-Haenszel rate ratio							0.68 (0.60, 0.77)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 68,976 patients who experienced single exposure to either solifenacin or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7d. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Tolterodine

	Current Use of Trospium			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Acute myocardial infarction							
Propensity score stratum							
1	2	459	4.36 (0.53, 15.76)	20	4,938	4.05 (2.47, 6.25)	1.08 (0.33, 4.43)
2	2	554	3.61 (0.44, 13.03)	23	4,647	4.95 (3.14, 7.43)	0.73 (0.23, 2.95)
3	4	562	7.11 (1.94, 18.22)	36	4,125	8.73 (6.11, 12.08)	0.82 (0.33, 2.27)
4	3	594	5.05 (1.04, 14.77)	17	3,486	4.88 (2.84, 7.81)	1.04 (0.35, 3.58)
5	8	609	13.14 (5.67, 25.88)	19	3,695	5.14 (3.10, 8.03)	2.55 (1.13, 6.11)
6	2	677	2.95 (0.36, 10.66)	16	3,642	4.39 (2.51, 7.13)	0.67 (0.20, 2.86)
7	4	624	6.41 (1.75, 16.40)	19	3,246	5.85 (3.52, 9.14)	1.09 (0.41, 3.29)
8	4	605	6.61 (1.80, 16.92)	23	3,336	6.89 (4.37, 10.34)	0.96 (0.37, 2.81)
9	1	592	1.69 (0.04, 9.41)	15	2,357	6.36 (3.56, 10.50)	0.27 (0.06, 1.72)
10	2	296	6.75 (0.82, 24.37)	14	878	15.95 (8.72, 26.77)	0.42 (0.12, 1.84)
Stratified Mantel-Haenszel rate ratio							0.93 (0.64, 1.35)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 42,536 patients who experienced single exposure to either trospium or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7d. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Tolterodine

	Current Use of Trospium			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Stroke							
Propensity score stratum							
1	3	461	6.50 (1.34, 19.00)	22	4,932	4.46 (2.80, 6.75)	1.46 (0.52, 4.85)
2	6	548	10.94 (4.02, 23.82)	26	4,646	5.60 (3.66, 8.20)	1.96 (0.86, 4.86)
3	2	566	3.54 (0.43, 12.77)	28	4,137	6.77 (4.50, 9.78)	0.52 (0.17, 2.07)
4	4	591	6.77 (1.84, 17.32)	19	3,478	5.46 (3.29, 8.53)	1.24 (0.47, 3.73)
5	5	607	8.24 (2.67, 19.22)	27	3,702	7.29 (4.81, 10.61)	1.13 (0.48, 2.98)
6	3	674	4.45 (0.92, 13.02)	32	3,640	8.79 (6.01, 12.41)	0.51 (0.19, 1.62)
7	6	626	9.59 (3.52, 20.87)	28	3,251	8.61 (5.72, 12.45)	1.11 (0.49, 2.74)
8	8	607	13.17 (5.69, 25.95)	32	3,317	9.65 (6.60, 13.62)	1.37 (0.66, 3.03)
9	4	587	6.81 (1.86, 17.45)	31	2,350	13.19 (8.96, 18.73)	0.52 (0.21, 1.46)
10	2	296	6.76 (0.82, 24.41)	11	878	12.53 (6.26, 22.42)	0.54 (0.15, 2.47)
Stratified Mantel-Haenszel rate ratio							0.96 (0.70, 1.33)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 42,536 patients who experienced single exposure to either trospium or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7d. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Tolterodine

	Current Use of Trospium			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Coronary heart disease death							
Propensity score stratum							
1	0	462	0.00 (0.00, 7.98)	9	4,956	1.82 (0.83, 3.45)	0.00 (0.00, 5.43)
2	3	557	5.39 (1.11, 15.74)	9	4,669	1.93 (0.88, 3.66)	2.79 (0.80, 11.20)
3	2	566	3.53 (0.43, 12.76)	20	4,152	4.82 (2.94, 7.44)	0.73 (0.22, 3.02)
4	2	596	3.35 (0.41, 12.12)	13	3,510	3.70 (1.97, 6.33)	0.91 (0.26, 4.00)
5	5	617	8.10 (2.63, 18.90)	17	3,716	4.57 (2.66, 7.32)	1.77 (0.69, 5.00)
6	2	678	2.95 (0.36, 10.66)	11	3,664	3.00 (1.50, 5.37)	0.98 (0.27, 4.51)
7	4	627	6.38 (1.74, 16.33)	6	3,282	1.83 (0.67, 3.98)	3.49 (0.91, 14.71)
8	1	621	1.61 (0.04, 8.97)	13	3,348	3.88 (2.07, 6.64)	0.41 (0.09, 2.76)
9	0	593	0.00 (0.00, 6.22)	6	2,375	2.53 (0.93, 5.50)	0.00 (0.00, 3.40)
10	4	297	13.49 (3.68, 34.54)	10	887	11.28 (5.41, 20.74)	1.20 (0.38, 4.15)
Stratified Mantel-Haenszel rate ratio							1.15 (0.73, 1.80)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 42,536 patients who experienced single exposure to either trospium or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7d. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Tolterodine

	Current Use of Trospium			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cerebrovascular disease death							
Propensity score stratum							
1	2	462	4.33 (0.52, 15.64)	4	4,956	0.81 (0.22, 2.07)	5.36 (0.96, 37.42)
2	2	557	3.59 (0.43, 12.97)	7	4,669	1.50 (0.60, 3.09)	2.40 (0.56, 12.58)
3	1	566	1.77 (0.04, 9.84)	10	4,152	2.41 (1.16, 4.43)	0.73 (0.15, 5.16)
4	1	596	1.68 (0.04, 9.35)	6	3,510	1.71 (0.63, 3.72)	0.98 (0.17, 8.09)
5	1	617	1.62 (0.04, 9.02)	12	3,716	3.23 (1.67, 5.64)	0.50 (0.11, 3.39)
6	1	678	1.48 (0.04, 8.22)	8	3,664	2.18 (0.94, 4.30)	0.68 (0.13, 5.04)
7	3	627	4.78 (0.99, 13.98)	17	3,282	5.18 (3.02, 8.29)	0.92 (0.31, 3.19)
8	3	621	4.83 (1.00, 14.12)	16	3,348	4.78 (2.73, 7.76)	1.01 (0.34, 3.53)
9	0	593	0.00 (0.00, 6.22)	10	2,375	4.21 (2.02, 7.74)	0.00 (0.00, 1.79)
10	0	297	0.00 (0.00, 12.44)	3	887	3.38 (0.70, 9.89)	0.00 (0.00, 7.23)
Stratified Mantel-Haenszel rate ratio							0.86 (0.49, 1.49)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 42,536 patients who experienced single exposure to either trospium or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7d. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Tolterodine

	Current Use of Trospium			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cardiovascular mortality							
Propensity score stratum							
1	2	462	4.33 (0.52, 15.64)	13	4,956	2.62 (1.40, 4.49)	1.65 (0.47, 7.29)
2	5	557	8.98 (2.92, 20.95)	16	4,669	3.43 (1.96, 5.56)	2.62 (1.01, 7.49)
3	3	566	5.30 (1.09, 15.49)	29	4,152	6.99 (4.68, 10.03)	0.76 (0.28, 2.45)
4	3	596	5.03 (1.04, 14.71)	19	3,510	5.41 (3.26, 8.45)	0.93 (0.32, 3.16)
5	6	617	9.72 (3.57, 21.15)	29	3,716	7.80 (5.23, 11.21)	1.25 (0.55, 3.05)
6	3	678	4.43 (0.91, 12.94)	19	3,664	5.19 (3.12, 8.10)	0.85 (0.30, 2.90)
7	7	627	11.16 (4.49, 23.00)	23	3,282	7.01 (4.44, 10.52)	1.59 (0.71, 3.83)
8	4	621	6.44 (1.76, 16.49)	28	3,348	8.36 (5.56, 12.09)	0.77 (0.31, 2.20)
9	0	593	0.00 (0.00, 6.22)	16	2,375	6.74 (3.85, 10.94)	0.00 (0.00, 1.04)
10	4	297	13.49 (3.68, 34.54)	13	887	14.66 (7.81, 25.08)	0.92 (0.32, 2.98)
Stratified Mantel-Haenszel rate ratio							1.02 (0.72, 1.45)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 42,536 patients who experienced single exposure to either trospium or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7d. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Tolterodine

	Current Use of Trospium			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Major adverse cardiovascular event							
Propensity score stratum							
1	6	458	13.10 (4.81, 28.52)	46	4,916	9.36 (6.85, 12.48)	1.40 (0.66, 3.29)
2	12	546	21.98 (11.36, 38.40)	54	4,624	11.68 (8.77, 15.24)	1.88 (1.04, 3.56)
3	6	562	10.68 (3.92, 23.25)	69	4,114	16.77 (13.05, 21.23)	0.64 (0.31, 1.46)
4	8	589	13.59 (5.87, 26.78)	43	3,456	12.44 (9.00, 16.76)	1.09 (0.55, 2.35)
5	14	599	23.38 (12.78, 39.23)	54	3,682	14.67 (11.02, 19.14)	1.59 (0.91, 2.91)
6	6	674	8.91 (3.27, 19.39)	53	3,618	14.65 (10.97, 19.16)	0.61 (0.29, 1.41)
7	14	623	22.46 (12.28, 37.69)	53	3,215	16.49 (12.35, 21.56)	1.36 (0.78, 2.49)
8	12	592	20.28 (10.48, 35.42)	59	3,306	17.85 (13.59, 23.02)	1.14 (0.63, 2.14)
9	5	587	8.52 (2.77, 19.89)	49	2,333	21.01 (15.54, 27.77)	0.41 (0.18, 1.01)
10	7	296	23.66 (9.51, 48.75)	27	869	31.08 (20.48, 45.21)	0.76 (0.35, 1.79)
Stratified Mantel-Haenszel rate ratio							1.03 (0.82, 1.29)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 42,536 patients who experienced single exposure to either trospium or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7d. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Tolterodine

	Current Use of Trospium			Current Use of Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
All-cause death							
Propensity score stratum							
1	14	462	30.30 (16.57, 50.84)	82	4,956	16.55 (13.16, 20.54)	1.83 (1.08, 3.25)
2	15	557	26.94 (15.08, 44.43)	100	4,669	21.42 (17.43, 26.05)	1.26 (0.76, 2.18)
3	16	566	28.26 (16.15, 45.90)	106	4,152	25.53 (20.90, 30.88)	1.11 (0.68, 1.88)
4	16	596	26.84 (15.34, 43.58)	70	3,510	19.94 (15.55, 25.20)	1.35 (0.80, 2.34)
5	16	617	25.91 (14.81, 42.08)	85	3,716	22.87 (18.27, 28.28)	1.13 (0.69, 1.95)
6	14	678	20.66 (11.30, 34.67)	80	3,664	21.83 (17.31, 27.17)	0.95 (0.56, 1.68)
7	20	627	31.89 (19.48, 49.26)	86	3,282	26.21 (20.96, 32.36)	1.22 (0.76, 2.00)
8	16	621	25.77 (14.73, 41.85)	93	3,348	27.78 (22.42, 34.03)	0.93 (0.56, 1.59)
9	13	593	21.93 (11.68, 37.51)	61	2,375	25.68 (19.64, 32.99)	0.85 (0.49, 1.57)
10	13	297	43.84 (23.34, 74.96)	41	887	46.25 (33.19, 62.74)	0.95 (0.52, 1.80)
Stratified Mantel-Haenszel rate ratio							1.12 (0.94, 1.33)

CI = confidence interval.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 42,536 patients who experienced single exposure to either trospium or tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving tolterodine at entry.

Table CV7f. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Any OAB Drug Except Oxybutynin

	Current Use of Oxybutynin			Current Use of Any Other OAB Drug Except Oxybutynin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Acute myocardial infarction							
Propensity score stratum							
1	18	4,263	4.22 (2.50, 6.67)	38	16,715	2.27 (1.61, 3.12)	1.86 (1.06, 3.34)
2	22	3,682	5.98 (3.74, 9.05)	44	13,018	3.38 (2.46, 4.54)	1.77 (1.06, 3.01)
3	18	3,684	4.89 (2.90, 7.72)	52	10,987	4.73 (3.53, 6.21)	1.03 (0.61, 1.79)
4	20	3,265	6.13 (3.74, 9.46)	42	9,559	4.39 (3.17, 5.94)	1.39 (0.82, 2.43)
5	22	2,908	7.56 (4.74, 11.45)	31	8,510	3.64 (2.48, 5.17)	2.08 (1.18, 3.70)
6	23	2,687	8.56 (5.43, 12.85)	54	7,572	7.13 (5.36, 9.31)	1.20 (0.74, 1.99)
7	20	2,470	8.10 (4.95, 12.51)	42	6,339	6.63 (4.77, 8.96)	1.22 (0.72, 2.13)
8	18	2,133	8.44 (5.00, 13.34)	37	5,330	6.94 (4.89, 9.57)	1.22 (0.69, 2.19)
9	21	1,857	11.31 (7.00, 17.28)	37	4,109	9.00 (6.34, 12.41)	1.26 (0.73, 2.20)
10	16	1,668	9.59 (5.48, 15.58)	28	3,060	9.15 (6.08, 13.22)	1.05 (0.56, 2.01)
Stratified Mantel-Haenszel rate ratio							1.36 (1.15, 1.61)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either oxybutynin or any other OAB drug except oxybutynin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except oxybutynin at entry.

Table CV7f. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Any OAB Drug Except Oxybutynin

	Current Use of Oxybutynin			Current Use of Any Other OAB Drug Except Oxybutynin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Stroke							
Propensity score stratum							
1	21	4,254	4.94 (3.06, 7.55)	49	16,693	2.94 (2.17, 3.88)	1.68 (1.01, 2.86)
2	10	3,690	2.71 (1.30, 4.98)	52	13,018	3.99 (2.98, 5.24)	0.68 (0.36, 1.35)
3	29	3,666	7.91 (5.30, 11.36)	67	10,977	6.10 (4.73, 7.75)	1.30 (0.84, 2.03)
4	24	3,267	7.35 (4.71, 10.93)	52	9,552	5.44 (4.07, 7.14)	1.35 (0.83, 2.23)
5	30	2,907	10.32 (6.96, 14.73)	67	8,452	7.93 (6.14, 10.07)	1.30 (0.85, 2.03)
6	29	2,684	10.81 (7.24, 15.52)	56	7,550	7.42 (5.60, 9.63)	1.46 (0.93, 2.32)
7	23	2,463	9.34 (5.92, 14.01)	58	6,331	9.16 (6.96, 11.84)	1.02 (0.63, 1.68)
8	23	2,126	10.82 (6.86, 16.23)	50	5,316	9.41 (6.98, 12.40)	1.15 (0.70, 1.92)
9	13	1,859	6.99 (3.72, 11.96)	43	4,091	10.51 (7.61, 14.16)	0.67 (0.37, 1.26)
10	23	1,662	13.84 (8.77, 20.76)	38	3,044	12.48 (8.83, 17.13)	1.11 (0.65, 1.91)
Stratified Mantel-Haenszel rate ratio							1.17 (1.00, 1.37)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either oxybutynin or any other OAB drug except oxybutynin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except oxybutynin at entry.

Table CV7f. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Any OAB Drug Except Oxybutynin

	Current Use of Oxybutynin			Current Use of Any Other OAB Drug Except Oxybutynin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Coronary heart disease death							
Propensity score stratum							
1	10	4,281	2.34 (1.12, 4.30)	12	16,795	0.71 (0.37, 1.25)	3.27 (1.33, 8.26)
2	13	3,703	3.51 (1.87, 6.00)	22	13,093	1.68 (1.05, 2.54)	2.09 (1.03, 4.33)
3	11	3,702	2.97 (1.48, 5.32)	22	11,050	1.99 (1.25, 3.01)	1.49 (0.72, 3.21)
4	6	3,293	1.82 (0.67, 3.97)	13	9,611	1.35 (0.72, 2.31)	1.35 (0.51, 3.80)
5	11	2,925	3.76 (1.88, 6.73)	18	8,539	2.11 (1.25, 3.33)	1.78 (0.82, 3.99)
6	13	2,707	4.80 (2.56, 8.21)	32	7,609	4.21 (2.88, 5.94)	1.14 (0.60, 2.24)
7	16	2,481	6.45 (3.69, 10.47)	21	6,380	3.29 (2.04, 5.03)	1.96 (0.99, 3.94)
8	14	2,147	6.52 (3.57, 10.94)	25	5,360	4.66 (3.02, 6.88)	1.40 (0.72, 2.80)
9	17	1,864	9.12 (5.31, 14.60)	22	4,127	5.33 (3.34, 8.07)	1.71 (0.88, 3.37)
10	15	1,671	8.98 (5.02, 14.81)	23	3,072	7.49 (4.75, 11.23)	1.20 (0.61, 2.40)
Stratified Mantel-Haenszel rate ratio							1.60 (1.29, 2.00)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either oxybutynin or any other OAB drug except oxybutynin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except oxybutynin at entry.

Table CV7f. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Any OAB Drug Except Oxybutynin

	Current Use of Oxybutynin			Current Use of Any Other OAB Drug Except Oxybutynin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cerebrovascular disease death							
Propensity score stratum							
1	4	4,281	0.93 (0.25, 2.39)	12	16,795	0.71 (0.37, 1.25)	1.31 (0.44, 4.31)
2	2	3,703	0.54 (0.07, 1.95)	9	13,093	0.69 (0.31, 1.30)	0.79 (0.20, 3.80)
3	5	3,702	1.35 (0.44, 3.15)	21	11,050	1.90 (1.18, 2.91)	0.71 (0.29, 1.94)
4	11	3,293	3.34 (1.67, 5.98)	13	9,611	1.35 (0.72, 2.31)	2.47 (1.04, 5.97)
5	18	2,925	6.15 (3.65, 9.73)	15	8,539	1.76 (0.98, 2.90)	3.50 (1.64, 7.47)
6	14	2,707	5.17 (2.83, 8.68)	21	7,609	2.76 (1.71, 4.22)	1.87 (0.93, 3.86)
7	14	2,481	5.64 (3.08, 9.47)	18	6,380	2.82 (1.67, 4.46)	2.00 (0.96, 4.26)
8	10	2,147	4.66 (2.23, 8.57)	17	5,360	3.17 (1.85, 5.08)	1.47 (0.66, 3.40)
9	8	1,864	4.29 (1.85, 8.46)	16	4,127	3.88 (2.22, 6.30)	1.11 (0.47, 2.74)
10	14	1,671	8.38 (4.58, 14.06)	15	3,072	4.88 (2.73, 8.05)	1.72 (0.78, 3.81)
Stratified Mantel-Haenszel rate ratio							1.70 (1.32, 2.19)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either oxybutynin or any other OAB drug except oxybutynin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except oxybutynin at entry.

Table CV7f. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Any OAB Drug Except Oxybutynin

	Current Use of Oxybutynin			Current Use of Any Other OAB Drug Except Oxybutynin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cardiovascular mortality							
Propensity score stratum							
1	13	4,281	3.04 (1.62, 5.19)	23	16,795	1.37 (0.87, 2.05)	2.22 (1.11, 4.56)
2	15	3,703	4.05 (2.27, 6.68)	31	13,093	2.37 (1.61, 3.36)	1.71 (0.92, 3.27)
3	16	3,702	4.32 (2.47, 7.02)	39	11,050	3.53 (2.51, 4.82)	1.22 (0.69, 2.24)
4	17	3,293	5.16 (3.01, 8.26)	26	9,611	2.71 (1.77, 3.96)	1.91 (1.01, 3.65)
5	29	2,925	9.91 (6.64, 14.24)	33	8,539	3.86 (2.66, 5.43)	2.57 (1.52, 4.36)
6	25	2,707	9.24 (5.98, 13.63)	52	7,609	6.83 (5.10, 8.96)	1.35 (0.84, 2.22)
7	30	2,481	12.09 (8.16, 17.26)	39	6,380	6.11 (4.35, 8.36)	1.98 (1.21, 3.27)
8	23	2,147	10.72 (6.79, 16.08)	41	5,360	7.65 (5.49, 10.38)	1.40 (0.83, 2.39)
9	25	1,864	13.41 (8.68, 19.80)	38	4,127	9.21 (6.52, 12.64)	1.46 (0.87, 2.48)
10	28	1,671	16.76 (11.14, 24.22)	38	3,072	12.37 (8.75, 16.98)	1.35 (0.82, 2.27)
Stratified Mantel-Haenszel rate ratio							1.64 (1.38, 1.93)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either oxybutynin or any other OAB drug except oxybutynin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except oxybutynin at entry.

Table CV7f. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Any OAB Drug Except Oxybutynin

	Current Use of Oxybutynin			Current Use of Any Other OAB Drug Except Oxybutynin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Major adverse cardiovascular event							
Propensity score stratum							
1	42	4,236	9.92 (7.15, 13.40)	90	16,613	5.42 (4.36, 6.66)	1.83 (1.27, 2.67)
2	34	3,669	9.27 (6.42, 12.95)	101	12,952	7.80 (6.35, 9.48)	1.19 (0.81, 1.77)
3	47	3,648	12.88 (9.47, 17.13)	123	10,914	11.27 (9.37, 13.45)	1.14 (0.82, 1.61)
4	46	3,239	14.20 (10.40, 18.94)	102	9,500	10.74 (8.75, 13.03)	1.32 (0.93, 1.89)
5	56	2,890	19.38 (14.64, 25.17)	107	8,424	12.70 (10.41, 15.35)	1.53 (1.10, 2.13)
6	58	2,663	21.78 (16.54, 28.15)	126	7,513	16.77 (13.97, 19.97)	1.30 (0.95, 1.79)
7	51	2,453	20.79 (15.48, 27.33)	112	6,292	17.80 (14.66, 21.42)	1.17 (0.84, 1.64)
8	46	2,112	21.78 (15.95, 29.05)	100	5,287	18.91 (15.39, 23.01)	1.15 (0.81, 1.65)
9	41	1,852	22.14 (15.89, 30.03)	93	4,074	22.82 (18.42, 27.96)	0.97 (0.67, 1.41)
10	49	1,659	29.53 (21.85, 39.04)	80	3,032	26.38 (20.92, 32.83)	1.12 (0.78, 1.62)
Stratified Mantel-Haenszel rate ratio							1.25 (1.12, 1.39)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either oxybutynin or any other OAB drug except oxybutynin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except oxybutynin at entry.

Table CV7f. Propensity Score Stratified Analysis Comparing Current Use of Oxybutynin Against Current Use of Any OAB Drug Except Oxybutynin

	Current Use of Oxybutynin			Current Use of Any Other OAB Drug Except Oxybutynin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
All-cause death							
Propensity score stratum							
1	45	4,281	10.51 (7.67, 14.07)	90	16,795	5.36 (4.31, 6.59)	1.96 (1.37, 2.84)
2	35	3,703	9.45 (6.58, 13.14)	127	13,093	9.70 (8.09, 11.54)	0.97 (0.68, 1.43)
3	77	3,702	20.80 (16.42, 26.00)	149	11,050	13.48 (11.41, 15.83)	1.54 (1.17, 2.04)
4	76	3,293	23.08 (18.18, 28.88)	150	9,611	15.61 (13.21, 18.31)	1.48 (1.12, 1.96)
5	91	2,925	31.11 (25.05, 38.20)	162	8,539	18.97 (16.16, 22.13)	1.64 (1.27, 2.13)
6	90	2,707	33.25 (26.74, 40.87)	193	7,609	25.36 (21.91, 29.21)	1.31 (1.02, 1.69)
7	107	2,481	43.12 (35.34, 52.11)	190	6,380	29.78 (25.70, 34.33)	1.45 (1.14, 1.84)
8	106	2,147	49.38 (40.43, 59.73)	216	5,360	40.30 (35.10, 46.04)	1.23 (0.97, 1.55)
9	104	1,864	55.78 (45.58, 67.59)	186	4,127	45.07 (38.82, 52.03)	1.24 (0.97, 1.58)
10	136	1,671	81.40 (68.29, 96.28)	183	3,072	59.57 (51.25, 68.85)	1.37 (1.09, 1.72)
Stratified Mantel-Haenszel rate ratio							1.38 (1.27, 1.50)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either oxybutynin or any other OAB drug except oxybutynin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving oxybutynin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving oxybutynin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except oxybutynin at entry.

Table CV7g. Propensity Score Stratified Analysis Comparing Current Use of Tolterodine Against Current Use of Any OAB Drug Except Tolterodine

	Current Use of Tolterodine			Current Use of Any Other OAB Drug Except Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Acute myocardial infarction							
Propensity score stratum							
1	8	1,643	4.87 (2.10, 9.59)	41	10,190	4.02 (2.89, 5.46)	1.21 (0.60, 2.61)
2	16	2,674	5.98 (3.42, 9.72)	64	11,677	5.48 (4.22, 7.00)	1.09 (0.65, 1.91)
3	19	3,210	5.92 (3.56, 9.24)	44	10,078	4.37 (3.17, 5.86)	1.36 (0.79, 2.37)
4	22	3,431	6.41 (4.02, 9.71)	37	8,123	4.56 (3.21, 6.28)	1.41 (0.82, 2.45)
5	29	4,002	7.25 (4.85, 10.41)	41	7,412	5.53 (3.97, 7.50)	1.31 (0.80, 2.16)
6	21	4,103	5.12 (3.17, 7.82)	35	6,634	5.28 (3.67, 7.34)	0.97 (0.56, 1.71)
7	27	4,453	6.06 (4.00, 8.82)	32	6,077	5.27 (3.60, 7.43)	1.15 (0.67, 1.98)
8	20	4,355	4.59 (2.81, 7.09)	28	5,531	5.06 (3.36, 7.32)	0.91 (0.50, 1.67)
9	29	4,847	5.98 (4.01, 8.59)	34	5,629	6.04 (4.18, 8.44)	0.99 (0.59, 1.68)
10	28	4,768	5.87 (3.90, 8.49)	20	4,983	4.01 (2.45, 6.20)	1.46 (0.78, 2.74)
Stratified Mantel-Haenszel rate ratio							1.17 (0.98, 1.39)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either tolterodine or any other OAB drug except tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving tolterodine at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving tolterodine at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except tolterodine at entry.

Table CV7g. Propensity Score Stratified Analysis Comparing Current Use of Tolterodine Against Current Use of Any OAB Drug Except Tolterodine

	Current Use of Tolterodine			Current Use of Any Other OAB Drug Except Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Stroke							
Propensity score stratum							
1	7	1,643	4.26 (1.71, 8.78)	50	10,181	4.91 (3.65, 6.47)	0.87 (0.43, 1.92)
2	20	2,674	7.48 (4.57, 11.55)	69	11,664	5.92 (4.60, 7.49)	1.26 (0.78, 2.11)
3	17	3,207	5.30 (3.09, 8.49)	66	10,047	6.57 (5.08, 8.36)	0.81 (0.48, 1.39)
4	20	3,419	5.85 (3.57, 9.03)	61	8,102	7.53 (5.76, 9.67)	0.78 (0.47, 1.31)
5	34	3,992	8.52 (5.90, 11.90)	39	7,402	5.27 (3.75, 7.20)	1.62 (1.00, 2.63)
6	31	4,108	7.55 (5.13, 10.71)	35	6,608	5.30 (3.69, 7.37)	1.42 (0.86, 2.38)
7	37	4,447	8.32 (5.86, 11.47)	50	6,067	8.24 (6.12, 10.87)	1.01 (0.65, 1.58)
8	38	4,345	8.75 (6.19, 12.00)	36	5,518	6.52 (4.57, 9.03)	1.34 (0.83, 2.18)
9	43	4,835	8.89 (6.44, 11.98)	44	5,599	7.86 (5.71, 10.55)	1.13 (0.73, 1.76)
10	30	4,775	6.28 (4.24, 8.97)	29	4,981	5.82 (3.90, 8.36)	1.08 (0.63, 1.86)
Stratified Mantel-Haenszel rate ratio							1.12 (0.96, 1.31)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either tolterodine or any other OAB drug except tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving tolterodine at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving tolterodine at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except tolterodine at entry.

Table CV7g. Propensity Score Stratified Analysis Comparing Current Use of Tolterodine Against Current Use of Any OAB Drug Except Tolterodine

	Current Use of Tolterodine			Current Use of Any Other OAB Drug Except Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Coronary heart disease death							
Propensity score stratum							
1	2	1,645	1.22 (0.15, 4.39)	24	10,204	2.35 (1.51, 3.50)	0.52 (0.16, 2.08)
2	12	2,683	4.47 (2.31, 7.81)	35	11,721	2.99 (2.08, 4.15)	1.50 (0.79, 2.95)
3	6	3,228	1.86 (0.68, 4.05)	28	10,117	2.77 (1.84, 4.00)	0.67 (0.30, 1.65)
4	15	3,437	4.36 (2.44, 7.20)	24	8,169	2.94 (1.88, 4.37)	1.49 (0.76, 2.95)
5	10	4,023	2.49 (1.19, 4.57)	21	7,454	2.82 (1.74, 4.31)	0.88 (0.41, 1.96)
6	14	4,131	3.39 (1.85, 5.69)	18	6,665	2.70 (1.60, 4.27)	1.25 (0.60, 2.67)
7	21	4,480	4.69 (2.90, 7.17)	19	6,107	3.11 (1.87, 4.86)	1.51 (0.77, 2.96)
8	12	4,373	2.74 (1.42, 4.79)	18	5,579	3.23 (1.91, 5.10)	0.85 (0.40, 1.87)
9	17	4,892	3.48 (2.02, 5.56)	17	5,675	3.00 (1.75, 4.80)	1.16 (0.56, 2.42)
10	11	4,815	2.28 (1.14, 4.09)	11	5,024	2.19 (1.09, 3.92)	1.04 (0.42, 2.65)
Stratified Mantel-Haenszel rate ratio							1.12 (0.89, 1.41)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either tolterodine or any other OAB drug except tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving tolterodine at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving tolterodine at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except tolterodine at entry.

Table CV7g. Propensity Score Stratified Analysis Comparing Current Use of Tolterodine Against Current Use of Any OAB Drug Except Tolterodine

	Current Use of Tolterodine			Current Use of Any Other OAB Drug Except Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cerebrovascular disease death							
Propensity score stratum							
1	1	1,645	0.61 (0.02, 3.39)	12	10,204	1.18 (0.61, 2.05)	0.52 (0.11, 3.49)
2	3	2,683	1.12 (0.23, 3.27)	24	11,721	2.05 (1.31, 3.05)	0.55 (0.20, 1.80)
3	4	3,228	1.24 (0.34, 3.17)	18	10,117	1.78 (1.05, 2.81)	0.70 (0.26, 2.11)
4	7	3,437	2.04 (0.82, 4.20)	21	8,169	2.57 (1.59, 3.93)	0.79 (0.35, 1.93)
5	15	4,023	3.73 (2.09, 6.15)	18	7,454	2.41 (1.43, 3.82)	1.54 (0.75, 3.24)
6	16	4,131	3.87 (2.21, 6.29)	10	6,665	1.50 (0.72, 2.76)	2.58 (1.04, 6.36)
7	16	4,480	3.57 (2.04, 5.80)	22	6,107	3.60 (2.26, 5.45)	0.99 (0.51, 1.98)
8	14	4,373	3.20 (1.75, 5.37)	14	5,579	2.51 (1.37, 4.21)	1.28 (0.57, 2.89)
9	13	4,892	2.66 (1.42, 4.54)	12	5,675	2.11 (1.09, 3.69)	1.26 (0.53, 3.01)
10	13	4,815	2.70 (1.44, 4.62)	10	5,024	1.99 (0.95, 3.66)	1.36 (0.53, 3.46)
Stratified Mantel-Haenszel rate ratio							1.17 (0.90, 1.51)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either tolterodine or any other OAB drug except tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving tolterodine at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving tolterodine at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except tolterodine at entry.

Table CV7g. Propensity Score Stratified Analysis Comparing Current Use of Tolterodine Against Current Use of Any OAB Drug Except Tolterodine

	Current Use of Tolterodine			Current Use of Any Other OAB Drug Except Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cardiovascular mortality							
Propensity score stratum							
1	3	1,645	1.82 (0.38, 5.33)	35	10,204	3.43 (2.39, 4.77)	0.53 (0.20, 1.69)
2	15	2,683	5.59 (3.13, 9.22)	57	11,721	4.86 (3.68, 6.30)	1.15 (0.67, 2.06)
3	10	3,228	3.10 (1.49, 5.70)	44	10,117	4.35 (3.16, 5.84)	0.71 (0.37, 1.44)
4	21	3,437	6.11 (3.78, 9.34)	44	8,169	5.39 (3.91, 7.23)	1.13 (0.67, 1.95)
5	25	4,023	6.21 (4.02, 9.17)	39	7,454	5.23 (3.72, 7.15)	1.19 (0.71, 2.01)
6	30	4,131	7.26 (4.90, 10.37)	28	6,665	4.20 (2.79, 6.07)	1.73 (1.00, 3.00)
7	37	4,480	8.26 (5.82, 11.39)	41	6,107	6.71 (4.82, 9.11)	1.23 (0.77, 1.97)
8	26	4,373	5.95 (3.88, 8.71)	30	5,579	5.38 (3.63, 7.68)	1.11 (0.64, 1.93)
9	30	4,892	6.13 (4.14, 8.75)	28	5,675	4.93 (3.28, 7.13)	1.24 (0.72, 2.16)
10	23	4,815	4.78 (3.03, 7.17)	20	5,024	3.98 (2.43, 6.15)	1.20 (0.62, 2.30)
Stratified Mantel-Haenszel rate ratio							1.16 (0.98, 1.38)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either tolterodine or any other OAB drug except tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving tolterodine at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving tolterodine at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except tolterodine at entry.

Table CV7g. Propensity Score Stratified Analysis Comparing Current Use of Tolterodine Against Current Use of Any OAB Drug Except Tolterodine

	Current Use of Tolterodine			Current Use of Any Other OAB Drug Except Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Major adverse cardiovascular event							
Propensity score stratum							
1	15	1,641	9.14 (5.12, 15.08)	108	10,167	10.62 (8.71, 12.82)	0.86 (0.52, 1.48)
2	43	2,665	16.14 (11.68, 21.74)	151	11,620	12.99 (11.00, 15.24)	1.24 (0.89, 1.75)
3	39	3,189	12.23 (8.70, 16.72)	117	10,008	11.69 (9.67, 14.01)	1.05 (0.73, 1.51)
4	47	3,414	13.77 (10.12, 18.31)	113	8,058	14.02 (11.56, 16.86)	0.98 (0.70, 1.39)
5	66	3,972	16.61 (12.85, 21.14)	90	7,361	12.23 (9.83, 15.03)	1.36 (0.98, 1.89)
6	63	4,084	15.43 (11.85, 19.74)	73	6,577	11.10 (8.70, 13.96)	1.39 (0.98, 1.97)
7	72	4,422	16.28 (12.74, 20.51)	89	6,037	14.74 (11.84, 18.14)	1.10 (0.80, 1.52)
8	62	4,326	14.33 (10.99, 18.37)	70	5,472	12.79 (9.97, 16.16)	1.12 (0.79, 1.60)
9	79	4,792	16.49 (13.05, 20.55)	83	5,552	14.95 (11.91, 18.53)	1.10 (0.80, 1.52)
10	63	4,728	13.33 (10.24, 17.05)	57	4,940	11.54 (8.74, 14.95)	1.15 (0.79, 1.68)
Stratified Mantel-Haenszel rate ratio							1.15 (1.03, 1.28)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either tolterodine or any other OAB drug except tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving tolterodine at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving tolterodine at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except tolterodine at entry.

Table CV7g. Propensity Score Stratified Analysis Comparing Current Use of Tolterodine Against Current Use of Any OAB Drug Except Tolterodine

	Current Use of Tolterodine			Current Use of Any Other OAB Drug Except Tolterodine			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
All-cause death							
Propensity score stratum							
1	26	1,645	15.80 (10.32, 23.16)	205	10,204	20.09 (17.43, 23.04)	0.79 (0.54, 1.19)
2	71	2,683	26.46 (20.67, 33.38)	244	11,721	20.82 (18.29, 23.60)	1.27 (0.98, 1.66)
3	54	3,228	16.73 (12.57, 21.83)	208	10,117	20.56 (17.86, 23.55)	0.81 (0.61, 1.10)
4	96	3,437	27.93 (22.62, 34.11)	167	8,169	20.44 (17.46, 23.79)	1.37 (1.06, 1.77)
5	100	4,023	24.86 (20.22, 30.23)	171	7,454	22.94 (19.63, 26.65)	1.08 (0.84, 1.39)
6	110	4,131	26.63 (21.88, 32.09)	160	6,665	24.01 (20.43, 28.03)	1.11 (0.87, 1.42)
7	120	4,480	26.79 (22.21, 32.03)	155	6,107	25.38 (21.54, 29.70)	1.06 (0.83, 1.35)
8	101	4,373	23.10 (18.81, 28.06)	132	5,579	23.66 (19.80, 28.06)	0.98 (0.75, 1.27)
9	98	4,892	20.03 (16.26, 24.41)	115	5,675	20.26 (16.73, 24.32)	0.99 (0.75, 1.31)
10	93	4,815	19.31 (15.59, 23.66)	107	5,024	21.30 (17.45, 25.74)	0.91 (0.68, 1.21)
Stratified Mantel-Haenszel rate ratio							1.04 (0.96, 1.14)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either tolterodine or any other OAB drug except tolterodine at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving tolterodine at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving tolterodine at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except tolterodine at entry.

Table CV7i. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Any OAB Drug Except Solifenacin

	Current Use of Solifenacin			Current Use of Any Other OAB Drug Except Solifenacin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Acute myocardial infarction							
Propensity score stratum							
1	34	9,108	3.73 (2.59, 5.22)	160	24,836	6.44 (5.48, 7.52)	0.58 (0.41, 0.84)
2	21	5,914	3.55 (2.20, 5.43)	60	10,582	5.67 (4.33, 7.30)	0.63 (0.38, 1.04)
3	31	3,957	7.83 (5.32, 11.12)	46	5,742	8.01 (5.87, 10.69)	0.98 (0.61, 1.58)
4	15	3,009	4.99 (2.79, 8.22)	20	4,077	4.91 (3.00, 7.58)	1.02 (0.50, 2.09)
5	15	2,591	5.79 (3.24, 9.55)	17	3,071	5.54 (3.22, 8.86)	1.05 (0.50, 2.23)
6	11	2,471	4.45 (2.22, 7.97)	19	2,853	6.66 (4.01, 10.40)	0.67 (0.31, 1.48)
7	4	2,333	1.71 (0.47, 4.39)	12	2,389	5.02 (2.59, 8.77)	0.34 (0.12, 1.13)
8	3	2,208	1.36 (0.28, 3.97)	2	2,127	0.94 (0.11, 3.40)	1.45 (0.17, 17.31)
9	4	1,967	2.03 (0.55, 5.21)	6	1,810	3.32 (1.22, 7.22)	0.61 (0.16, 2.59)
10	0	1,762	0.00 (0.00, 2.09)	1	1,681	0.59 (0.02, 3.31)	0.00 (0.00, 37.22)
Stratified Mantel-Haenszel rate ratio							0.71 (0.58, 0.87)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either solifenacin or any other OAB drug except solifenacin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except solifenacin at entry.

Table CV7i. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Any OAB Drug Except Solifenacin

	Current Use of Solifenacin			Current Use of Any Other OAB Drug Except Solifenacin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Stroke							
Propensity score stratum							
1	45	9,065	4.96 (3.62, 6.64)	193	24,843	7.77 (6.71, 8.95)	0.64 (0.47, 0.89)
2	30	5,903	5.08 (3.43, 7.25)	81	10,533	7.69 (6.11, 9.56)	0.66 (0.44, 1.02)
3	30	3,951	7.59 (5.12, 10.84)	42	5,731	7.33 (5.28, 9.91)	1.04 (0.64, 1.70)
4	17	2,999	5.67 (3.30, 9.08)	24	4,075	5.89 (3.77, 8.76)	0.96 (0.50, 1.87)
5	13	2,591	5.02 (2.67, 8.58)	25	3,068	8.15 (5.27, 12.03)	0.62 (0.31, 1.25)
6	15	2,463	6.09 (3.41, 10.04)	20	2,855	7.00 (4.28, 10.82)	0.87 (0.43, 1.79)
7	14	2,323	6.03 (3.30, 10.11)	8	2,386	3.35 (1.45, 6.61)	1.80 (0.65, 4.95)
8	4	2,207	1.81 (0.49, 4.64)	5	2,125	2.35 (0.76, 5.49)	0.77 (0.18, 3.58)
9	6	1,966	3.05 (1.12, 6.64)	4	1,808	2.21 (0.60, 5.66)	1.38 (0.30, 6.65)
10	2	1,761	1.14 (0.14, 4.10)	2	1,681	1.19 (0.14, 4.30)	0.95 (0.10, 13.16)
Stratified Mantel-Haenszel rate ratio							0.78 (0.65, 0.93)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either solifenacin or any other OAB drug except solifenacin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except solifenacin at entry.

Table CV7i. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Any OAB Drug Except Solifenacin

	Current Use of Solifenacin			Current Use of Any Other OAB Drug Except Solifenacin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Coronary heart disease death							
Propensity score stratum							
1	12	9,157	1.31 (0.68, 2.29)	104	25,021	4.16 (3.40, 5.04)	0.32 (0.18, 0.57)
2	8	5,951	1.34 (0.58, 2.65)	45	10,621	4.24 (3.09, 5.67)	0.32 (0.16, 0.68)
3	14	3,980	3.52 (1.92, 5.90)	27	5,774	4.68 (3.08, 6.80)	0.75 (0.39, 1.49)
4	6	3,019	1.99 (0.73, 4.33)	13	4,090	3.18 (1.69, 5.43)	0.63 (0.24, 1.76)
5	3	2,603	1.15 (0.24, 3.37)	12	3,082	3.89 (2.01, 6.80)	0.30 (0.09, 1.10)
6	6	2,479	2.42 (0.89, 5.27)	11	2,866	3.84 (1.92, 6.87)	0.63 (0.23, 1.86)
7	2	2,335	0.86 (0.10, 3.09)	4	2,390	1.67 (0.46, 4.28)	0.51 (0.09, 3.57)
8	1	2,211	0.45 (0.01, 2.52)	0	2,128	0.00 (0.00, 1.73)	
9	1	1,968	0.51 (0.01, 2.83)	0	1,813	0.00 (0.00, 2.03)	
10	0	1,762	0.00 (0.00, 2.09)	0	1,682	0.00 (0.00, 2.19)	
Stratified Mantel-Haenszel rate ratio							0.44 (0.33, 0.61)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either solifenacin or any other OAB drug except solifenacin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except solifenacin at entry.

Table CV7i. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Any OAB Drug Except Solifenacin

	Current Use of Solifenacin			Current Use of Any Other OAB Drug Except Solifenacin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cerebrovascular disease death							
Propensity score stratum							
1	10	9,157	1.09 (0.52, 2.01)	89	25,021	3.56 (2.86, 4.38)	0.31 (0.17, 0.59)
2	7	5,951	1.18 (0.47, 2.42)	30	10,621	2.82 (1.91, 4.03)	0.42 (0.19, 0.97)
3	6	3,980	1.51 (0.55, 3.28)	16	5,774	2.77 (1.58, 4.50)	0.54 (0.22, 1.46)
4	3	3,019	0.99 (0.20, 2.90)	7	4,090	1.71 (0.69, 3.53)	0.58 (0.15, 2.54)
5	7	2,603	2.69 (1.08, 5.54)	8	3,082	2.60 (1.12, 5.11)	1.04 (0.34, 3.27)
6	0	2,479	0.00 (0.00, 1.49)	3	2,866	1.05 (0.22, 3.06)	0.00 (0.00, 2.80)
7	2	2,335	0.86 (0.10, 3.09)	1	2,390	0.42 (0.01, 2.33)	2.05 (0.11, 120.79)
8	1	2,211	0.45 (0.01, 2.52)	1	2,128	0.47 (0.01, 2.62)	0.96 (0.05, 75.54)
9	1	1,968	0.51 (0.01, 2.83)	0	1,813	0.00 (0.00, 2.03)	
10	0	1,762	0.00 (0.00, 2.09)	0	1,682	0.00 (0.00, 2.19)	
Stratified Mantel-Haenszel rate ratio							0.46 (0.31, 0.66)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either solifenacin or any other OAB drug except solifenacin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except solifenacin at entry.

Table CV7i. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Any OAB Drug Except Solifenacin

	Current Use of Solifenacin			Current Use of Any Other OAB Drug Except Solifenacin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cardiovascular mortality							
Propensity score stratum							
1	21	9,157	2.29 (1.42, 3.51)	189	25,021	7.55 (6.52, 8.71)	0.30 (0.20, 0.48)
2	15	5,951	2.52 (1.41, 4.16)	74	10,621	6.97 (5.47, 8.75)	0.36 (0.21, 0.64)
3	20	3,980	5.02 (3.07, 7.76)	41	5,774	7.10 (5.10, 9.63)	0.71 (0.41, 1.24)
4	9	3,019	2.98 (1.36, 5.66)	20	4,090	4.89 (2.99, 7.55)	0.61 (0.28, 1.40)
5	8	2,603	3.07 (1.33, 6.06)	20	3,082	6.49 (3.96, 10.02)	0.47 (0.21, 1.12)
6	6	2,479	2.42 (0.89, 5.27)	14	2,866	4.89 (2.67, 8.20)	0.50 (0.19, 1.37)
7	3	2,335	1.28 (0.26, 3.75)	5	2,390	2.09 (0.68, 4.88)	0.61 (0.14, 3.16)
8	2	2,211	0.90 (0.11, 3.27)	1	2,128	0.47 (0.01, 2.62)	1.92 (0.10, 113.55)
9	2	1,968	1.02 (0.12, 3.67)	0	1,813	0.00 (0.00, 2.03)	
10	0	1,762	0.00 (0.00, 2.09)	0	1,682	0.00 (0.00, 2.19)	
Stratified Mantel-Haenszel rate ratio							0.44 (0.34, 0.56)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either solifenacin or any other OAB drug except solifenacin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except solifenacin at entry.

Table CV7i. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Any OAB Drug Except Solifenacin

	Current Use of Solifenacin			Current Use of Any Other OAB Drug Except Solifenacin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Major adverse cardiovascular event							
Propensity score stratum							
1	80	9,018	8.87 (7.03, 11.04)	394	24,668	15.97 (14.43, 17.63)	0.56 (0.44, 0.71)
2	56	5,868	9.54 (7.21, 12.39)	166	10,495	15.82 (13.50, 18.41)	0.60 (0.45, 0.82)
3	66	3,928	16.80 (12.99, 21.37)	102	5,699	17.90 (14.59, 21.73)	0.94 (0.69, 1.29)
4	36	2,988	12.05 (8.44, 16.68)	48	4,062	11.82 (8.71, 15.67)	1.02 (0.65, 1.60)
5	28	2,579	10.86 (7.21, 15.69)	50	3,057	16.36 (12.14, 21.56)	0.66 (0.42, 1.07)
6	28	2,455	11.41 (7.58, 16.49)	43	2,843	15.12 (10.95, 20.37)	0.75 (0.46, 1.24)
7	18	2,320	7.76 (4.60, 12.26)	20	2,385	8.39 (5.12, 12.95)	0.92 (0.47, 1.84)
8	7	2,204	3.18 (1.28, 6.54)	8	2,124	3.77 (1.63, 7.42)	0.84 (0.28, 2.66)
9	10	1,965	5.09 (2.44, 9.36)	10	1,805	5.54 (2.66, 10.19)	0.92 (0.35, 2.46)
10	2	1,761	1.14 (0.14, 4.10)	3	1,680	1.79 (0.37, 5.22)	0.64 (0.09, 5.55)
Stratified Mantel-Haenszel rate ratio							0.70 (0.61, 0.80)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either solifenacin or any other OAB drug except solifenacin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except solifenacin at entry.

Table CV7i. Propensity Score Stratified Analysis Comparing Current Use of Solifenacin Against Current Use of Any OAB Drug Except Solifenacin

	Current Use of Solifenacin			Current Use of Any Other OAB Drug Except Solifenacin			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
All-cause death							
Propensity score stratum							
1	147	9,157	16.05 (13.56, 18.87)	690	25,021	27.58 (25.56, 29.71)	0.58 (0.49, 0.70)
2	83	5,951	13.95 (11.11, 17.29)	290	10,621	27.30 (24.25, 30.63)	0.51 (0.40, 0.65)
3	120	3,980	30.15 (25.00, 36.05)	222	5,774	38.45 (33.56, 43.85)	0.78 (0.63, 0.98)
4	54	3,019	17.89 (13.44, 23.34)	89	4,090	21.76 (17.47, 26.78)	0.82 (0.58, 1.17)
5	38	2,603	14.60 (10.33, 20.04)	69	3,082	22.39 (17.42, 28.33)	0.65 (0.44, 0.98)
6	41	2,479	16.54 (11.87, 22.44)	60	2,866	20.94 (15.98, 26.95)	0.79 (0.53, 1.19)
7	24	2,335	10.28 (6.59, 15.29)	21	2,390	8.78 (5.44, 13.43)	1.17 (0.62, 2.21)
8	16	2,211	7.24 (4.14, 11.75)	8	2,128	3.76 (1.62, 7.41)	1.92 (0.70, 5.19)
9	6	1,968	3.05 (1.12, 6.64)	3	1,813	1.65 (0.34, 4.84)	1.84 (0.33, 11.39)
10	4	1,762	2.27 (0.62, 5.81)	5	1,682	2.97 (0.97, 6.94)	0.76 (0.18, 3.55)
Stratified Mantel-Haenszel rate ratio							0.67 (0.60, 0.74)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either solifenacin or any other OAB drug except solifenacin at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving solifenacin at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving solifenacin at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except solifenacin at entry.

Table CV7j. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Any OAB Drug Except Trospium

	Current Use of Trospium			Current Use of Any Other OAB Drug Except Trospium			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Acute myocardial infarction							
Propensity score stratum							
1	1	627	1.59 (0.04, 8.88)	68	16,356	4.16 (3.23, 5.27)	0.38 (0.10, 2.21)
2	2	498	4.02 (0.49, 14.52)	56	12,566	4.46 (3.37, 5.79)	0.90 (0.31, 3.41)
3	1	483	2.07 (0.05, 11.53)	51	11,404	4.47 (3.33, 5.88)	0.46 (0.12, 2.70)
4	6	523	11.47 (4.21, 24.96)	80	10,564	7.57 (6.01, 9.43)	1.51 (0.74, 3.44)
5	4	710	5.63 (1.54, 14.43)	65	12,699	5.12 (3.95, 6.52)	1.10 (0.47, 2.96)
6	7	677	10.33 (4.15, 21.29)	52	9,837	5.29 (3.95, 6.93)	1.95 (0.96, 4.32)
7	3	725	4.14 (0.85, 12.10)	52	9,318	5.58 (4.17, 7.32)	0.74 (0.29, 2.29)
8	3	805	3.73 (0.77, 10.89)	27	8,518	3.17 (2.09, 4.61)	1.18 (0.43, 3.82)
9	5	865	5.78 (1.88, 13.49)	58	8,067	7.19 (5.46, 9.29)	0.80 (0.37, 1.99)
10	4	841	4.76 (1.30, 12.18)	47	6,773	6.94 (5.10, 9.23)	0.69 (0.29, 1.88)
Stratified Mantel-Haenszel rate ratio							0.98 (0.70, 1.37)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either trospium or any other OAB drug except trospium at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except trospium at entry.

Table CV7j. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Any OAB Drug Except Trospium

	Current Use of Trospium			Current Use of Any Other OAB Drug Except Trospium			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Stroke							
Propensity score stratum							
1	2	625	3.20 (0.39, 11.56)	74	16,350	4.53 (3.55, 5.68)	0.71 (0.24, 2.64)
2	3	497	6.04 (1.25, 17.66)	66	12,542	5.26 (4.07, 6.69)	1.15 (0.45, 3.50)
3	2	482	4.15 (0.50, 15.00)	56	11,380	4.92 (3.72, 6.39)	0.84 (0.29, 3.19)
4	5	528	9.48 (3.08, 22.11)	81	10,540	7.69 (6.10, 9.55)	1.23 (0.57, 3.00)
5	9	705	12.77 (5.84, 24.23)	71	12,683	5.60 (4.37, 7.06)	2.28 (1.22, 4.58)
6	4	679	5.89 (1.60, 15.08)	74	9,844	7.52 (5.90, 9.44)	0.78 (0.34, 2.09)
7	5	724	6.90 (2.24, 16.11)	69	9,285	7.43 (5.78, 9.41)	0.93 (0.43, 2.27)
8	5	797	6.27 (2.04, 14.63)	60	8,487	7.07 (5.39, 9.10)	0.89 (0.40, 2.19)
9	7	862	8.12 (3.26, 16.73)	56	8,074	6.94 (5.24, 9.01)	1.17 (0.58, 2.57)
10	8	833	9.60 (4.15, 18.92)	76	6,735	11.28 (8.89, 14.12)	0.85 (0.44, 1.76)
Stratified Mantel-Haenszel rate ratio							1.06 (0.79, 1.41)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either trospium or any other OAB drug except trospium at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except trospium at entry.

Table CV7j. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Any OAB Drug Except Trospium

	Current Use of Trospium			Current Use of Any Other OAB Drug Except Trospium			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Coronary heart disease death							
Propensity score stratum							
1	0	629	0.00 (0.00, 5.86)	40	16,401	2.44 (1.74, 3.32)	0.00 (0.00, 2.52)
2	2	498	4.02 (0.49, 14.51)	26	12,605	2.06 (1.35, 3.02)	1.95 (0.62, 7.78)
3	4	483	8.28 (2.25, 21.19)	22	11,449	1.92 (1.20, 2.91)	4.31 (1.66, 12.68)
4	4	530	7.55 (2.06, 19.34)	34	10,617	3.20 (2.22, 4.48)	2.36 (0.96, 6.61)
5	2	713	2.80 (0.34, 10.13)	45	12,766	3.53 (2.57, 4.72)	0.80 (0.27, 3.05)
6	3	682	4.40 (0.91, 12.86)	31	9,910	3.13 (2.13, 4.44)	1.41 (0.52, 4.51)
7	1	732	1.37 (0.03, 7.61)	29	9,375	3.09 (2.07, 4.44)	0.44 (0.11, 2.66)
8	5	805	6.21 (2.02, 14.49)	20	8,563	2.34 (1.43, 3.61)	2.66 (1.07, 7.30)
9	3	870	3.45 (0.71, 10.07)	31	8,149	3.80 (2.58, 5.40)	0.91 (0.34, 2.90)
10	1	855	1.17 (0.03, 6.52)	27	6,817	3.96 (2.61, 5.76)	0.30 (0.07, 1.79)
Stratified Mantel-Haenszel rate ratio							1.22 (0.81, 1.83)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either trospium or any other OAB drug except trospium at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except trospium at entry.

Table CV7j. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Any OAB Drug Except Trospium

	Current Use of Trospium			Current Use of Any Other OAB Drug Except Trospium			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cerebrovascular disease death							
Propensity score stratum							
1	1	629	1.59 (0.04, 8.86)	20	16,401	1.22 (0.74, 1.88)	1.30 (0.31, 8.15)
2	1	498	2.01 (0.05, 11.19)	15	12,605	1.19 (0.67, 1.96)	1.69 (0.38, 10.97)
3	2	483	4.14 (0.50, 14.95)	15	11,449	1.31 (0.73, 2.16)	3.16 (0.92, 13.58)
4	2	530	3.78 (0.46, 13.64)	20	10,617	1.88 (1.15, 2.91)	2.00 (0.61, 8.25)
5	4	713	5.61 (1.53, 14.36)	31	12,766	2.43 (1.65, 3.45)	2.31 (0.93, 6.53)
6	1	682	1.47 (0.04, 8.17)	32	9,910	3.23 (2.21, 4.56)	0.45 (0.11, 2.72)
7	2	732	2.73 (0.33, 9.86)	21	9,375	2.24 (1.39, 3.42)	1.22 (0.38, 4.99)
8	1	805	1.24 (0.03, 6.92)	19	8,563	2.22 (1.34, 3.47)	0.56 (0.13, 3.52)
9	3	870	3.45 (0.71, 10.07)	25	8,149	3.07 (1.99, 4.53)	1.12 (0.41, 3.68)
10	4	855	4.68 (1.28, 11.98)	35	6,817	5.13 (3.58, 7.14)	0.91 (0.37, 2.55)
Stratified Mantel-Haenszel rate ratio							1.22 (0.78, 1.90)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either trospium or any other OAB drug except trospium at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except trospium at entry.

Table CV7j. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Any OAB Drug Except Trospium

	Current Use of Trospium			Current Use of Any Other OAB Drug Except Trospium			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Cardiovascular mortality							
Propensity score stratum							
1	1	629	1.59 (0.04, 8.86)	57	16,401	3.48 (2.63, 4.50)	0.46 (0.12, 2.65)
2	3	498	6.03 (1.24, 17.61)	40	12,605	3.17 (2.27, 4.32)	1.90 (0.72, 5.96)
3	6	483	12.41 (4.56, 27.02)	36	11,449	3.14 (2.20, 4.35)	3.95 (1.81, 9.46)
4	6	530	11.33 (4.16, 24.66)	53	10,617	4.99 (3.74, 6.53)	2.27 (1.08, 5.28)
5	6	713	8.41 (3.09, 18.31)	75	12,766	5.88 (4.62, 7.36)	1.43 (0.70, 3.27)
6	4	682	5.87 (1.60, 15.02)	62	9,910	6.26 (4.80, 8.02)	0.94 (0.40, 2.52)
7	3	732	4.10 (0.84, 11.97)	49	9,375	5.23 (3.87, 6.91)	0.78 (0.30, 2.43)
8	6	805	7.45 (2.73, 16.22)	38	8,563	4.44 (3.14, 6.09)	1.68 (0.77, 4.00)
9	6	870	6.89 (2.53, 15.01)	55	8,149	6.75 (5.08, 8.78)	1.02 (0.49, 2.37)
10	5	855	5.85 (1.90, 13.65)	60	6,817	8.80 (6.72, 11.33)	0.66 (0.30, 1.64)
Stratified Mantel-Haenszel rate ratio							1.25 (0.92, 1.69)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either trospium or any other OAB drug except trospium at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except trospium at entry.

Table CV7j. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Any OAB Drug Except Trospium

	Current Use of Trospium			Current Use of Any Other OAB Drug Except Trospium			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Major adverse cardiovascular event							
Propensity score stratum							
1	4	624	6.41 (1.75, 16.42)	152	16,304	9.32 (7.90, 10.93)	0.69 (0.31, 1.80)
2	6	496	12.09 (4.44, 26.32)	133	12,503	10.64 (8.91, 12.61)	1.14 (0.57, 2.54)
3	7	481	14.54 (5.85, 29.96)	123	11,337	10.85 (9.02, 12.94)	1.34 (0.69, 2.85)
4	14	521	26.86 (14.68, 45.06)	176	10,490	16.78 (14.39, 19.45)	1.60 (0.98, 2.76)
5	15	702	21.37 (11.96, 35.25)	160	12,616	12.68 (10.79, 14.81)	1.69 (1.04, 2.86)
6	11	675	16.30 (8.14, 29.17)	137	9,776	14.01 (11.77, 16.57)	1.16 (0.67, 2.15)
7	9	717	12.56 (5.74, 23.84)	130	9,231	14.08 (11.77, 16.72)	0.89 (0.49, 1.75)
8	10	797	12.54 (6.02, 23.07)	98	8,442	11.61 (9.42, 14.15)	1.08 (0.60, 2.07)
9	13	857	15.18 (8.08, 25.95)	119	7,992	14.89 (12.34, 17.82)	1.02 (0.60, 1.81)
10	15	819	18.31 (10.25, 30.21)	137	6,692	20.47 (17.19, 24.20)	0.89 (0.55, 1.53)
Stratified Mantel-Haenszel rate ratio							1.13 (0.93, 1.38)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either trospium or any other OAB drug except trospium at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except trospium at entry.

Table CV7j. Propensity Score Stratified Analysis Comparing Current Use of Trospium Against Current Use of Any OAB Drug Except Trospium

	Current Use of Trospium			Current Use of Any Other OAB Drug Except Trospium			
	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Events	Person-time (Years)	Crude Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
All-cause death							
Propensity score stratum							
1	6	629	9.54 (3.50, 20.76)	258	16,401	15.73 (13.87, 17.77)	0.61 (0.31, 1.34)
2	11	498	22.09 (11.03, 39.53)	200	12,605	15.87 (13.74, 18.22)	1.39 (0.81, 2.55)
3	22	483	45.51 (28.52, 68.91)	240	11,449	20.96 (18.39, 23.79)	2.17 (1.45, 3.36)
4	22	530	41.55 (26.04, 62.90)	260	10,617	24.49 (21.60, 27.65)	1.70 (1.13, 2.62)
5	17	713	23.84 (13.89, 38.17)	315	12,766	24.68 (22.03, 27.56)	0.97 (0.62, 1.57)
6	20	682	29.33 (17.91, 45.29)	221	9,910	22.30 (19.46, 25.44)	1.32 (0.86, 2.08)
7	14	732	19.11 (10.45, 32.07)	199	9,375	21.23 (18.38, 24.39)	0.90 (0.55, 1.55)
8	23	805	28.56 (18.11, 42.86)	193	8,563	22.54 (19.47, 25.95)	1.27 (0.85, 1.96)
9	20	870	22.98 (14.04, 35.49)	196	8,149	24.05 (20.80, 27.66)	0.96 (0.62, 1.52)
10	23	855	26.91 (17.06, 40.38)	206	6,817	30.22 (26.23, 34.64)	0.89 (0.60, 1.37)
Stratified Mantel-Haenszel rate ratio							1.16 (1.00, 1.35)

CI = confidence interval; OAB = overactive bladder.

Note 1: Incidence rates are per 1,000 person-years.

Note 2: The propensity score was estimated through logistic regression using 117,120 patients who experienced single exposure to either trospium or any other OAB drug except trospium at cohort entry. This model adjusted for age at cohort entry, sex, calendar year at cohort entry, and the comorbidities and exposure to medications identified in Table CV1.

Note 3: Patients were grouped into propensity score strata defined by the percentiles of the patients receiving trospium at entry. Trimming of these scores was performed by removing patients with propensity scores below the first percentile of patients receiving trospium at entry and patients with propensity scores above the 99th percentile for those receiving any OAB except trospium at entry.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Composite Event (N = 4,117)		Colon and Rectum (N = 545)		Pancreas (N = 138)		Lung and Bronchus (N = 495)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sex										
Male	34,262	29.6%	1,917	46.6%	233	42.8%	48	34.8%	214	43.2%
Female	81,533	70.4%	2,200	53.4%	312	57.2%	90	65.2%	281	56.8%
Age at cohort entry (years)										
18-24	2,214	1.9%	3	0.1%	0		0		0	
25-34	5,001	4.3%	10	0.2%	0		0		0	
35-44	11,932	10.3%	73	1.8%	5	0.9%	0		3	0.6%
45-54	18,138	15.7%	273	6.6%	14	2.6%	4	2.9%	25	5.1%
55-64	23,113	20.0%	838	20.4%	84	15.4%	22	15.9%	89	18.0%
65-74	24,213	20.9%	1,216	29.5%	158	29.0%	40	29.0%	165	33.3%
75-84	22,284	19.2%	1,328	32.3%	225	41.3%	62	44.9%	173	34.9%
85+	8,900	7.7%	376	9.1%	59	10.8%	10	7.2%	40	8.1%
Calendar year at cohort entry										
2004	11,867	10.2%	731	17.8%	106	19.4%	27	19.6%	102	20.6%
2005	12,044	10.4%	642	15.6%	97	17.8%	20	14.5%	88	17.8%
2006	11,589	10.0%	622	15.1%	88	16.1%	27	19.6%	70	14.1%
2007	11,896	10.3%	538	13.1%	61	11.2%	17	12.3%	78	15.8%
2008	11,798	10.2%	483	11.7%	68	12.5%	19	13.8%	41	8.3%
2009	12,991	11.2%	402	9.8%	57	10.5%	11	8.0%	47	9.5%
2010	13,495	11.7%	375	9.1%	36	6.6%	9	6.5%	39	7.9%
2011	14,769	12.8%	229	5.6%	24	4.4%	6	4.3%	21	4.2%
2012	15,346	13.3%	95	2.3%	8	1.5%	2	1.4%	9	1.8%

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Composite Event (N = 4,117)		Colon and Rectum (N = 545)		Pancreas (N = 138)		Lung and Bronchus (N = 495)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Index of Multiple Deprivation (Quintiles)										
Q1	25,751	22.2%	1,002	24.3%	125	22.9%	44	31.9%	95	19.2%
Q2	23,671	20.4%	905	22.0%	118	21.7%	26	18.8%	86	17.4%
Q3	23,277	20.1%	845	20.5%	110	20.2%	29	21.0%	106	21.4%
Q4	23,589	20.4%	722	17.5%	114	20.9%	21	15.2%	89	18.0%
Q5	19,507	16.8%	643	15.6%	78	14.3%	18	13.0%	119	24.0%
Overactive bladder	57,675	49.8%	1,827	44.4%	244	44.8%	56	40.6%	221	44.6%
Hypertension										
Diagnosis codes only	33,672	29.1%	1,273	30.9%	183	33.6%	36	26.1%	152	30.7%
Medications only	4,952	4.3%	81	2.0%	9	1.7%	4	2.9%	8	1.6%
Diagnosis codes and medications	54,403	47.0%	2,357	57.3%	327	60.0%	91	65.9%	287	58.0%
Diabetes										
Diagnosis codes only	2,626	2.3%	159	3.9%	22	4.0%	8	5.8%	24	4.8%
Medications only	335	0.3%	7	0.2%	2	0.4%	1	0.7%	1	0.2%
Diagnosis codes and medications	9,889	8.5%	479	11.6%	83	15.2%	22	15.9%	55	11.1%
Smoking										
Current	18,789	16.2%	662	16.1%	56	10.3%	15	10.9%	210	42.4%
Former	40,474	35.0%	1,755	42.6%	231	42.4%	65	47.1%	221	44.6%
Non-smoker	55,140	47.6%	1,648	40.0%	250	45.9%	55	39.9%	58	11.7%
Unknown	1,392	1.2%	52	1.3%	8	1.5%	3	2.2%	6	1.2%

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Composite Event (N = 4,117)		Colon and Rectum (N = 545)		Pancreas (N = 138)		Lung and Bronchus (N = 495)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
History of acute myocardial infarction	4,526	3.9%	284	6.9%	35	6.4%	17	12.3%	42	8.5%
History of stroke	7,952	6.9%	357	8.7%	56	10.3%	12	8.7%	48	9.7%
History of transient ischemic attack	4,628	4.0%	240	5.8%	39	7.2%	6	4.3%	28	5.7%
History of coronary heart disease	14,754	12.7%	787	19.1%	103	18.9%	36	26.1%	111	22.4%
History of heart failure	3,668	3.2%	201	4.9%	34	6.2%	10	7.2%	29	5.9%
History of peripheral artery disease or peripheral vascular disease	7,998	6.9%	394	9.6%	54	9.9%	18	13.0%	77	15.6%
Dyslipidemia	14,719	12.7%	660	16.0%	89	16.3%	24	17.4%	84	17.0%
Atrial fibrillation	6,565	5.7%	340	8.3%	53	9.7%	13	9.4%	39	7.9%
Chronic obstructive pulmonary disease	6,900	6.0%	400	9.7%	42	7.7%	7	5.1%	141	28.5%
Dementia	2,104	1.8%	53	1.3%	8	1.5%	4	2.9%	9	1.8%
Hemiplegia and paraplegia	1,696	1.5%	52	1.3%	7	1.3%	1	0.7%	10	2.0%
Liver disease	1,260	1.1%	30	0.7%	3	0.6%	2	1.4%	9	1.8%
Peptic ulcer disease	5,930	5.1%	261	6.3%	44	8.1%	8	5.8%	43	8.7%
Renal disease	12,173	10.5%	493	12.0%	75	13.8%	17	12.3%	57	11.5%
Dialysis	74	0.1%	2	<0.1%	0		0		0	
Rheumatological disease	6,314	5.5%	256	6.2%	36	6.6%	13	9.4%	47	9.5%
Gout	4,525	3.9%	251	6.1%	28	5.1%	9	6.5%	37	7.5%
Organ transplantation	128	0.1%	5	0.1%	0		1	0.7%	1	0.2%
Polycystic ovary syndrome (females only)	815	1.0%	6	0.3%	0		0		1	0.4%

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Composite Event (N = 4,117)		Colon and Rectum (N = 545)		Pancreas (N = 138)		Lung and Bronchus (N = 495)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Endometrial polyps or other benign growths of the uterine lining (females only)	1,055	1.3%	34	1.5%	3	1.0%	3	3.3%	2	0.7%
Menopause (females only)	19,299	23.7%	540	24.5%	63	20.2%	19	21.1%	78	27.8%
BRCA1 and BRCA2 mutations	2	<0.1%	0		0		0		0	
Body mass index										
< 20	3,856	3.3%	119	2.9%	10	1.8%	3	2.2%	34	6.9%
20 to < 25	20,190	17.4%	757	18.4%	91	16.7%	31	22.5%	93	18.8%
25 to < 30	26,431	22.8%	1,032	25.1%	150	27.5%	36	26.1%	128	25.9%
30 to < 40	22,958	19.8%	781	19.0%	110	20.2%	28	20.3%	90	18.2%
40+	4,208	3.6%	88	2.1%	8	1.5%	2	1.4%	9	1.8%
Unknown	38,152	32.9%	1,340	32.5%	176	32.3%	38	27.5%	141	28.5%
Obesity treatment	6,084	5.3%	131	3.2%	11	2.0%	5	3.6%	13	2.6%
Family history of cancer										
Melanoma of the skin	4	<0.1%	0		0		0		0	
Colon and rectum	1,002	0.9%	32	0.8%	5	0.9%	1	0.7%	3	0.6%
Lung and bronchus	9	<0.1%	1	<0.1%	0		0		1	0.2%
Prostate (males only)	81	0.2%	9	0.5%	0		0		0	
Breast (females only)	1,636	2.0%	67	3.0%	2	0.6%	0		7	2.5%
Corpus uteri (females only)	16	<0.1%	1	<0.1%	0		0		0	

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Composite Event (N = 4,117)		Colon and Rectum (N = 545)		Pancreas (N = 138)		Lung and Bronchus (N = 495)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
History of alcohol use										
Non-drinker	15,793	13.6%	496	12.0%	60	11.0%	24	17.4%	59	11.9%
Low-moderate intake (1-6 units/wk)	60,295	52.1%	2,144	52.1%	295	54.1%	72	52.2%	247	49.9%
Heavy or very heavy intake (7+ units/wk)	21,136	18.3%	872	21.2%	100	18.3%	25	18.1%	93	18.8%
Drinker - unknown quantity	6,900	6.0%	216	5.2%	36	6.6%	3	2.2%	33	6.7%
Unknown	11,671	10.1%	389	9.4%	54	9.9%	14	10.1%	63	12.7%
Alcoholism or alcohol-related diseases	3,401	2.9%	105	2.6%	9	1.7%	0		32	6.5%
Bilateral mastectomy (females only)	20	<0.1%	1	<0.1%	1	0.3%	0		0	
Health services utilization [mean (SD)]										
Outpatient visits (in year before cohort entry)	10.7	9.39	11.7	9.56	11.7	9.09	15.5	15.25	13.1	11.19
Hospitalizations (in year before cohort entry)	0.5	1.28	0.6	1.17	0.5	1.11	0.9	1.59	0.7	1.40
Sigmoidoscopies/ colonoscopies (in year before cohort entry)	0.0	0.09	0.0	0.10	0.0	0.09	0.0	0.12	0.0	0.11
Mammograms (females only, in year before cohort entry)	0.0	0.13	0.0	0.11	0.0	0.11	0.0	0.11	0.0	0.06
Number of prescriptions for study drugs (during follow-up)	12.6	22.65	9.8	17.21	12.0	20.75	11.6	14.34	12.3	20.22
Number of different OAB drugs received (during follow-up)	1.4	0.68	1.3	0.61	1.3	0.64	1.4	0.62	1.3	0.63
Duration of enrollment prior to cohort entry (years)	9.3	5.46	9.0	5.07	8.9	4.79	8.1	4.71	8.6	5.23

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

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Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Composite Event (N = 4,117)		Colon and Rectum (N = 545)		Pancreas (N = 138)		Lung and Bronchus (N = 495)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Duration of follow-up (years)	3.4	2.47	2.3	1.99	2.6	1.96	2.8	2.11	2.6	2.11
Previous exposure to study drug in the year before cohort entry										
Oxybutynin	2,189	1.9%	107	2.6%	17	3.1%	6	4.3%	13	2.6%
Tolterodine	2,664	2.3%	111	2.7%	24	4.4%	1	0.7%	19	3.8%
Darifenacin	10	<0.1%	0		0		0		0	
Solifenacin	378	0.3%	6	0.1%	2	0.4%	0		0	
Trospium	431	0.4%	23	0.6%	5	0.9%	0		3	0.6%
Fesoterodine	33	<0.1%	0		0		0		0	
Previous exposure to study drug in the 5 years before cohort entry										
Oxybutynin	6,062	5.2%	303	7.4%	46	8.4%	13	9.4%	46	9.3%
Tolterodine	7,256	6.3%	349	8.5%	61	11.2%	10	7.2%	46	9.3%
Darifenacin	15	<0.1%	0		0		0		0	
Solifenacin	797	0.7%	11	0.3%	3	0.6%	0		0	
Trospium	1,207	1.0%	66	1.6%	12	2.2%	1	0.7%	9	1.8%
Fesoterodine	57	<0.1%	0		0		0		0	
Previous exposure to study drug before cohort entry										
Oxybutynin	11,634	10.0%	531	12.9%	73	13.4%	19	13.8%	77	15.6%
Tolterodine	10,009	8.6%	428	10.4%	67	12.3%	13	9.4%	57	11.5%
Darifenacin	15	<0.1%	0		0		0		0	
Solifenacin	813	0.7%	11	0.3%	3	0.6%	0		0	
Trospium	1,477	1.3%	71	1.7%	13	2.4%	1	0.7%	10	2.0%
Fesoterodine	57	<0.1%	0		0		0		0	

OAB = overactive bladder.

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Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Composite Event (N = 4,117)		Colon and Rectum (N = 545)		Pancreas (N = 138)		Lung and Bronchus (N = 495)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Exposure to radiation	11	<0.1%	0		0		0		0	
Increased cardiovascular risk	49,971	43.2%	2,298	55.8%	319	58.5%	83	60.1%	360	72.7%
Hormone replacement therapy (females only)	29,660	36.4%	929	42.2%	129	41.3%	37	41.1%	125	44.5%
Tamoxifen	253	0.2%	7	0.2%	2	0.4%	0		0	
Letrozole	15	<0.1%	0		0		0		0	
Thyroid hormone replacement	11,915	10.3%	365	8.9%	48	8.8%	15	10.9%	47	9.5%
Digoxin	3,370	2.9%	179	4.3%	28	5.1%	6	4.3%	16	3.2%
Nitrates and other anti-anginal drugs	8,751	7.6%	458	11.1%	60	11.0%	17	12.3%	66	13.3%
Lipid-lowering drugs	37,066	32.0%	1,639	39.8%	231	42.4%	75	54.3%	207	41.8%
Non-aspirin NSAIDs	85,956	74.2%	3,029	73.6%	399	73.2%	103	74.6%	383	77.4%
Low-dose aspirin and other antiplatelets	36,387	31.4%	1,749	42.5%	241	44.2%	70	50.7%	242	48.9%
Immunosuppressive agents	1,312	1.1%	48	1.2%	5	0.9%	3	2.2%	10	2.0%
Antiarrhythmic drugs	3,076	2.7%	153	3.7%	20	3.7%	0		17	3.4%
Thrombolytic therapy	0		0		0		0		0	
Warfarin	6,486	5.6%	324	7.9%	42	7.7%	18	13.0%	36	7.3%

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Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Melanoma of the Skin (N = 182)		Breast (Female) (N = 886)		Corpus Uteri (Female) (N = 136)		Prostate (Male) (N = 932)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sex										
Male	34,262	29.6%	49	26.9%					932	100%
Female	81,533	70.4%	133	73.1%	886	100%	136	100%		
Age at cohort entry (years)										
18-24	2,214	1.9%	1	0.5%	0		0		0	
25-34	5,001	4.3%	5	2.7%	4	0.5%	0		0	
35-44	11,932	10.3%	11	6.0%	41	4.6%	4	2.9%	1	0.1%
45-54	18,138	15.7%	17	9.3%	138	15.6%	11	8.1%	32	3.4%
55-64	23,113	20.0%	37	20.3%	219	24.7%	42	30.9%	199	21.4%
65-74	24,213	20.9%	40	22.0%	215	24.3%	35	25.7%	315	33.8%
75-84	22,284	19.2%	52	28.6%	205	23.1%	31	22.8%	302	32.4%
85+	8,900	7.7%	19	10.4%	64	7.2%	13	9.6%	83	8.9%
Calendar year at cohort entry										
2004	11,867	10.2%	30	16.5%	160	18.1%	14	10.3%	140	15.0%
2005	12,044	10.4%	23	12.6%	130	14.7%	23	16.9%	147	15.8%
2006	11,589	10.0%	28	15.4%	157	17.7%	18	13.2%	116	12.4%
2007	11,896	10.3%	28	15.4%	117	13.2%	27	19.9%	107	11.5%
2008	11,798	10.2%	15	8.2%	115	13.0%	18	13.2%	124	13.3%
2009	12,991	11.2%	24	13.2%	79	8.9%	15	11.0%	97	10.4%
2010	13,495	11.7%	23	12.6%	67	7.6%	10	7.4%	105	11.3%
2011	14,769	12.8%	10	5.5%	52	5.9%	9	6.6%	58	6.2%
2012	15,346	13.3%	1	0.5%	9	1.0%	2	1.5%	38	4.1%

OAB = overactive bladder.

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Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Melanoma of the Skin (N = 182)		Breast (Female) (N = 886)		Corpus Uteri (Female) (N = 136)		Prostate (Male) (N = 932)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Index of Multiple Deprivation (Quintiles)										
Q1	25,751	22.2%	43	23.6%	207	23.4%	31	22.8%	248	26.6%
Q2	23,671	20.4%	43	23.6%	225	25.4%	25	18.4%	207	22.2%
Q3	23,277	20.1%	40	22.0%	180	20.3%	33	24.3%	205	22.0%
Q4	23,589	20.4%	42	23.1%	145	16.4%	21	15.4%	148	15.9%
Q5	19,507	16.8%	14	7.7%	129	14.6%	26	19.1%	124	13.3%
Overactive bladder	57,675	49.8%	96	52.7%	546	61.6%	82	60.3%	264	28.3%
Hypertension										
Diagnosis codes only	33,672	29.1%	42	23.1%	280	31.6%	38	27.9%	300	32.2%
Medications only	4,952	4.3%	4	2.2%	34	3.8%	1	0.7%	10	1.1%
Diagnosis codes and medications	54,403	47.0%	105	57.7%	444	50.1%	86	63.2%	537	57.6%
Diabetes										
Diagnosis codes only	2,626	2.3%	4	2.2%	30	3.4%	5	3.7%	36	3.9%
Medications only	335	0.3%	0		2	0.2%	0		1	0.1%
Diagnosis codes and medications	9,889	8.5%	18	9.9%	68	7.7%	24	17.6%	105	11.3%
Smoking										
Current	18,789	16.2%	24	13.2%	97	10.9%	11	8.1%	103	11.1%
Former	40,474	35.0%	53	29.1%	307	34.7%	38	27.9%	454	48.7%
Non-smoker	55,140	47.6%	102	56.0%	473	53.4%	86	63.2%	363	38.9%
Unknown	1,392	1.2%	3	1.6%	9	1.0%	1	0.7%	12	1.3%

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	Patients Without Cancer Endpoint (N = 115,795)		Melanoma of the Skin (N = 182)		Breast (Female) (N = 886)		Corpus Uteri (Female) (N = 136)		Prostate (Male) (N = 932)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
History of acute myocardial infarction	4,526	3.9%	12	6.6%	28	3.2%	2	1.5%	86	9.2%
History of stroke	7,952	6.9%	17	9.3%	52	5.9%	11	8.1%	89	9.5%
History of transient ischemic attack	4,628	4.0%	10	5.5%	44	5.0%	4	2.9%	56	6.0%
History of coronary heart disease	14,754	12.7%	34	18.7%	103	11.6%	11	8.1%	213	22.9%
History of heart failure	3,668	3.2%	10	5.5%	27	3.0%	6	4.4%	40	4.3%
History of peripheral artery disease or peripheral vascular disease	7,998	6.9%	7	3.8%	69	7.8%	10	7.4%	64	6.9%
Dyslipidemia	14,719	12.7%	29	15.9%	123	13.9%	22	16.2%	163	17.5%
Atrial fibrillation	6,565	5.7%	10	5.5%	46	5.2%	6	4.4%	90	9.7%
Chronic obstructive pulmonary disease	6,900	6.0%	6	3.3%	45	5.1%	4	2.9%	84	9.0%
Dementia	2,104	1.8%	4	2.2%	12	1.4%	1	0.7%	7	0.8%
Hemiplegia and paraplegia	1,696	1.5%	2	1.1%	9	1.0%	3	2.2%	9	1.0%
Liver disease	1,260	1.1%	1	0.5%	1	0.1%	2	1.5%	6	0.6%
Peptic ulcer disease	5,930	5.1%	6	3.3%	38	4.3%	6	4.4%	64	6.9%
Renal disease	12,173	10.5%	23	12.6%	84	9.5%	16	11.8%	105	11.3%
Dialysis	74	0.1%	0		1	0.1%	0		0	
Rheumatological disease	6,314	5.5%	7	3.8%	66	7.4%	7	5.1%	36	3.9%
Gout	4,525	3.9%	12	6.6%	20	2.3%	5	3.7%	80	8.6%
Organ transplantation	128	0.1%	0		1	0.1%	0		1	0.1%
Polycystic ovary syndrome (females only)	815	1.0%	0		3	0.3%	0		0	

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Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Melanoma of the Skin (N = 182)		Breast (Female) (N = 886)		Corpus Uteri (Female) (N = 136)		Prostate (Male) (N = 932)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Endometrial polyps or other benign growths of the uterine lining (females only)	1,055	1.3%	0		19	2.1%	4	2.9%	0	
Menopause (females only)	19,299	23.7%	22	16.5%	253	28.6%	36	26.5%	0	
BRCA1 and BRCA2 mutations	2	<0.1%	0		0		0		0	
Body mass index										
< 20	3,856	3.3%	3	1.6%	26	2.9%	1	0.7%	19	2.0%
20 to < 25	20,190	17.4%	39	21.4%	164	18.5%	18	13.2%	179	19.2%
25 to < 30	26,431	22.8%	48	26.4%	198	22.3%	22	16.2%	249	26.7%
30 to < 40	22,958	19.8%	33	18.1%	171	19.3%	33	24.3%	168	18.0%
40+	4,208	3.6%	3	1.6%	28	3.2%	14	10.3%	8	0.9%
Unknown	38,152	32.9%	56	30.8%	299	33.7%	48	35.3%	309	33.2%
Obesity treatment	6,084	5.3%	4	2.2%	40	4.5%	12	8.8%	19	2.0%
Family history of cancer										
Melanoma of the skin	4	<0.1%	0		0		0		0	
Colon and rectum	1,002	0.9%	2	1.1%	11	1.2%	0		5	0.5%
Lung and bronchus	9	<0.1%	0		0		0		0	
Prostate (males only)	81	0.2%	0		0		0		8	0.9%
Breast (females only)	1,636	2.0%	4	3.0%	48	5.4%	3	2.2%	0	
Corpus uteri (females only)	16	<0.1%	1	0.8%	0		0		0	

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	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
History of alcohol use										
Non-drinker	15,793	13.6%	21	11.5%	129	14.6%	20	14.7%	81	8.7%
Low-moderate intake (1-6 units/wk)	60,295	52.1%	91	50.0%	487	55.0%	71	52.2%	475	51.0%
Heavy or very heavy intake (7+ units/wk)	21,136	18.3%	47	25.8%	132	14.9%	20	14.7%	279	29.9%
Drinker - unknown quantity	6,900	6.0%	9	4.9%	60	6.8%	11	8.1%	30	3.2%
Unknown	11,671	10.1%	14	7.7%	78	8.8%	14	10.3%	67	7.2%
Alcoholism or alcohol-related diseases	3,401	2.9%	2	1.1%	13	1.5%	1	0.7%	26	2.8%
Bilateral mastectomy (females only)	20	<0.1%	0		0		0		0	
Health services utilization [mean (SD)]										
Outpatient visits (in year before cohort entry)	10.7	9.39	10.3	7.35	11.5	9.30	10.6	8.09	10.6	8.77
Hospitalizations (in year before cohort entry)	0.5	1.28	0.6	1.29	0.5	0.97	0.4	0.88	0.6	1.11
Sigmoidoscopies/ colonoscopies (in year before cohort entry)	0.0	0.09	0.0	0.00	0.0	0.07	0.0	0.00	0.0	0.11
Mammograms (females only, in year before cohort entry)	0.0	0.13	0.0	0.15	0.0	0.11	0.0	0.17	0.0	
Number of prescriptions for study drugs (during follow-up)	12.6	22.65	9.4	16.89	10.9	18.27	8.7	14.94	7.4	14.49
Number of different OAB drugs received (during follow-up)	1.4	0.68	1.3	0.52	1.4	0.65	1.3	0.60	1.2	0.56
Duration of enrollment prior to cohort entry (years)	9.3	5.46	8.2	4.80	8.7	5.03	9.1	5.10	9.4	5.12

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	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Duration of follow-up (years)	3.4	2.47	2.6	2.03	2.5	1.99	2.0	1.78	1.7	1.82
Previous exposure to study drug in the year before cohort entry										
Oxybutynin	2,189	1.9%	5	2.7%	25	2.8%	3	2.2%	17	1.8%
Tolterodine	2,664	2.3%	4	2.2%	18	2.0%	3	2.2%	21	2.3%
Darifenacin	10	<0.1%	0		0		0		0	
Solifenacin	378	0.3%	1	0.5%	2	0.2%	0		1	0.1%
Trospium	431	0.4%	1	0.5%	8	0.9%	0		4	0.4%
Fesoterodine	33	<0.1%	0		0		0		0	
Previous exposure to study drug in the 5 years before cohort entry										
Oxybutynin	6,062	5.2%	17	9.3%	64	7.2%	8	5.9%	53	5.7%
Tolterodine	7,256	6.3%	17	9.3%	86	9.7%	10	7.4%	59	6.3%
Darifenacin	15	<0.1%	0		0		0		0	
Solifenacin	797	0.7%	1	0.5%	3	0.3%	0		3	0.3%
Trospium	1,207	1.0%	1	0.5%	15	1.7%	2	1.5%	10	1.1%
Fesoterodine	57	<0.1%	0		0		0		0	
Previous exposure to study drug before cohort entry										
Oxybutynin	11,634	10.0%	24	13.2%	129	14.6%	18	13.2%	99	10.6%
Tolterodine	10,009	8.6%	22	12.1%	106	12.0%	12	8.8%	73	7.8%
Darifenacin	15	<0.1%	0		0		0		0	
Solifenacin	813	0.7%	1	0.5%	3	0.3%	0		3	0.3%
Trospium	1,477	1.3%	1	0.5%	15	1.7%	2	1.5%	11	1.2%
Fesoterodine	57	<0.1%	0		0		0		0	

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Melanoma of the Skin (N = 182)		Breast (Female) (N = 886)		Corpus Uteri (Female) (N = 136)		Prostate (Male) (N = 932)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Exposure to radiation	11	<0.1%	0		0		0		0	
Increased cardiovascular risk	49,971	43.2%	80	44.0%	369	41.6%	73	53.7%	529	56.8%
Hormone replacement therapy (females only)	29,660	36.4%	45	33.8%	397	44.8%	55	40.4%	0	
Tamoxifen	253	0.2%	0		3	0.3%	1	0.7%	0	
Letrozole	15	<0.1%	0		0		0		0	
Thyroid hormone replacement	11,915	10.3%	24	13.2%	116	13.1%	15	11.0%	32	3.4%
Digoxin	3,370	2.9%	6	3.3%	23	2.6%	6	4.4%	54	5.8%
Nitrates and other anti-anginal drugs	8,751	7.6%	16	8.8%	66	7.4%	4	2.9%	117	12.6%
Lipid-lowering drugs	37,066	32.0%	66	36.3%	261	29.5%	48	35.3%	401	43.0%
Non-aspirin NSAIDs	85,956	74.2%	124	68.1%	688	77.7%	103	75.7%	653	70.1%
Low-dose aspirin and other antiplatelets	36,387	31.4%	74	40.7%	280	31.6%	39	28.7%	429	46.0%
Immunosuppressive agents	1,312	1.1%	1	0.5%	11	1.2%	1	0.7%	6	0.6%
Antiarrhythmic drugs	3,076	2.7%	8	4.4%	21	2.4%	1	0.7%	50	5.4%
Thrombolytic therapy	0		0		0		0		0	
Warfarin	6,486	5.6%	13	7.1%	44	5.0%	6	4.4%	89	9.5%

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Urinary Bladder (N = 534)		Kidney and Renal Pelvis (N = 125)		Non-Hodgkin Lymphoma (N = 144)	
	n	(%)	n	(%)	n	(%)	n	(%)
Sex								
Male	34,262	29.6%	325	60.9%	53	42.4%	63	43.8%
Female	81,533	70.4%	209	39.1%	72	57.6%	81	56.3%
Age at cohort entry (years)								
18-24	2,214	1.9%	1	0.2%	1	0.8%	0	
25-34	5,001	4.3%	1	0.2%	0		0	
35-44	11,932	10.3%	5	0.9%	2	1.6%	1	0.7%
45-54	18,138	15.7%	17	3.2%	9	7.2%	6	4.2%
55-64	23,113	20.0%	88	16.5%	29	23.2%	29	20.1%
65-74	24,213	20.9%	156	29.2%	34	27.2%	58	40.3%
75-84	22,284	19.2%	199	37.3%	38	30.4%	41	28.5%
85+	8,900	7.7%	67	12.5%	12	9.6%	9	6.3%
Calendar year at cohort entry								
2004	11,867	10.2%	88	16.5%	29	23.2%	35	24.3%
2005	12,044	10.4%	63	11.8%	25	20.0%	26	18.1%
2006	11,589	10.0%	73	13.7%	19	15.2%	26	18.1%
2007	11,896	10.3%	73	13.7%	13	10.4%	17	11.8%
2008	11,798	10.2%	54	10.1%	9	7.2%	20	13.9%
2009	12,991	11.2%	50	9.4%	13	10.4%	9	6.3%
2010	13,495	11.7%	71	13.3%	11	8.8%	4	2.8%
2011	14,769	12.8%	39	7.3%	4	3.2%	6	4.2%
2012	15,346	13.3%	23	4.3%	2	1.6%	1	0.7%

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Urinary Bladder (N = 534)		Kidney and Renal Pelvis (N = 125)		Non-Hodgkin Lymphoma (N = 144)	
	n	(%)	n	(%)	n	(%)	n	(%)
Index of Multiple Deprivation (Quintiles)								
Q1	25,751	22.2%	142	26.6%	31	24.8%	36	25.0%
Q2	23,671	20.4%	114	21.3%	28	22.4%	33	22.9%
Q3	23,277	20.1%	94	17.6%	24	19.2%	24	16.7%
Q4	23,589	20.4%	91	17.0%	26	20.8%	25	17.4%
Q5	19,507	16.8%	93	17.4%	16	12.8%	26	18.1%
Overactive bladder	57,675	49.8%	189	35.4%	50	40.0%	79	54.9%
Hypertension								
Diagnosis codes only	33,672	29.1%	163	30.5%	29	23.2%	50	34.7%
Medications only	4,952	4.3%	5	0.9%	2	1.6%	4	2.8%
Diagnosis codes and medications	54,403	47.0%	320	59.9%	85	68.0%	75	52.1%
Diabetes								
Diagnosis codes only	2,626	2.3%	21	3.9%	5	4.0%	4	2.8%
Medications only	335	0.3%	0		0		0	
Diagnosis codes and medications	9,889	8.5%	67	12.5%	17	13.6%	20	13.9%
Smoking								
Current	18,789	16.2%	105	19.7%	20	16.0%	21	14.6%
Former	40,474	35.0%	268	50.2%	50	40.0%	68	47.2%
Non-smoker	55,140	47.6%	155	29.0%	52	41.6%	54	37.5%
Unknown	1,392	1.2%	6	1.1%	3	2.4%	1	0.7%

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Urinary Bladder (N = 534)		Kidney and Renal Pelvis (N = 125)		Non-Hodgkin Lymphoma (N = 144)	
	n	(%)	n	(%)	n	(%)	n	(%)
History of acute myocardial infarction	4,526	3.9%	44	8.2%	9	7.2%	9	6.3%
History of stroke	7,952	6.9%	49	9.2%	8	6.4%	15	10.4%
History of transient ischemic attack	4,628	4.0%	33	6.2%	7	5.6%	13	9.0%
History of coronary heart disease	14,754	12.7%	122	22.8%	25	20.0%	29	20.1%
History of heart failure	3,668	3.2%	29	5.4%	5	4.0%	11	7.6%
History of peripheral artery disease or peripheral vascular disease	7,998	6.9%	62	11.6%	14	11.2%	19	13.2%
Dyslipidemia	14,719	12.7%	74	13.9%	26	20.8%	26	18.1%
Atrial fibrillation	6,565	5.7%	52	9.7%	16	12.8%	15	10.4%
Chronic obstructive pulmonary disease	6,900	6.0%	51	9.6%	10	8.0%	10	6.9%
Dementia	2,104	1.8%	5	0.9%	0		3	2.1%
Hemiplegia and paraplegia	1,696	1.5%	7	1.3%	1	0.8%	3	2.1%
Liver disease	1,260	1.1%	2	0.4%	2	1.6%	2	1.4%
Peptic ulcer disease	5,930	5.1%	36	6.7%	5	4.0%	11	7.6%
Renal disease	12,173	10.5%	81	15.2%	19	15.2%	16	11.1%
Dialysis	74	0.1%	0		1	0.8%	0	
Rheumatological disease	6,314	5.5%	28	5.2%	6	4.8%	10	6.9%
Gout	4,525	3.9%	43	8.1%	12	9.6%	5	3.5%
Organ transplantation	128	0.1%	0		1	0.8%	0	
Polycystic ovary syndrome (females only)	815	1.0%	1	0.5%	1	1.4%	0	

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Urinary Bladder (N = 534)		Kidney and Renal Pelvis (N = 125)		Non-Hodgkin Lymphoma (N = 144)	
	n	(%)	n	(%)	n	(%)	n	(%)
Endometrial polyps or other benign growths of the uterine lining (females only)	1,055	1.3%	2	1.0%	0		1	1.2%
Menopause (females only)	19,299	23.7%	38	18.2%	12	16.7%	19	23.5%
BRCA1 and BRCA2 mutations	2	<0.1%	0		0		0	
Body mass index								
< 20	3,856	3.3%	18	3.4%	3	2.4%	2	1.4%
20 to < 25	20,190	17.4%	84	15.7%	26	20.8%	32	22.2%
25 to < 30	26,431	22.8%	146	27.3%	24	19.2%	31	21.5%
30 to < 40	22,958	19.8%	94	17.6%	25	20.0%	29	20.1%
40+	4,208	3.6%	7	1.3%	6	4.8%	3	2.1%
Unknown	38,152	32.9%	185	34.6%	41	32.8%	47	32.6%
Obesity treatment	6,084	5.3%	16	3.0%	6	4.8%	5	3.5%
Family history of cancer								
Melanoma of the skin	4	<0.1%	0		0		0	
Colon and rectum	1,002	0.9%	2	0.4%	0		3	2.1%
Lung and bronchus	9	<0.1%	0		0		0	
Prostate (males only)	81	0.2%	1	0.3%	0		0	
Breast (females only)	1,636	2.0%	2	1.0%	1	1.4%	0	
Corpus uteri (females only)	16	<0.1%	0		0		0	

OAB = overactive bladder.
Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.
[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Urinary Bladder (N = 534)		Kidney and Renal Pelvis (N = 125)		Non-Hodgkin Lymphoma (N = 144)	
	n	(%)	n	(%)	n	(%)	n	(%)
History of alcohol use								
Non-drinker	15,793	13.6%	57	10.7%	26	20.8%	19	13.2%
Low-moderate intake (1-6 units/wk)	60,295	52.1%	284	53.2%	51	40.8%	71	49.3%
Heavy or very heavy intake (7+ units/wk)	21,136	18.3%	119	22.3%	25	20.0%	32	22.2%
Drinker - unknown quantity	6,900	6.0%	19	3.6%	10	8.0%	5	3.5%
Unknown	11,671	10.1%	55	10.3%	13	10.4%	17	11.8%
Alcoholism or alcohol-related diseases	3,401	2.9%	15	2.8%	2	1.6%	5	3.5%
Bilateral mastectomy (females only)	20	<0.1%	0		0		0	
Health services utilization [mean (SD)]								
Outpatient visits (in year before cohort entry)	10.7	9.39	11.8	8.83	12.1	9.76	12.8	9.29
Hospitalizations (in year before cohort entry)	0.5	1.28	0.7	1.26	0.6	1.22	0.6	1.05
Sigmoidoscopies/ colonoscopies (in year before cohort entry)	0.0	0.09	0.0	0.13	0.0	0.09	0.0	0.19
Mammograms (females only, in year before cohort entry)	0.0	0.13	0.0	0.07	0.0	0.24	0.0	0.11
Number of prescriptions for study drugs (during follow-up)	12.6	22.65	7.4	13.54	7.9	11.47	11.3	19.01
Number of different OAB drugs received (during follow-up)	1.4	0.68	1.4	0.64	1.3	0.57	1.3	0.63
Duration of enrollment prior to cohort entry (years)	9.3	5.46	9.5	5.18	9.0	4.85	9.2	5.53

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Urinary Bladder (N = 534)		Kidney and Renal Pelvis (N = 125)		Non-Hodgkin Lymphoma (N = 144)	
	n	(%)	n	(%)	n	(%)	n	(%)
Duration of follow-up (years)	3.4	2.47	1.6	1.77	2.6	2.04	2.6	2.16
Previous exposure to study drug in the year before cohort entry								
Oxybutynin	2,189	1.9%	10	1.9%	10	8.0%	1	0.7%
Tolterodine	2,664	2.3%	15	2.8%	3	2.4%	3	2.1%
Darifenacin	10	<0.1%	0		0		0	
Solifenacin	378	0.3%	0		0		0	
Trospium	431	0.4%	2	0.4%	0		0	
Fesoterodine	33	<0.1%	0		0		0	
Previous exposure to study drug in the 5 years before cohort entry								
Oxybutynin	6,062	5.2%	27	5.1%	16	12.8%	13	9.0%
Tolterodine	7,256	6.3%	35	6.6%	10	8.0%	15	10.4%
Darifenacin	15	<0.1%	0		0		0	
Solifenacin	797	0.7%	0		1	0.8%	0	
Trospium	1,207	1.0%	11	2.1%	1	0.8%	4	2.8%
Fesoterodine	57	<0.1%	0		0		0	
Previous exposure to study drug before cohort entry								
Oxybutynin	11,634	10.0%	48	9.0%	24	19.2%	20	13.9%
Tolterodine	10,009	8.6%	50	9.4%	12	9.6%	16	11.1%
Darifenacin	15	<0.1%	0		0		0	
Solifenacin	813	0.7%	0		1	0.8%	0	
Trospium	1,477	1.3%	11	2.1%	2	1.6%	5	3.5%
Fesoterodine	57	<0.1%	0		0		0	

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N1. Characteristics of Subjects by Any Cancer Event and by Specific Cancer Event Type at Cohort Entry[a]

	Patients Without Cancer Endpoint (N = 115,795)		Urinary Bladder (N = 534)		Kidney and Renal Pelvis (N = 125)		Non-Hodgkin Lymphoma (N = 144)	
	n	(%)	n	(%)	n	(%)	n	(%)
Exposure to radiation	11	<0.1%	0		0		0	
Increased cardiovascular risk	49,971	43.2%	320	59.9%	81	64.8%	84	58.3%
Hormone replacement therapy (females only)	29,660	36.4%	77	36.8%	28	38.9%	36	44.4%
Tamoxifen	253	0.2%	1	0.2%	0		0	
Letrozole	15	<0.1%	0		0		0	
Thyroid hormone replacement	11,915	10.3%	40	7.5%	12	9.6%	16	11.1%
Digoxin	3,370	2.9%	26	4.9%	4	3.2%	10	6.9%
Nitrates and other anti-anginal drugs	8,751	7.6%	76	14.2%	14	11.2%	22	15.3%
Lipid-lowering drugs	37,066	32.0%	239	44.8%	57	45.6%	54	37.5%
Non-aspirin NSAIDs	85,956	74.2%	377	70.6%	97	77.6%	102	70.8%
Low-dose aspirin and other antiplatelets	36,387	31.4%	258	48.3%	53	42.4%	63	43.8%
Immunosuppressive agents	1,312	1.1%	9	1.7%	2	1.6%	0	
Antiarrhythmic drugs	3,076	2.7%	20	3.7%	3	2.4%	13	9.0%
Thrombolytic therapy	0		0		0		0	
Warfarin	6,486	5.6%	53	9.9%	10	8.0%	13	9.0%

OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Unless otherwise specified.

Table N3.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	1,397	50,816	161,852	8.63	(8.18, 9.10)	8.56	(8.11, 9.02)
Oxybutynin	538	20,122	59,441	9.05	(8.30, 9.85)	8.78	(8.05, 9.55)
Tolterodine	628	19,296	73,429	8.55	(7.90, 9.25)	8.28	(7.65, 8.96)
Darifenacin	12	647	1,699	7.06	(3.65, 12.34)	7.18	(3.64, 12.64)
Solifenacin	415	20,848	50,964	8.14	(7.38, 8.97)	8.39	(7.60, 9.25)
Trospium	343	10,967	40,211	8.53	(7.65, 9.48)	8.24	(7.39, 9.17)
Fesoterodine	79	5,892	9,896	7.98	(6.32, 9.95)	8.60	(6.78, 10.75)
Male, ever treated with							
Any OAB drug	628	15,151	45,706	13.74	(12.69, 14.86)	13.61	(12.57, 14.72)
Oxybutynin	252	6,037	17,020	14.81	(13.03, 16.75)	14.68	(12.92, 16.61)
Tolterodine	263	5,670	20,505	12.83	(11.32, 14.47)	12.34	(10.89, 13.93)
Darifenacin	6	154	371	16.18	(5.94, 35.21)	14.33	(5.13, 31.43)
Solifenacin	160	5,305	12,052	13.28	(11.30, 15.50)	13.07	(11.12, 15.26)
Trospium	152	3,152	10,574	14.37	(12.18, 16.85)	13.53	(11.46, 15.87)
Fesoterodine	36	1,496	2,304	15.62	(10.94, 21.63)	15.19	(10.63, 21.05)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	769	35,665	116,146	6.62	(6.16, 7.11)	6.55	(6.10, 7.03)
Oxybutynin	286	14,085	42,421	6.74	(5.98, 7.57)	6.44	(5.71, 7.23)
Tolterodine	365	13,626	52,924	6.90	(6.21, 7.64)	6.67	(6.01, 7.40)
Darifenacin	6	493	1,328	4.52	(1.66, 9.84)	4.34	(1.58, 9.47)
Solifenacin	255	15,543	38,912	6.55	(5.77, 7.41)	6.54	(5.76, 7.40)
Trospium	191	7,815	29,637	6.44	(5.56, 7.43)	6.15	(5.30, 7.09)
Fesoterodine	43	4,396	7,592	5.66	(4.10, 7.63)	5.99	(4.29, 8.11)
Overall, aged < 65 years ever treated with							
Any OAB drug	326	25,571	77,376	4.21	(3.77, 4.70)	4.22	(3.77, 4.70)
Oxybutynin	111	9,620	27,103	4.10	(3.37, 4.93)	4.11	(3.38, 4.94)
Tolterodine	150	9,264	33,818	4.44	(3.75, 5.20)	4.25	(3.60, 4.99)
Darifenacin	4	312	761	5.26	(1.43, 13.47)	5.04	(1.23, 13.21)
Solifenacin	106	10,584	24,817	4.27	(3.50, 5.17)	4.37	(3.57, 5.30)
Trospium	77	5,052	18,052	4.27	(3.37, 5.33)	4.10	(3.23, 5.13)
Fesoterodine	25	3,143	5,114	4.89	(3.16, 7.22)	5.06	(3.25, 7.51)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	110	6,563	18,939	5.81	(4.77, 7.00)	5.89	(4.84, 7.09)
Oxybutynin	40	2,616	7,112	5.62	(4.02, 7.66)	5.90	(4.22, 8.04)
Tolterodine	41	2,336	8,150	5.03	(3.61, 6.82)	4.80	(3.44, 6.51)
Darifenacin	1	60	135	7.43	(0.19, 41.40)	7.54	(0.19, 41.99)
Solifenacin	35	2,255	4,945	7.08	(4.93, 9.84)	6.95	(4.84, 9.67)
Trospium	26	1,185	3,875	6.71	(4.38, 9.83)	6.50	(4.25, 9.53)
Fesoterodine	8	643	956	8.37	(3.61, 16.48)	8.14	(3.51, 16.03)
Female, aged < 65 years ever treated with							
Any OAB drug	216	19,008	58,437	3.70	(3.22, 4.22)	3.67	(3.20, 4.20)
Oxybutynin	71	7,004	19,990	3.55	(2.77, 4.48)	3.52	(2.75, 4.44)
Tolterodine	109	6,928	25,668	4.25	(3.49, 5.12)	4.08	(3.35, 4.92)
Darifenacin	3	252	626	4.79	(0.99, 14.01)	4.23	(0.86, 12.37)
Solifenacin	71	8,329	19,872	3.57	(2.79, 4.51)	3.53	(2.75, 4.45)
Trospium	51	3,867	14,176	3.60	(2.68, 4.73)	3.31	(2.46, 4.36)
Fesoterodine	17	2,500	4,157	4.09	(2.38, 6.55)	4.06	(2.36, 6.50)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	1,071	28,924	84,476	12.68	(11.93, 13.46)	12.69	(11.94, 13.47)
Oxybutynin	427	11,781	32,339	13.20	(11.98, 14.52)	13.22	(11.99, 14.54)
Tolterodine	478	11,769	39,611	12.07	(11.01, 13.20)	12.12	(11.05, 13.25)
Darifenacin	8	387	938	8.53	(3.68, 16.80)	9.21	(3.93, 18.22)
Solifenacin	309	11,420	26,147	11.82	(10.54, 13.21)	12.22	(10.89, 13.68)
Trospium	266	6,856	22,159	12.00	(10.60, 13.54)	12.19	(10.76, 13.74)
Fesoterodine	54	2,999	4,783	11.29	(8.48, 14.73)	11.97	(8.95, 15.67)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	518	9,734	26,767	19.35	(17.72, 21.09)	19.30	(17.67, 21.03)
Oxybutynin	212	3,822	9,907	21.40	(18.61, 24.48)	21.14	(18.38, 24.20)
Tolterodine	222	3,860	12,355	17.97	(15.68, 20.49)	17.90	(15.62, 20.41)
Darifenacin	5	106	236	21.15	(6.87, 49.37)	19.34	(6.23, 45.22)
Solifenacin	125	3,359	7,107	17.59	(14.64, 20.96)	17.57	(14.62, 20.93)
Trospium	126	2,230	6,699	18.81	(15.67, 22.39)	18.71	(15.58, 22.28)
Fesoterodine	28	919	1,348	20.77	(13.80, 30.02)	20.39	(13.53, 29.50)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	553	19,190	57,709	9.58	(8.80, 10.42)	9.59	(8.81, 10.42)
Oxybutynin	215	7,959	22,431	9.58	(8.35, 10.96)	9.51	(8.28, 10.87)
Tolterodine	256	7,909	27,256	9.39	(8.28, 10.62)	9.41	(8.29, 10.64)
Darifenacin	3	281	702	4.28	(0.88, 12.49)	4.46	(0.90, 13.09)
Solifenacin	184	8,061	19,040	9.66	(8.32, 11.17)	9.72	(8.36, 11.24)
Trospium	140	4,626	15,460	9.06	(7.62, 10.69)	9.13	(7.68, 10.78)
Fesoterodine	26	2,080	3,435	7.57	(4.94, 11.09)	8.02	(5.17, 11.85)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	1,441	50,816	161,881	8.90	(8.45, 9.37)	8.82	(8.37, 9.29)
Oxybutynin	553	20,122	59,455	9.30	(8.54, 10.11)	9.01	(8.27, 9.79)
Tolterodine	649	19,296	73,443	8.84	(8.17, 9.54)	8.56	(7.91, 9.24)
Darifenacin	12	647	1,699	7.06	(3.65, 12.34)	7.17	(3.64, 12.64)
Solifenacin	430	20,848	50,963	8.44	(7.66, 9.27)	8.70	(7.89, 9.57)
Trospium	354	10,967	40,225	8.80	(7.91, 9.77)	8.50	(7.63, 9.43)
Fesoterodine	81	5,892	9,896	8.18	(6.50, 10.17)	8.81	(6.97, 10.99)
Male, ever treated with							
Any OAB drug	654	15,151	45,717	14.31	(13.23, 15.45)	14.16	(13.09, 15.28)
Oxybutynin	260	6,037	17,022	15.27	(13.47, 17.25)	15.11	(13.33, 17.07)
Tolterodine	277	5,670	20,511	13.50	(11.96, 15.19)	12.99	(11.50, 14.61)
Darifenacin	6	154	371	16.17	(5.94, 35.20)	14.33	(5.13, 31.42)
Solifenacin	167	5,305	12,050	13.86	(11.84, 16.13)	13.64	(11.65, 15.87)
Trospium	156	3,152	10,581	14.74	(12.52, 17.25)	13.87	(11.77, 16.23)
Fesoterodine	37	1,496	2,304	16.06	(11.30, 22.13)	15.63	(10.99, 21.56)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	787	35,665	116,164	6.77	(6.31, 7.27)	6.71	(6.25, 7.19)
Oxybutynin	293	14,085	42,433	6.91	(6.14, 7.74)	6.59	(5.85, 7.39)
Tolterodine	372	13,626	52,931	7.03	(6.33, 7.78)	6.80	(6.13, 7.53)
Darifenacin	6	493	1,328	4.52	(1.66, 9.84)	4.34	(1.58, 9.47)
Solifenacin	263	15,543	38,913	6.76	(5.97, 7.63)	6.74	(5.95, 7.61)
Trospium	198	7,815	29,644	6.68	(5.78, 7.68)	6.37	(5.51, 7.32)
Fesoterodine	44	4,396	7,592	5.80	(4.21, 7.78)	6.12	(4.40, 8.26)
Overall, aged < 65 years ever treated with							
Any OAB drug	333	25,571	77,386	4.30	(3.85, 4.79)	4.31	(3.86, 4.79)
Oxybutynin	112	9,620	27,112	4.13	(3.40, 4.97)	4.14	(3.41, 4.98)
Tolterodine	155	9,264	33,821	4.58	(3.89, 5.36)	4.39	(3.73, 5.14)
Darifenacin	4	312	761	5.26	(1.43, 13.47)	5.04	(1.23, 13.21)
Solifenacin	110	10,584	24,817	4.43	(3.64, 5.34)	4.52	(3.71, 5.46)
Trospium	81	5,052	18,054	4.49	(3.56, 5.58)	4.29	(3.40, 5.35)
Fesoterodine	26	3,143	5,114	5.08	(3.32, 7.45)	5.25	(3.41, 7.73)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	109	6,563	18,942	5.75	(4.72, 6.94)	5.83	(4.79, 7.03)
Oxybutynin	39	2,616	7,115	5.48	(3.90, 7.49)	5.75	(4.09, 7.86)
Tolterodine	41	2,336	8,150	5.03	(3.61, 6.82)	4.80	(3.44, 6.51)
Darifenacin	1	60	135	7.43	(0.19, 41.40)	7.54	(0.19, 41.99)
Solifenacin	35	2,255	4,945	7.08	(4.93, 9.84)	6.95	(4.84, 9.67)
Trospium	26	1,185	3,875	6.71	(4.38, 9.83)	6.50	(4.25, 9.53)
Fesoterodine	8	643	956	8.37	(3.61, 16.48)	8.14	(3.51, 16.03)
Female, aged < 65 years ever treated with							
Any OAB drug	224	19,008	58,445	3.83	(3.35, 4.37)	3.81	(3.32, 4.34)
Oxybutynin	73	7,004	19,997	3.65	(2.86, 4.59)	3.61	(2.83, 4.54)
Tolterodine	114	6,928	25,671	4.44	(3.66, 5.33)	4.26	(3.51, 5.12)
Darifenacin	3	252	626	4.79	(0.99, 14.01)	4.23	(0.86, 12.37)
Solifenacin	75	8,329	19,872	3.77	(2.97, 4.73)	3.73	(2.93, 4.67)
Trospium	55	3,867	14,179	3.88	(2.92, 5.05)	3.57	(2.69, 4.65)
Fesoterodine	18	2,500	4,157	4.33	(2.57, 6.84)	4.31	(2.55, 6.81)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	1,108	28,925	84,495	13.11	(12.35, 13.91)	13.12	(12.36, 13.91)
Oxybutynin	441	11,782	32,343	13.64	(12.39, 14.97)	13.65	(12.40, 14.98)
Tolterodine	494	11,769	39,621	12.47	(11.39, 13.62)	12.52	(11.44, 13.68)
Darifenacin	8	387	938	8.53	(3.68, 16.80)	9.20	(3.93, 18.21)
Solifenacin	320	11,420	26,146	12.24	(10.93, 13.66)	12.68	(11.32, 14.16)
Trospium	273	6,856	22,170	12.31	(10.90, 13.86)	12.50	(11.06, 14.08)
Fesoterodine	55	2,999	4,783	11.50	(8.66, 14.97)	12.21	(9.16, 15.94)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	545	9,735	26,775	20.35	(18.68, 22.14)	20.29	(18.62, 22.06)
Oxybutynin	221	3,823	9,907	22.31	(19.46, 25.45)	22.01	(19.19, 25.11)
Tolterodine	236	3,860	12,361	19.09	(16.73, 21.69)	19.02	(16.67, 21.61)
Darifenacin	5	106	236	21.15	(6.87, 49.35)	19.33	(6.23, 45.20)
Solifenacin	132	3,359	7,105	18.58	(15.54, 22.03)	18.56	(15.53, 22.01)
Trospium	130	2,230	6,705	19.39	(16.20, 23.02)	19.29	(16.12, 22.91)
Fesoterodine	29	919	1,348	21.51	(14.41, 30.89)	21.15	(14.14, 30.40)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	563	19,190	57,719	9.75	(8.96, 10.59)	9.76	(8.97, 10.60)
Oxybutynin	220	7,959	22,435	9.81	(8.55, 11.19)	9.73	(8.48, 11.11)
Tolterodine	258	7,909	27,260	9.46	(8.34, 10.69)	9.48	(8.36, 10.71)
Darifenacin	3	281	702	4.28	(0.88, 12.49)	4.46	(0.90, 13.09)
Solifenacin	188	8,061	19,041	9.87	(8.51, 11.39)	9.93	(8.56, 11.46)
Trospium	143	4,626	15,465	9.25	(7.79, 10.89)	9.32	(7.85, 10.98)
Fesoterodine	26	2,080	3,435	7.57	(4.94, 11.09)	8.02	(5.17, 11.85)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	4,129	119,859	399,365	10.34	(10.03, 10.66)	10.34	(10.03, 10.66)
Oxybutynin	1,739	50,446	155,883	11.16	(10.64, 11.69)	10.90	(10.39, 11.43)
Tolterodine	1,935	46,649	191,057	10.13	(9.68, 10.59)	9.92	(9.49, 10.38)
Darifenacin	17	648	1,696	10.02	(5.84, 16.05)	10.42	(5.97, 16.83)
Solifenacin	1,233	48,759	126,880	9.72	(9.18, 10.28)	10.24	(9.67, 10.83)
Trospium	423	11,097	40,636	10.41	(9.44, 11.45)	10.04	(9.10, 11.05)
Fesoterodine	91	5,889	9,881	9.21	(7.42, 11.31)	10.00	(8.01, 12.31)
Male, ever treated with							
Any OAB drug	1,925	36,157	113,294	16.99	(16.24, 17.77)	16.99	(16.24, 17.77)
Oxybutynin	832	15,599	45,873	18.14	(16.93, 19.41)	18.25	(17.03, 19.53)
Tolterodine	850	14,149	54,167	15.69	(14.65, 16.78)	15.39	(14.37, 16.46)
Darifenacin	8	155	372	21.50	(9.28, 42.36)	19.82	(8.33, 39.42)
Solifenacin	510	12,512	29,851	17.09	(15.63, 18.63)	16.89	(15.45, 18.42)
Trospium	181	3,179	10,647	17.00	(14.61, 19.67)	15.97	(13.72, 18.49)
Fesoterodine	41	1,494	2,298	17.84	(12.81, 24.21)	17.46	(12.51, 23.70)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	2,204	83,702	286,071	7.70	(7.39, 8.03)	7.70	(7.39, 8.03)
Oxybutynin	907	34,847	110,011	8.24	(7.72, 8.80)	7.99	(7.48, 8.53)
Tolterodine	1,085	32,500	136,889	7.93	(7.46, 8.41)	7.76	(7.30, 8.24)
Darifenacin	9	493	1,324	6.80	(3.11, 12.91)	6.70	(3.04, 12.74)
Solifenacin	723	36,247	97,029	7.45	(6.92, 8.01)	7.61	(7.06, 8.19)
Trospium	242	7,918	29,989	8.07	(7.08, 9.15)	7.69	(6.75, 8.73)
Fesoterodine	50	4,395	7,583	6.59	(4.89, 8.69)	7.04	(5.18, 9.34)
Overall, aged < 65 years ever treated with							
Any OAB drug	930	61,567	194,816	4.77	(4.47, 5.09)	4.77	(4.47, 5.09)
Oxybutynin	357	24,666	72,998	4.89	(4.40, 5.43)	4.91	(4.42, 5.45)
Tolterodine	430	23,128	90,532	4.75	(4.31, 5.22)	4.59	(4.16, 5.04)
Darifenacin	5	312	758	6.60	(2.14, 15.39)	7.03	(2.07, 16.83)
Solifenacin	303	25,490	63,516	4.77	(4.25, 5.34)	4.90	(4.36, 5.49)
Trospium	93	5,120	18,262	5.09	(4.11, 6.24)	4.84	(3.90, 5.94)
Fesoterodine	26	3,142	5,112	5.09	(3.32, 7.45)	5.26	(3.41, 7.74)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	311	16,149	48,041	6.47	(5.77, 7.23)	6.47	(5.77, 7.23)
Oxybutynin	125	6,953	19,678	6.35	(5.29, 7.57)	6.61	(5.50, 7.88)
Tolterodine	134	6,136	22,321	6.00	(5.03, 7.11)	5.74	(4.81, 6.80)
Darifenacin	2	60	132	15.10	(1.83, 54.56)	15.60	(1.89, 56.35)
Solifenacin	99	5,426	12,353	8.01	(6.51, 9.76)	7.77	(6.31, 9.46)
Trospium	29	1,201	3,909	7.42	(4.97, 10.66)	7.17	(4.80, 10.30)
Fesoterodine	8	642	954	8.39	(3.62, 16.53)	8.18	(3.53, 16.11)
Female, aged < 65 years ever treated with							
Any OAB drug	619	45,418	146,775	4.22	(3.89, 4.56)	4.22	(3.89, 4.56)
Oxybutynin	232	17,713	53,321	4.35	(3.81, 4.95)	4.36	(3.82, 4.96)
Tolterodine	296	16,992	68,211	4.34	(3.86, 4.86)	4.21	(3.75, 4.72)
Darifenacin	3	252	626	4.80	(0.99, 14.01)	4.23	(0.86, 12.38)
Solifenacin	204	20,064	51,163	3.99	(3.46, 4.57)	3.97	(3.44, 4.55)
Trospium	64	3,919	14,354	4.46	(3.43, 5.69)	4.08	(3.14, 5.22)
Fesoterodine	18	2,500	4,158	4.33	(2.57, 6.84)	4.30	(2.55, 6.81)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	3,199	67,598	204,549	15.64	(15.10, 16.19)	15.64	(15.10, 16.19)
Oxybutynin	1,382	29,310	82,885	16.67	(15.81, 17.58)	16.60	(15.74, 17.50)
Tolterodine	1,505	28,063	100,525	14.97	(14.22, 15.75)	15.00	(14.26, 15.78)
Darifenacin	12	387	938	12.80	(6.61, 22.35)	13.64	(7.01, 23.89)
Solifenacin	930	26,291	63,364	14.68	(13.75, 15.65)	15.32	(14.35, 16.35)
Trospium	330	6,938	22,374	14.75	(13.20, 16.43)	14.99	(13.41, 16.71)
Fesoterodine	65	2,997	4,768	13.63	(10.52, 17.37)	14.51	(11.15, 18.55)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	1,614	22,992	65,253	24.73	(23.54, 25.97)	24.73	(23.54, 25.97)
Oxybutynin	707	9,805	26,195	26.99	(25.04, 29.06)	26.82	(24.88, 28.87)
Tolterodine	716	9,459	31,846	22.48	(20.87, 24.19)	22.49	(20.87, 24.20)
Darifenacin	6	106	240	25.03	(9.18, 54.47)	22.92	(8.39, 49.94)
Solifenacin	411	7,891	17,498	23.49	(21.27, 25.87)	23.60	(21.37, 26.00)
Trospium	152	2,248	6,738	22.56	(19.11, 26.44)	22.46	(19.02, 26.33)
Fesoterodine	33	918	1,344	24.55	(16.90, 34.48)	24.29	(16.69, 34.15)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	1,585	44,606	139,296	11.38	(10.83, 11.95)	11.38	(10.83, 11.95)
Oxybutynin	675	19,505	56,690	11.91	(11.03, 12.84)	11.82	(10.94, 12.75)
Tolterodine	789	18,604	68,679	11.49	(10.70, 12.32)	11.50	(10.71, 12.33)
Darifenacin	6	281	698	8.59	(3.15, 18.71)	9.29	(3.37, 20.30)
Solifenacin	519	18,400	45,867	11.32	(10.36, 12.33)	11.45	(10.48, 12.48)
Trospium	178	4,690	15,636	11.38	(9.77, 13.18)	11.50	(9.87, 13.32)
Fesoterodine	32	2,079	3,425	9.34	(6.39, 13.19)	9.93	(6.71, 14.12)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	4,117	119,859	399,365	10.31	(10.00, 10.63)	10.31	(10.00, 10.63)
Oxybutynin	1,736	50,446	155,883	11.14	(10.62, 11.67)	10.88	(10.38, 11.41)
Tolterodine	1,930	46,649	191,057	10.10	(9.66, 10.56)	9.90	(9.46, 10.35)
Darifenacin	17	648	1,696	10.02	(5.84, 16.05)	10.42	(5.97, 16.83)
Solifenacin	1,226	48,759	126,880	9.66	(9.13, 10.22)	10.18	(9.62, 10.77)
Trospium	421	11,097	40,636	10.36	(9.39, 11.40)	9.99	(9.06, 11.00)
Fesoterodine	89	5,889	9,881	9.01	(7.23, 11.08)	9.78	(7.82, 12.07)
Male, ever treated with							
Any OAB drug	1,917	36,157	113,294	16.92	(16.17, 17.70)	16.92	(16.17, 17.70)
Oxybutynin	831	15,599	45,873	18.12	(16.90, 19.39)	18.23	(17.01, 19.51)
Tolterodine	847	14,149	54,167	15.64	(14.60, 16.73)	15.33	(14.32, 16.40)
Darifenacin	8	155	372	21.50	(9.28, 42.36)	19.82	(8.33, 39.42)
Solifenacin	506	12,512	29,851	16.95	(15.51, 18.49)	16.76	(15.33, 18.29)
Trospium	181	3,179	10,647	17.00	(14.61, 19.67)	15.97	(13.72, 18.49)
Fesoterodine	40	1,494	2,298	17.41	(12.44, 23.71)	17.02	(12.14, 23.19)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	2,200	83,702	286,071	7.69	(7.37, 8.02)	7.69	(7.37, 8.02)
Oxybutynin	905	34,847	110,011	8.23	(7.70, 8.78)	7.97	(7.46, 8.51)
Tolterodine	1,083	32,500	136,889	7.91	(7.45, 8.40)	7.75	(7.29, 8.22)
Darifenacin	9	493	1,324	6.80	(3.11, 12.91)	6.70	(3.04, 12.74)
Solifenacin	720	36,247	97,029	7.42	(6.89, 7.98)	7.58	(7.03, 8.15)
Trospium	240	7,918	29,989	8.00	(7.02, 9.08)	7.62	(6.69, 8.66)
Fesoterodine	49	4,395	7,583	6.46	(4.78, 8.54)	6.91	(5.07, 9.20)
Overall, aged < 65 years ever treated with							
Any OAB drug	928	61,567	194,816	4.76	(4.46, 5.08)	4.76	(4.46, 5.08)
Oxybutynin	356	24,666	72,998	4.88	(4.38, 5.41)	4.90	(4.40, 5.44)
Tolterodine	428	23,128	90,532	4.73	(4.29, 5.20)	4.57	(4.14, 5.02)
Darifenacin	5	312	758	6.60	(2.14, 15.39)	7.03	(2.07, 16.83)
Solifenacin	301	25,490	63,516	4.74	(4.22, 5.31)	4.88	(4.33, 5.46)
Trospium	91	5,120	18,262	4.98	(4.01, 6.12)	4.74	(3.81, 5.83)
Fesoterodine	25	3,142	5,112	4.89	(3.16, 7.22)	5.07	(3.26, 7.52)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	311	16,149	48,041	6.47	(5.77, 7.23)	6.47	(5.77, 7.23)
Oxybutynin	125	6,953	19,678	6.35	(5.29, 7.57)	6.61	(5.50, 7.88)
Tolterodine	134	6,136	22,321	6.00	(5.03, 7.11)	5.74	(4.81, 6.80)
Darifenacin	2	60	132	15.10	(1.83, 54.56)	15.60	(1.89, 56.35)
Solifenacin	99	5,426	12,353	8.01	(6.51, 9.76)	7.77	(6.31, 9.46)
Trospium	29	1,201	3,909	7.42	(4.97, 10.66)	7.17	(4.80, 10.30)
Fesoterodine	8	642	954	8.39	(3.62, 16.53)	8.18	(3.53, 16.11)
Female, aged < 65 years ever treated with							
Any OAB drug	617	45,418	146,775	4.20	(3.88, 4.55)	4.20	(3.88, 4.55)
Oxybutynin	231	17,713	53,321	4.33	(3.79, 4.93)	4.34	(3.80, 4.94)
Tolterodine	294	16,992	68,211	4.31	(3.83, 4.83)	4.18	(3.72, 4.69)
Darifenacin	3	252	626	4.80	(0.99, 14.01)	4.23	(0.86, 12.38)
Solifenacin	202	20,064	51,163	3.95	(3.42, 4.53)	3.93	(3.40, 4.51)
Trospium	62	3,919	14,354	4.32	(3.31, 5.54)	3.95	(3.02, 5.07)
Fesoterodine	17	2,500	4,158	4.09	(2.38, 6.55)	4.06	(2.36, 6.50)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	3,189	67,598	204,549	15.59	(15.05, 16.14)	15.59	(15.05, 16.14)
Oxybutynin	1,380	29,310	82,885	16.65	(15.78, 17.55)	16.58	(15.72, 17.48)
Tolterodine	1,502	28,063	100,525	14.94	(14.20, 15.72)	14.97	(14.23, 15.75)
Darifenacin	12	387	938	12.80	(6.61, 22.35)	13.64	(7.01, 23.89)
Solifenacin	925	26,291	63,364	14.60	(13.67, 15.57)	15.24	(14.26, 16.26)
Trospium	330	6,938	22,374	14.75	(13.20, 16.43)	14.99	(13.41, 16.71)
Fesoterodine	64	2,997	4,768	13.42	(10.34, 17.14)	14.26	(10.93, 18.27)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	1,606	22,992	65,253	24.61	(23.42, 25.85)	24.61	(23.42, 25.85)
Oxybutynin	706	9,805	26,195	26.95	(25.00, 29.02)	26.78	(24.84, 28.83)
Tolterodine	713	9,459	31,846	22.39	(20.78, 24.09)	22.39	(20.78, 24.10)
Darifenacin	6	106	240	25.03	(9.18, 54.47)	22.92	(8.39, 49.94)
Solifenacin	407	7,891	17,498	23.26	(21.06, 25.63)	23.38	(21.16, 25.77)
Trospium	152	2,248	6,738	22.56	(19.11, 26.44)	22.46	(19.02, 26.33)
Fesoterodine	32	918	1,344	23.81	(16.29, 33.61)	23.52	(16.06, 33.25)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	1,583	44,606	139,296	11.36	(10.81, 11.94)	11.36	(10.81, 11.94)
Oxybutynin	674	19,505	56,690	11.89	(11.01, 12.82)	11.80	(10.93, 12.73)
Tolterodine	789	18,604	68,679	11.49	(10.70, 12.32)	11.50	(10.71, 12.33)
Darifenacin	6	281	698	8.59	(3.15, 18.71)	9.29	(3.37, 20.30)
Solifenacin	518	18,400	45,867	11.29	(10.34, 12.31)	11.42	(10.46, 12.46)
Trospium	178	4,690	15,636	11.38	(9.77, 13.18)	11.50	(9.87, 13.32)
Fesoterodine	32	2,079	3,425	9.34	(6.39, 13.19)	9.93	(6.71, 14.12)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	545	119,859	399,365	1.36	(1.25, 1.48)	1.36	(1.25, 1.48)
Oxybutynin	236	50,446	155,883	1.51	(1.33, 1.72)	1.46	(1.28, 1.66)
Tolterodine	262	46,649	191,057	1.37	(1.21, 1.55)	1.34	(1.18, 1.51)
Darifenacin	3	648	1,696	1.77	(0.36, 5.17)	1.81	(0.37, 5.28)
Solifenacin	153	48,759	126,880	1.21	(1.02, 1.41)	1.29	(1.09, 1.51)
Trospium	66	11,097	40,636	1.62	(1.26, 2.07)	1.55	(1.20, 1.97)
Fesoterodine	8	5,889	9,881	0.81	(0.35, 1.60)	0.92	(0.39, 1.82)
Male, ever treated with							
Any OAB drug	233	36,157	113,294	2.06	(1.80, 2.34)	2.06	(1.80, 2.34)
Oxybutynin	90	15,599	45,873	1.96	(1.58, 2.41)	1.98	(1.59, 2.43)
Tolterodine	104	14,149	54,167	1.92	(1.57, 2.33)	1.88	(1.54, 2.28)
Darifenacin	1	155	372	2.69	(0.07, 14.97)	2.14	(0.05, 11.93)
Solifenacin	60	12,512	29,851	2.01	(1.53, 2.59)	2.00	(1.53, 2.58)
Trospium	25	3,179	10,647	2.35	(1.52, 3.47)	2.14	(1.38, 3.16)
Fesoterodine	5	1,494	2,298	2.18	(0.71, 5.08)	2.10	(0.68, 4.90)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	312	83,702	286,071	1.09	(0.97, 1.22)	1.09	(0.97, 1.22)
Oxybutynin	146	34,847	110,011	1.33	(1.12, 1.56)	1.25	(1.06, 1.48)
Tolterodine	158	32,500	136,889	1.15	(0.98, 1.35)	1.13	(0.96, 1.32)
Darifenacin	2	493	1,324	1.51	(0.18, 5.46)	1.68	(0.20, 6.05)
Solifenacin	93	36,247	97,029	0.96	(0.77, 1.17)	1.01	(0.81, 1.24)
Trospium	41	7,918	29,989	1.37	(0.98, 1.85)	1.31	(0.94, 1.78)
Fesoterodine	3	4,395	7,583	0.40	(0.08, 1.16)	0.45	(0.08, 1.35)
Overall, aged < 65 years ever treated with							
Any OAB drug	62	61,567	194,816	0.32	(0.24, 0.41)	0.32	(0.24, 0.41)
Oxybutynin	27	24,666	72,998	0.37	(0.24, 0.54)	0.37	(0.24, 0.54)
Tolterodine	34	23,128	90,532	0.38	(0.26, 0.52)	0.36	(0.25, 0.51)
Darifenacin	0	312	758	0.00	(0.00, 4.87)	0.00	Not Est.
Solifenacin	14	25,490	63,516	0.22	(0.12, 0.37)	0.22	(0.12, 0.38)
Trospium	1	5,120	18,262	0.05	(0.00, 0.31)	0.06	(0.00, 0.34)
Fesoterodine	3	3,142	5,112	0.59	(0.12, 1.72)	0.69	(0.14, 2.04)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	27	16,149	48,041	0.56	(0.37, 0.82)	0.56	(0.37, 0.82)
Oxybutynin	10	6,953	19,678	0.51	(0.24, 0.93)	0.53	(0.25, 0.97)
Tolterodine	15	6,136	22,321	0.67	(0.38, 1.11)	0.64	(0.36, 1.06)
Darifenacin	0	60	132	0.00	(0.00, 27.86)	0.00	Not Est.
Solifenacin	4	5,426	12,353	0.32	(0.09, 0.83)	0.31	(0.09, 0.80)
Trospium	1	1,201	3,909	0.26	(0.01, 1.43)	0.25	(0.01, 1.37)
Fesoterodine	2	642	954	2.10	(0.25, 7.58)	2.05	(0.25, 7.42)
Female, aged < 65 years ever treated with							
Any OAB drug	35	45,418	146,775	0.24	(0.17, 0.33)	0.24	(0.17, 0.33)
Oxybutynin	17	17,713	53,321	0.32	(0.19, 0.51)	0.32	(0.18, 0.51)
Tolterodine	19	16,992	68,211	0.28	(0.17, 0.43)	0.27	(0.16, 0.42)
Darifenacin	0	252	626	0.00	(0.00, 5.90)	0.00	Not Est.
Solifenacin	10	20,064	51,163	0.20	(0.09, 0.36)	0.19	(0.09, 0.36)
Trospium	0	3,919	14,354	0.00	(0.00, 0.26)	0.00	Not Est.
Fesoterodine	1	2,500	4,158	0.24	(0.01, 1.34)	0.25	(0.01, 1.39)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	483	67,598	204,549	2.36	(2.16, 2.58)	2.36	(2.16, 2.58)
Oxybutynin	209	29,310	82,885	2.52	(2.19, 2.89)	2.50	(2.17, 2.86)
Tolterodine	228	28,063	100,525	2.27	(1.98, 2.58)	2.27	(1.99, 2.59)
Darifenacin	3	387	938	3.20	(0.66, 9.35)	3.53	(0.73, 10.32)
Solifenacin	139	26,291	63,364	2.19	(1.84, 2.59)	2.30	(1.93, 2.72)
Trospium	65	6,938	22,374	2.91	(2.24, 3.70)	2.96	(2.29, 3.78)
Fesoterodine	5	2,997	4,768	1.05	(0.34, 2.45)	1.13	(0.36, 2.66)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	206	22,992	65,253	3.16	(2.74, 3.62)	3.16	(2.74, 3.62)
Oxybutynin	80	9,805	26,195	3.05	(2.42, 3.80)	3.04	(2.41, 3.79)
Tolterodine	89	9,459	31,846	2.79	(2.24, 3.44)	2.80	(2.24, 3.44)
Darifenacin	1	106	240	4.17	(0.11, 23.24)	3.72	(0.09, 20.72)
Solifenacin	56	7,891	17,498	3.20	(2.42, 4.16)	3.24	(2.45, 4.21)
Trospium	24	2,248	6,738	3.56	(2.28, 5.30)	3.54	(2.27, 5.27)
Fesoterodine	3	918	1,344	2.23	(0.46, 6.52)	2.13	(0.44, 6.24)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	277	44,606	139,296	1.99	(1.76, 2.24)	1.99	(1.76, 2.24)
Oxybutynin	129	19,505	56,690	2.28	(1.90, 2.70)	2.24	(1.87, 2.66)
Tolterodine	139	18,604	68,679	2.02	(1.70, 2.39)	2.03	(1.71, 2.39)
Darifenacin	2	281	698	2.86	(0.35, 10.35)	3.44	(0.42, 12.43)
Solifenacin	83	18,400	45,867	1.81	(1.44, 2.24)	1.86	(1.48, 2.31)
Trospium	41	4,690	15,636	2.62	(1.88, 3.56)	2.69	(1.93, 3.66)
Fesoterodine	2	2,079	3,425	0.58	(0.07, 2.11)	0.66	(0.06, 2.46)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	138	119,859	399,365	0.35	(0.29, 0.41)	0.35	(0.29, 0.41)
Oxybutynin	61	50,446	155,883	0.39	(0.30, 0.50)	0.38	(0.29, 0.49)
Tolterodine	70	46,649	191,057	0.37	(0.29, 0.46)	0.36	(0.28, 0.45)
Darifenacin	0	648	1,696	0.00	(0.00, 2.18)	0.00	Not Est.
Solifenacin	41	48,759	126,880	0.32	(0.23, 0.44)	0.33	(0.24, 0.45)
Trospium	13	11,097	40,636	0.32	(0.17, 0.55)	0.30	(0.16, 0.52)
Fesoterodine	3	5,889	9,881	0.30	(0.06, 0.89)	0.40	(0.08, 1.17)
Male, ever treated with							
Any OAB drug	48	36,157	113,294	0.42	(0.31, 0.56)	0.42	(0.31, 0.56)
Oxybutynin	26	15,599	45,873	0.57	(0.37, 0.83)	0.56	(0.37, 0.83)
Tolterodine	20	14,149	54,167	0.37	(0.23, 0.57)	0.36	(0.22, 0.56)
Darifenacin	0	155	372	0.00	(0.00, 9.91)	0.00	Not Est.
Solifenacin	10	12,512	29,851	0.34	(0.16, 0.62)	0.33	(0.16, 0.60)
Trospium	4	3,179	10,647	0.38	(0.10, 0.96)	0.32	(0.09, 0.83)
Fesoterodine	0	1,494	2,298	0.00	(0.00, 1.61)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	90	83,702	286,071	0.31	(0.25, 0.39)	0.31	(0.25, 0.39)
Oxybutynin	35	34,847	110,011	0.32	(0.22, 0.44)	0.30	(0.21, 0.42)
Tolterodine	50	32,500	136,889	0.37	(0.27, 0.48)	0.36	(0.26, 0.47)
Darifenacin	0	493	1,324	0.00	(0.00, 2.79)	0.00	Not Est.
Solifenacin	31	36,247	97,029	0.32	(0.22, 0.45)	0.33	(0.22, 0.47)
Trospium	9	7,918	29,989	0.30	(0.14, 0.57)	0.29	(0.13, 0.56)
Fesoterodine	3	4,395	7,583	0.40	(0.08, 1.16)	0.56	(0.11, 1.64)
Overall, aged < 65 years ever treated with							
Any OAB drug	20	61,567	194,816	0.10	(0.06, 0.16)	0.10	(0.06, 0.16)
Oxybutynin	10	24,666	72,998	0.14	(0.07, 0.25)	0.14	(0.07, 0.26)
Tolterodine	7	23,128	90,532	0.08	(0.03, 0.16)	0.07	(0.03, 0.15)
Darifenacin	0	312	758	0.00	(0.00, 4.87)	0.00	Not Est.
Solifenacin	7	25,490	63,516	0.11	(0.04, 0.23)	0.11	(0.04, 0.22)
Trospium	2	5,120	18,262	0.11	(0.01, 0.40)	0.11	(0.01, 0.41)
Fesoterodine	0	3,142	5,112	0.00	(0.00, 0.72)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	4	16,149	48,041	0.08	(0.02, 0.21)	0.08	(0.02, 0.21)
Oxybutynin	1	6,953	19,678	0.05	(0.00, 0.28)	0.05	(0.00, 0.30)
Tolterodine	2	6,136	22,321	0.09	(0.01, 0.32)	0.09	(0.01, 0.31)
Darifenacin	0	60	132	0.00	(0.00, 27.86)	0.00	Not Est.
Solifenacin	1	5,426	12,353	0.08	(0.00, 0.45)	0.08	(0.00, 0.43)
Trospium	0	1,201	3,909	0.00	(0.00, 0.94)	0.00	Not Est.
Fesoterodine	0	642	954	0.00	(0.00, 3.87)	0.00	Not Est.
Female, aged < 65 years ever treated with							
Any OAB drug	16	45,418	146,775	0.11	(0.06, 0.18)	0.11	(0.06, 0.18)
Oxybutynin	9	17,713	53,321	0.17	(0.08, 0.32)	0.17	(0.08, 0.32)
Tolterodine	5	16,992	68,211	0.07	(0.02, 0.17)	0.07	(0.02, 0.16)
Darifenacin	0	252	626	0.00	(0.00, 5.90)	0.00	Not Est.
Solifenacin	6	20,064	51,163	0.12	(0.04, 0.26)	0.12	(0.04, 0.25)
Trospium	2	3,919	14,354	0.14	(0.02, 0.50)	0.15	(0.02, 0.54)
Fesoterodine	0	2,500	4,158	0.00	(0.00, 0.89)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	118	67,598	204,549	0.58	(0.48, 0.69)	0.58	(0.48, 0.69)
Oxybutynin	51	29,310	82,885	0.62	(0.46, 0.81)	0.61	(0.45, 0.80)
Tolterodine	63	28,063	100,525	0.63	(0.48, 0.80)	0.63	(0.48, 0.80)
Darifenacin	0	387	938	0.00	(0.00, 3.93)	0.00	Not Est.
Solifenacin	34	26,291	63,364	0.54	(0.37, 0.75)	0.54	(0.37, 0.76)
Trospium	11	6,938	22,374	0.49	(0.25, 0.88)	0.48	(0.24, 0.86)
Fesoterodine	3	2,997	4,768	0.63	(0.13, 1.84)	0.78	(0.16, 2.29)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	44	22,992	65,253	0.67	(0.49, 0.91)	0.67	(0.49, 0.91)
Oxybutynin	25	9,805	26,195	0.95	(0.62, 1.41)	0.94	(0.61, 1.39)
Tolterodine	18	9,459	31,846	0.57	(0.33, 0.89)	0.57	(0.34, 0.89)
Darifenacin	0	106	240	0.00	(0.00, 15.39)	0.00	Not Est.
Solifenacin	9	7,891	17,498	0.51	(0.24, 0.98)	0.51	(0.23, 0.97)
Trospium	4	2,248	6,738	0.59	(0.16, 1.52)	0.56	(0.15, 1.44)
Fesoterodine	0	918	1,344	0.00	(0.00, 2.74)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	74	44,606	139,296	0.53	(0.42, 0.67)	0.53	(0.42, 0.67)
Oxybutynin	26	19,505	56,690	0.46	(0.30, 0.67)	0.45	(0.29, 0.66)
Tolterodine	45	18,604	68,679	0.66	(0.48, 0.88)	0.66	(0.48, 0.88)
Darifenacin	0	281	698	0.00	(0.00, 5.28)	0.00	Not Est.
Solifenacin	25	18,400	45,867	0.55	(0.35, 0.80)	0.55	(0.36, 0.82)
Trospium	7	4,690	15,636	0.45	(0.18, 0.92)	0.45	(0.18, 0.92)
Fesoterodine	3	2,079	3,425	0.88	(0.18, 2.56)	1.14	(0.23, 3.36)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	495	119,859	399,365	1.24	(1.13, 1.35)	1.24	(1.13, 1.35)
Oxybutynin	222	50,446	155,883	1.42	(1.24, 1.62)	1.38	(1.21, 1.58)
Tolterodine	238	46,649	191,057	1.25	(1.09, 1.41)	1.22	(1.07, 1.38)
Darifenacin	2	648	1,696	1.18	(0.14, 4.26)	1.05	(0.12, 3.81)
Solifenacin	141	48,759	126,880	1.11	(0.94, 1.31)	1.15	(0.96, 1.35)
Trospium	53	11,097	40,636	1.30	(0.98, 1.71)	1.25	(0.93, 1.64)
Fesoterodine	7	5,889	9,881	0.71	(0.28, 1.46)	0.81	(0.32, 1.67)
Male, ever treated with							
Any OAB drug	214	36,157	113,294	1.89	(1.64, 2.16)	1.89	(1.64, 2.16)
Oxybutynin	105	15,599	45,873	2.29	(1.87, 2.77)	2.29	(1.87, 2.77)
Tolterodine	98	14,149	54,167	1.81	(1.47, 2.20)	1.77	(1.44, 2.16)
Darifenacin	0	155	372	0.00	(0.00, 9.91)	0.00	Not Est.
Solifenacin	47	12,512	29,851	1.57	(1.16, 2.09)	1.56	(1.15, 2.07)
Trospium	23	3,179	10,647	2.16	(1.37, 3.24)	2.04	(1.29, 3.07)
Fesoterodine	3	1,494	2,298	1.31	(0.27, 3.82)	1.32	(0.27, 3.85)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	281	83,702	286,071	0.98	(0.87, 1.10)	0.98	(0.87, 1.10)
Oxybutynin	117	34,847	110,011	1.06	(0.88, 1.27)	1.02	(0.85, 1.23)
Tolterodine	140	32,500	136,889	1.02	(0.86, 1.21)	1.00	(0.84, 1.17)
Darifenacin	2	493	1,324	1.51	(0.18, 5.46)	1.47	(0.17, 5.32)
Solifenacin	94	36,247	97,029	0.97	(0.78, 1.19)	0.98	(0.79, 1.20)
Trospium	30	7,918	29,989	1.00	(0.67, 1.43)	0.94	(0.63, 1.34)
Fesoterodine	4	4,395	7,583	0.53	(0.14, 1.35)	0.60	(0.15, 1.56)
Overall, aged < 65 years ever treated with							
Any OAB drug	87	61,567	194,816	0.45	(0.36, 0.55)	0.45	(0.36, 0.55)
Oxybutynin	35	24,666	72,998	0.48	(0.33, 0.67)	0.48	(0.34, 0.67)
Tolterodine	35	23,128	90,532	0.39	(0.27, 0.54)	0.37	(0.26, 0.51)
Darifenacin	1	312	758	1.32	(0.03, 7.35)	1.17	(0.03, 6.54)
Solifenacin	26	25,490	63,516	0.41	(0.27, 0.60)	0.40	(0.26, 0.59)
Trospium	15	5,120	18,262	0.82	(0.46, 1.35)	0.78	(0.43, 1.28)
Fesoterodine	1	3,142	5,112	0.20	(0.00, 1.09)	0.19	(0.00, 1.05)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	17	16,149	48,041	0.35	(0.21, 0.57)	0.35	(0.21, 0.57)
Oxybutynin	10	6,953	19,678	0.51	(0.24, 0.93)	0.53	(0.25, 0.97)
Tolterodine	6	6,136	22,321	0.27	(0.10, 0.59)	0.26	(0.09, 0.56)
Darifenacin	0	60	132	0.00	(0.00, 27.86)	0.00	Not Est.
Solifenacin	4	5,426	12,353	0.32	(0.09, 0.83)	0.31	(0.09, 0.80)
Trospium	4	1,201	3,909	1.02	(0.28, 2.62)	0.99	(0.27, 2.54)
Fesoterodine	0	642	954	0.00	(0.00, 3.87)	0.00	Not Est.
Female, aged < 65 years ever treated with							
Any OAB drug	70	45,418	146,775	0.48	(0.37, 0.60)	0.48	(0.37, 0.60)
Oxybutynin	25	17,713	53,321	0.47	(0.30, 0.69)	0.47	(0.30, 0.69)
Tolterodine	29	16,992	68,211	0.43	(0.28, 0.61)	0.41	(0.27, 0.58)
Darifenacin	1	252	626	1.60	(0.04, 8.91)	1.56	(0.04, 8.68)
Solifenacin	22	20,064	51,163	0.43	(0.27, 0.65)	0.43	(0.27, 0.65)
Trospium	11	3,919	14,354	0.77	(0.38, 1.37)	0.71	(0.35, 1.26)
Fesoterodine	1	2,500	4,158	0.24	(0.01, 1.34)	0.25	(0.01, 1.39)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	408	67,598	204,549	1.99	(1.81, 2.20)	1.99	(1.81, 2.20)
Oxybutynin	187	29,310	82,885	2.26	(1.94, 2.60)	2.24	(1.93, 2.59)
Tolterodine	203	28,063	100,525	2.02	(1.75, 2.32)	2.02	(1.75, 2.32)
Darifenacin	1	387	938	1.07	(0.03, 5.94)	0.93	(0.02, 5.21)
Solifenacin	115	26,291	63,364	1.81	(1.50, 2.18)	1.86	(1.53, 2.23)
Trospium	38	6,938	22,374	1.70	(1.20, 2.33)	1.70	(1.20, 2.33)
Fesoterodine	6	2,997	4,768	1.26	(0.46, 2.74)	1.39	(0.50, 3.05)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	197	22,992	65,253	3.02	(2.61, 3.47)	3.02	(2.61, 3.47)
Oxybutynin	95	9,805	26,195	3.63	(2.93, 4.43)	3.58	(2.90, 4.38)
Tolterodine	92	9,459	31,846	2.89	(2.33, 3.54)	2.88	(2.32, 3.54)
Darifenacin	0	106	240	0.00	(0.00, 15.39)	0.00	Not Est.
Solifenacin	43	7,891	17,498	2.46	(1.78, 3.31)	2.48	(1.79, 3.34)
Trospium	19	2,248	6,738	2.82	(1.70, 4.40)	2.81	(1.69, 4.39)
Fesoterodine	3	918	1,344	2.23	(0.46, 6.52)	2.29	(0.47, 6.69)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	211	44,606	139,296	1.51	(1.32, 1.73)	1.51	(1.32, 1.73)
Oxybutynin	92	19,505	56,690	1.62	(1.31, 1.99)	1.61	(1.30, 1.98)
Tolterodine	111	18,604	68,679	1.62	(1.33, 1.95)	1.62	(1.33, 1.95)
Darifenacin	1	281	698	1.43	(0.04, 7.98)	1.37	(0.03, 7.65)
Solifenacin	72	18,400	45,867	1.57	(1.23, 1.98)	1.57	(1.23, 1.98)
Trospium	19	4,690	15,636	1.22	(0.73, 1.90)	1.18	(0.71, 1.84)
Fesoterodine	3	2,079	3,425	0.88	(0.18, 2.56)	0.97	(0.18, 2.89)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	182	119,859	399,365	0.46	(0.39, 0.53)	0.46	(0.39, 0.53)
Oxybutynin	74	50,446	155,883	0.47	(0.37, 0.60)	0.47	(0.37, 0.59)
Tolterodine	77	46,649	191,057	0.40	(0.32, 0.50)	0.40	(0.31, 0.50)
Darifenacin	0	648	1,696	0.00	(0.00, 2.18)	0.00	Not Est.
Solifenacin	67	48,759	126,880	0.53	(0.41, 0.67)	0.53	(0.41, 0.68)
Trospium	12	11,097	40,636	0.30	(0.15, 0.52)	0.27	(0.14, 0.47)
Fesoterodine	4	5,889	9,881	0.40	(0.11, 1.04)	0.47	(0.12, 1.21)
Male, ever treated with							
Any OAB drug	49	36,157	113,294	0.43	(0.32, 0.57)	0.43	(0.32, 0.57)
Oxybutynin	23	15,599	45,873	0.50	(0.32, 0.75)	0.50	(0.32, 0.75)
Tolterodine	20	14,149	54,167	0.37	(0.23, 0.57)	0.37	(0.22, 0.56)
Darifenacin	0	155	372	0.00	(0.00, 9.91)	0.00	Not Est.
Solifenacin	14	12,512	29,851	0.47	(0.26, 0.79)	0.47	(0.26, 0.78)
Trospium	3	3,179	10,647	0.28	(0.06, 0.82)	0.26	(0.05, 0.76)
Fesoterodine	1	1,494	2,298	0.44	(0.01, 2.42)	0.44	(0.01, 2.45)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	133	83,702	286,071	0.46	(0.39, 0.55)	0.46	(0.39, 0.55)
Oxybutynin	51	34,847	110,011	0.46	(0.35, 0.61)	0.46	(0.34, 0.60)
Tolterodine	57	32,500	136,889	0.42	(0.32, 0.54)	0.41	(0.31, 0.53)
Darifenacin	0	493	1,324	0.00	(0.00, 2.79)	0.00	Not Est.
Solifenacin	53	36,247	97,029	0.55	(0.41, 0.71)	0.56	(0.42, 0.74)
Trospium	9	7,918	29,989	0.30	(0.14, 0.57)	0.28	(0.13, 0.52)
Fesoterodine	3	4,395	7,583	0.40	(0.08, 1.16)	0.48	(0.09, 1.42)
Overall, aged < 65 years ever treated with							
Any OAB drug	58	61,567	194,816	0.30	(0.23, 0.38)	0.30	(0.23, 0.38)
Oxybutynin	21	24,666	72,998	0.29	(0.18, 0.44)	0.29	(0.18, 0.45)
Tolterodine	27	23,128	90,532	0.30	(0.20, 0.43)	0.29	(0.19, 0.43)
Darifenacin	0	312	758	0.00	(0.00, 4.87)	0.00	Not Est.
Solifenacin	21	25,490	63,516	0.33	(0.20, 0.51)	0.32	(0.20, 0.49)
Trospium	5	5,120	18,262	0.27	(0.09, 0.64)	0.23	(0.07, 0.53)
Fesoterodine	1	3,142	5,112	0.20	(0.00, 1.09)	0.19	(0.00, 1.05)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	8	16,149	48,041	0.17	(0.07, 0.33)	0.17	(0.07, 0.33)
Oxybutynin	4	6,953	19,678	0.20	(0.06, 0.52)	0.21	(0.06, 0.53)
Tolterodine	6	6,136	22,321	0.27	(0.10, 0.59)	0.26	(0.10, 0.57)
Darifenacin	0	60	132	0.00	(0.00, 27.86)	0.00	Not Est.
Solifenacin	3	5,426	12,353	0.24	(0.05, 0.71)	0.24	(0.05, 0.69)
Trospium	0	1,201	3,909	0.00	(0.00, 0.94)	0.00	Not Est.
Fesoterodine	0	642	954	0.00	(0.00, 3.87)	0.00	Not Est.
Female, aged < 65 years ever treated with							
Any OAB drug	50	45,418	146,775	0.34	(0.25, 0.45)	0.34	(0.25, 0.45)
Oxybutynin	17	17,713	53,321	0.32	(0.19, 0.51)	0.32	(0.19, 0.51)
Tolterodine	21	16,992	68,211	0.31	(0.19, 0.47)	0.30	(0.19, 0.46)
Darifenacin	0	252	626	0.00	(0.00, 5.90)	0.00	Not Est.
Solifenacin	18	20,064	51,163	0.35	(0.21, 0.56)	0.35	(0.21, 0.56)
Trospium	5	3,919	14,354	0.35	(0.11, 0.81)	0.30	(0.10, 0.70)
Fesoterodine	1	2,500	4,158	0.24	(0.01, 1.34)	0.25	(0.01, 1.39)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	124	67,598	204,549	0.61	(0.50, 0.72)	0.61	(0.50, 0.72)
Oxybutynin	53	29,310	82,885	0.64	(0.48, 0.84)	0.64	(0.48, 0.83)
Tolterodine	50	28,063	100,525	0.50	(0.37, 0.66)	0.50	(0.37, 0.66)
Darifenacin	0	387	938	0.00	(0.00, 3.93)	0.00	Not Est.
Solifenacin	46	26,291	63,364	0.73	(0.53, 0.97)	0.74	(0.54, 0.98)
Trospium	7	6,938	22,374	0.31	(0.13, 0.64)	0.31	(0.13, 0.64)
Fesoterodine	3	2,997	4,768	0.63	(0.13, 1.84)	0.74	(0.15, 2.17)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	41	22,992	65,253	0.63	(0.45, 0.85)	0.63	(0.45, 0.85)
Oxybutynin	19	9,805	26,195	0.73	(0.44, 1.13)	0.72	(0.43, 1.12)
Tolterodine	14	9,459	31,846	0.44	(0.24, 0.74)	0.44	(0.24, 0.74)
Darifenacin	0	106	240	0.00	(0.00, 15.39)	0.00	Not Est.
Solifenacin	11	7,891	17,498	0.63	(0.31, 1.12)	0.64	(0.32, 1.14)
Trospium	3	2,248	6,738	0.45	(0.09, 1.30)	0.45	(0.09, 1.31)
Fesoterodine	1	918	1,344	0.74	(0.02, 4.15)	0.76	(0.02, 4.25)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	83	44,606	139,296	0.60	(0.47, 0.74)	0.60	(0.47, 0.74)
Oxybutynin	34	19,505	56,690	0.60	(0.42, 0.84)	0.60	(0.42, 0.84)
Tolterodine	36	18,604	68,679	0.52	(0.37, 0.73)	0.52	(0.37, 0.73)
Darifenacin	0	281	698	0.00	(0.00, 5.28)	0.00	Not Est.
Solifenacin	35	18,400	45,867	0.76	(0.53, 1.06)	0.78	(0.54, 1.09)
Trospium	4	4,690	15,636	0.26	(0.07, 0.66)	0.25	(0.07, 0.64)
Fesoterodine	2	2,079	3,425	0.58	(0.07, 2.11)	0.73	(0.08, 2.64)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.f5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Breast Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	886	83,681	286,005	3.10	(2.90, 3.31)	3.10	(2.90, 3.31)
Oxybutynin	347	34,839	109,980	3.16	(2.83, 3.51)	3.11	(2.79, 3.45)
Tolterodine	438	32,494	136,864	3.20	(2.91, 3.51)	3.15	(2.86, 3.45)
Darifenacin	4	491	1,318	3.03	(0.83, 7.77)	2.73	(0.74, 6.98)
Solifenacin	290	36,239	97,004	2.99	(2.66, 3.35)	3.01	(2.67, 3.38)
Trospium	97	7,914	29,972	3.24	(2.62, 3.95)	3.09	(2.50, 3.77)
Fesoterodine	26	4,390	7,572	3.43	(2.24, 5.03)	3.40	(2.20, 5.00)
Female, aged < 65 years ever treated with							
Any OAB drug	332	45,406	146,742	2.26	(2.03, 2.52)	2.26	(2.03, 2.52)
Oxybutynin	115	17,709	53,310	2.16	(1.78, 2.59)	2.17	(1.79, 2.61)
Tolterodine	169	16,988	68,200	2.48	(2.12, 2.88)	2.41	(2.06, 2.81)
Darifenacin	2	250	620	3.23	(0.39, 11.65)	2.70	(0.33, 9.74)
Solifenacin	111	20,058	51,146	2.17	(1.79, 2.61)	2.16	(1.77, 2.60)
Trospium	31	3,918	14,348	2.16	(1.47, 3.07)	1.98	(1.34, 2.82)
Fesoterodine	12	2,497	4,153	2.89	(1.49, 5.05)	2.84	(1.47, 4.96)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.f5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Breast Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	554	44,595	139,263	3.98	(3.65, 4.32)	3.98	(3.65, 4.32)
Oxybutynin	232	19,500	56,671	4.09	(3.58, 4.66)	4.09	(3.58, 4.65)
Tolterodine	269	18,601	68,663	3.92	(3.46, 4.41)	3.92	(3.46, 4.41)
Darifenacin	2	281	698	2.86	(0.35, 10.35)	2.76	(0.33, 9.96)
Solifenacin	179	18,397	45,858	3.90	(3.35, 4.52)	3.92	(3.36, 4.54)
Trospium	66	4,687	15,624	4.22	(3.27, 5.37)	4.25	(3.29, 5.42)
Fesoterodine	14	2,077	3,420	4.09	(2.24, 6.87)	3.99	(2.14, 6.75)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.g5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Corpus Uteri Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	136	62,163	203,953	0.67	(0.56, 0.79)	0.71	(0.60, 0.84)
Oxybutynin	53	26,041	79,555	0.67	(0.50, 0.87)	0.69	(0.52, 0.91)
Tolterodine	69	23,725	96,618	0.71	(0.56, 0.90)	0.74	(0.58, 0.94)
Darifenacin	0	317	782	0.00	(0.00, 4.72)	0.00	Not Est.
Solifenacin	39	26,243	67,274	0.58	(0.41, 0.79)	0.62	(0.44, 0.85)
Trospium	16	5,483	19,888	0.80	(0.46, 1.31)	0.82	(0.47, 1.33)
Fesoterodine	1	3,120	5,315	0.19	(0.00, 1.05)	0.20	(0.01, 1.10)
Female, aged < 65 years ever treated with							
Any OAB drug	45	35,085	109,509	0.41	(0.30, 0.55)	0.46	(0.34, 0.62)
Oxybutynin	18	13,800	40,352	0.45	(0.26, 0.70)	0.50	(0.29, 0.78)
Tolterodine	23	12,805	50,308	0.46	(0.29, 0.69)	0.49	(0.31, 0.73)
Darifenacin	0	159	376	0.00	(0.00, 9.81)	0.00	Not Est.
Solifenacin	18	15,287	37,625	0.48	(0.28, 0.76)	0.54	(0.32, 0.85)
Trospium	5	2,766	9,811	0.51	(0.17, 1.19)	0.53	(0.17, 1.24)
Fesoterodine	0	1,895	3,121	0.00	(0.00, 1.18)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.g5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Corpus Uteri Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	91	30,852	94,443	0.96	(0.78, 1.18)	0.98	(0.79, 1.20)
Oxybutynin	35	13,677	39,204	0.89	(0.62, 1.24)	0.90	(0.62, 1.25)
Tolterodine	46	12,774	46,310	0.99	(0.73, 1.32)	1.01	(0.74, 1.35)
Darifenacin	0	176	406	0.00	(0.00, 9.08)	0.00	Not Est.
Solifenacin	21	12,232	29,649	0.71	(0.44, 1.08)	0.72	(0.44, 1.09)
Trospium	11	3,094	10,077	1.09	(0.54, 1.95)	1.12	(0.56, 2.01)
Fesoterodine	1	1,330	2,194	0.46	(0.01, 2.54)	0.41	(0.01, 2.26)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.h5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Prostate Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, ever treated with							
Any OAB drug	932	36,157	113,294	8.23	(7.71, 8.77)	8.23	(7.71, 8.77)
Oxybutynin	396	15,599	45,873	8.63	(7.80, 9.53)	8.71	(7.87, 9.61)
Tolterodine	399	14,149	54,167	7.37	(6.66, 8.13)	7.22	(6.53, 7.97)
Darifenacin	3	155	372	8.06	(1.66, 23.56)	7.59	(1.42, 22.52)
Solifenacin	248	12,512	29,851	8.31	(7.31, 9.41)	8.19	(7.20, 9.27)
Trospium	88	3,179	10,647	8.27	(6.63, 10.18)	7.74	(6.20, 9.54)
Fesoterodine	22	1,494	2,298	9.58	(6.00, 14.50)	9.48	(5.93, 14.38)
Male, aged < 65 years ever treated with							
Any OAB drug	175	16,149	48,041	3.64	(3.12, 4.22)	3.64	(3.12, 4.22)
Oxybutynin	66	6,953	19,678	3.35	(2.59, 4.27)	3.49	(2.70, 4.45)
Tolterodine	72	6,136	22,321	3.23	(2.52, 4.06)	3.08	(2.41, 3.88)
Darifenacin	1	60	132	7.55	(0.19, 42.08)	7.80	(0.20, 43.46)
Solifenacin	61	5,426	12,353	4.94	(3.78, 6.34)	4.78	(3.65, 6.14)
Trospium	12	1,201	3,909	3.07	(1.59, 5.36)	2.97	(1.53, 5.19)
Fesoterodine	4	642	954	4.19	(1.14, 10.74)	4.07	(1.11, 10.42)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.h5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Prostate Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged ≥ 65 years ever treated with							
Any OAB drug	757	22,992	65,253	11.60	(10.79, 12.46)	11.60	(10.79, 12.46)
Oxybutynin	330	9,805	26,195	12.60	(11.28, 14.03)	12.55	(11.23, 13.98)
Tolterodine	327	9,459	31,846	10.27	(9.19, 11.44)	10.28	(9.19, 11.45)
Darifenacin	2	106	240	8.34	(1.01, 30.14)	7.44	(0.90, 26.87)
Solifenacin	187	7,891	17,498	10.69	(9.21, 12.33)	10.70	(9.22, 12.35)
Trospium	76	2,248	6,738	11.28	(8.89, 14.12)	11.25	(8.86, 14.08)
Fesoterodine	18	918	1,344	13.39	(7.94, 21.17)	13.47	(7.95, 21.32)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	534	119,859	399,365	1.34	(1.23, 1.46)	1.34	(1.23, 1.46)
Oxybutynin	249	50,446	155,883	1.60	(1.41, 1.81)	1.55	(1.36, 1.75)
Tolterodine	230	46,649	191,057	1.20	(1.05, 1.37)	1.18	(1.03, 1.34)
Darifenacin	3	648	1,696	1.77	(0.36, 5.17)	2.15	(0.40, 6.37)
Solifenacin	173	48,759	126,880	1.36	(1.17, 1.58)	1.49	(1.28, 1.74)
Trospium	52	11,097	40,636	1.28	(0.96, 1.68)	1.28	(0.95, 1.68)
Fesoterodine	15	5,889	9,881	1.52	(0.85, 2.50)	1.64	(0.90, 2.72)
Male, ever treated with							
Any OAB drug	325	36,157	113,294	2.87	(2.57, 3.20)	2.87	(2.57, 3.20)
Oxybutynin	151	15,599	45,873	3.29	(2.79, 3.86)	3.31	(2.80, 3.88)
Tolterodine	142	14,149	54,167	2.62	(2.21, 3.09)	2.57	(2.17, 3.03)
Darifenacin	2	155	372	5.37	(0.65, 19.41)	5.45	(0.55, 20.01)
Solifenacin	94	12,512	29,851	3.15	(2.54, 3.85)	3.11	(2.51, 3.80)
Trospium	26	3,179	10,647	2.44	(1.60, 3.58)	2.40	(1.56, 3.52)
Fesoterodine	7	1,494	2,298	3.05	(1.22, 6.28)	2.84	(1.14, 5.86)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	209	83,702	286,071	0.73	(0.63, 0.84)	0.73	(0.63, 0.84)
Oxybutynin	98	34,847	110,011	0.89	(0.72, 1.09)	0.85	(0.69, 1.03)
Tolterodine	88	32,500	136,889	0.64	(0.52, 0.79)	0.63	(0.50, 0.77)
Darifenacin	1	493	1,324	0.76	(0.02, 4.21)	0.84	(0.02, 4.67)
Solifenacin	79	36,247	97,029	0.81	(0.64, 1.01)	0.86	(0.68, 1.07)
Trospium	26	7,918	29,989	0.87	(0.57, 1.27)	0.83	(0.54, 1.22)
Fesoterodine	8	4,395	7,583	1.06	(0.46, 2.08)	1.16	(0.48, 2.32)
Overall, aged < 65 years ever treated with							
Any OAB drug	93	61,567	194,816	0.48	(0.39, 0.58)	0.48	(0.39, 0.58)
Oxybutynin	41	24,666	72,998	0.56	(0.40, 0.76)	0.55	(0.40, 0.75)
Tolterodine	36	23,128	90,532	0.40	(0.28, 0.55)	0.38	(0.27, 0.53)
Darifenacin	1	312	758	1.32	(0.03, 7.35)	1.92	(0.05, 10.72)
Solifenacin	30	25,490	63,516	0.47	(0.32, 0.67)	0.53	(0.36, 0.76)
Trospium	15	5,120	18,262	0.82	(0.46, 1.35)	0.85	(0.47, 1.41)
Fesoterodine	4	3,142	5,112	0.78	(0.21, 2.00)	0.86	(0.23, 2.23)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	56	16,149	48,041	1.17	(0.88, 1.51)	1.17	(0.88, 1.51)
Oxybutynin	24	6,953	19,678	1.22	(0.78, 1.81)	1.27	(0.81, 1.89)
Tolterodine	22	6,136	22,321	0.99	(0.62, 1.49)	0.94	(0.59, 1.43)
Darifenacin	1	60	132	7.55	(0.19, 42.08)	7.80	(0.20, 43.46)
Solifenacin	20	5,426	12,353	1.62	(0.99, 2.50)	1.56	(0.95, 2.41)
Trospium	11	1,201	3,909	2.81	(1.40, 5.04)	2.71	(1.35, 4.86)
Fesoterodine	2	642	954	2.10	(0.25, 7.58)	2.05	(0.25, 7.42)
Female, aged < 65 years ever treated with							
Any OAB drug	37	45,418	146,775	0.25	(0.18, 0.35)	0.25	(0.18, 0.35)
Oxybutynin	17	17,713	53,321	0.32	(0.19, 0.51)	0.32	(0.18, 0.51)
Tolterodine	14	16,992	68,211	0.21	(0.11, 0.34)	0.20	(0.11, 0.33)
Darifenacin	0	252	626	0.00	(0.00, 5.90)	0.00	Not Est.
Solifenacin	10	20,064	51,163	0.20	(0.09, 0.36)	0.20	(0.09, 0.36)
Trospium	4	3,919	14,354	0.28	(0.08, 0.71)	0.24	(0.07, 0.62)
Fesoterodine	2	2,500	4,158	0.48	(0.06, 1.74)	0.47	(0.06, 1.71)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	441	67,598	204,549	2.16	(1.96, 2.37)	2.16	(1.96, 2.37)
Oxybutynin	208	29,310	82,885	2.51	(2.18, 2.87)	2.49	(2.16, 2.85)
Tolterodine	194	28,063	100,525	1.93	(1.67, 2.22)	1.94	(1.68, 2.23)
Darifenacin	2	387	938	2.13	(0.26, 7.70)	2.36	(0.29, 8.52)
Solifenacin	143	26,291	63,364	2.26	(1.90, 2.66)	2.41	(2.03, 2.84)
Trospium	37	6,938	22,374	1.65	(1.16, 2.28)	1.68	(1.18, 2.32)
Fesoterodine	11	2,997	4,768	2.31	(1.15, 4.13)	2.37	(1.17, 4.28)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	269	22,992	65,253	4.12	(3.64, 4.65)	4.12	(3.64, 4.65)
Oxybutynin	127	9,805	26,195	4.85	(4.04, 5.77)	4.80	(4.00, 5.72)
Tolterodine	120	9,459	31,846	3.77	(3.12, 4.51)	3.77	(3.13, 4.51)
Darifenacin	1	106	240	4.17	(0.11, 23.24)	3.72	(0.09, 20.72)
Solifenacin	74	7,891	17,498	4.23	(3.32, 5.31)	4.25	(3.33, 5.33)
Trospium	15	2,248	6,738	2.23	(1.25, 3.67)	2.17	(1.21, 3.58)
Fesoterodine	5	918	1,344	3.72	(1.21, 8.68)	3.42	(1.11, 7.99)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	172	44,606	139,296	1.23	(1.06, 1.43)	1.23	(1.06, 1.43)
Oxybutynin	81	19,505	56,690	1.43	(1.13, 1.78)	1.41	(1.12, 1.75)
Tolterodine	74	18,604	68,679	1.08	(0.85, 1.35)	1.08	(0.85, 1.36)
Darifenacin	1	281	698	1.43	(0.04, 7.98)	1.72	(0.04, 9.59)
Solifenacin	69	18,400	45,867	1.50	(1.17, 1.90)	1.55	(1.20, 1.96)
Trospium	22	4,690	15,636	1.41	(0.88, 2.13)	1.45	(0.91, 2.20)
Fesoterodine	6	2,079	3,425	1.75	(0.64, 3.81)	1.88	(0.66, 4.16)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	125	119,859	399,365	0.31	(0.26, 0.37)	0.31	(0.26, 0.37)
Oxybutynin	46	50,446	155,883	0.30	(0.22, 0.39)	0.29	(0.21, 0.38)
Tolterodine	66	46,649	191,057	0.35	(0.27, 0.44)	0.34	(0.26, 0.43)
Darifenacin	0	648	1,696	0.00	(0.00, 2.18)	0.00	Not Est.
Solifenacin	40	48,759	126,880	0.32	(0.23, 0.43)	0.34	(0.24, 0.46)
Trospium	9	11,097	40,636	0.22	(0.10, 0.42)	0.21	(0.09, 0.39)
Fesoterodine	0	5,889	9,881	0.00	(0.00, 0.37)	0.00	Not Est.
Male, ever treated with							
Any OAB drug	53	36,157	113,294	0.47	(0.35, 0.61)	0.47	(0.35, 0.61)
Oxybutynin	21	15,599	45,873	0.46	(0.28, 0.70)	0.46	(0.29, 0.71)
Tolterodine	26	14,149	54,167	0.48	(0.31, 0.70)	0.47	(0.31, 0.69)
Darifenacin	0	155	372	0.00	(0.00, 9.91)	0.00	Not Est.
Solifenacin	16	12,512	29,851	0.54	(0.31, 0.87)	0.55	(0.31, 0.89)
Trospium	2	3,179	10,647	0.19	(0.02, 0.68)	0.18	(0.02, 0.65)
Fesoterodine	0	1,494	2,298	0.00	(0.00, 1.61)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	72	83,702	286,071	0.25	(0.20, 0.32)	0.25	(0.20, 0.32)
Oxybutynin	25	34,847	110,011	0.23	(0.15, 0.34)	0.22	(0.14, 0.32)
Tolterodine	40	32,500	136,889	0.29	(0.21, 0.40)	0.29	(0.20, 0.39)
Darifenacin	0	493	1,324	0.00	(0.00, 2.79)	0.00	Not Est.
Solifenacin	24	36,247	97,029	0.25	(0.16, 0.37)	0.25	(0.16, 0.38)
Trospium	7	7,918	29,989	0.23	(0.09, 0.48)	0.22	(0.09, 0.45)
Fesoterodine	0	4,395	7,583	0.00	(0.00, 0.49)	0.00	Not Est.
Overall, aged < 65 years ever treated with							
Any OAB drug	30	61,567	194,816	0.15	(0.10, 0.22)	0.15	(0.10, 0.22)
Oxybutynin	12	24,666	72,998	0.16	(0.08, 0.29)	0.16	(0.08, 0.28)
Tolterodine	12	23,128	90,532	0.13	(0.07, 0.23)	0.13	(0.07, 0.22)
Darifenacin	0	312	758	0.00	(0.00, 4.87)	0.00	Not Est.
Solifenacin	10	25,490	63,516	0.16	(0.08, 0.29)	0.17	(0.08, 0.32)
Trospium	1	5,120	18,262	0.05	(0.00, 0.31)	0.05	(0.00, 0.25)
Fesoterodine	0	3,142	5,112	0.00	(0.00, 0.72)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	13	16,149	48,041	0.27	(0.14, 0.46)	0.27	(0.14, 0.46)
Oxybutynin	6	6,953	19,678	0.30	(0.11, 0.66)	0.32	(0.12, 0.69)
Tolterodine	4	6,136	22,321	0.18	(0.05, 0.46)	0.17	(0.05, 0.44)
Darifenacin	0	60	132	0.00	(0.00, 27.86)	0.00	Not Est.
Solifenacin	4	5,426	12,353	0.32	(0.09, 0.83)	0.34	(0.09, 0.87)
Trospium	0	1,201	3,909	0.00	(0.00, 0.94)	0.00	Not Est.
Fesoterodine	0	642	954	0.00	(0.00, 3.87)	0.00	Not Est.
Female, aged < 65 years ever treated with							
Any OAB drug	17	45,418	146,775	0.12	(0.07, 0.19)	0.12	(0.07, 0.19)
Oxybutynin	6	17,713	53,321	0.11	(0.04, 0.24)	0.11	(0.04, 0.24)
Tolterodine	8	16,992	68,211	0.12	(0.05, 0.23)	0.11	(0.05, 0.23)
Darifenacin	0	252	626	0.00	(0.00, 5.90)	0.00	Not Est.
Solifenacin	6	20,064	51,163	0.12	(0.04, 0.26)	0.12	(0.04, 0.25)
Trospium	1	3,919	14,354	0.07	(0.00, 0.39)	0.06	(0.00, 0.34)
Fesoterodine	0	2,500	4,158	0.00	(0.00, 0.89)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	95	67,598	204,549	0.46	(0.38, 0.57)	0.46	(0.38, 0.57)
Oxybutynin	34	29,310	82,885	0.41	(0.28, 0.57)	0.40	(0.28, 0.57)
Tolterodine	54	28,063	100,525	0.54	(0.40, 0.70)	0.54	(0.40, 0.70)
Darifenacin	0	387	938	0.00	(0.00, 3.93)	0.00	Not Est.
Solifenacin	30	26,291	63,364	0.47	(0.32, 0.68)	0.49	(0.33, 0.70)
Trospium	8	6,938	22,374	0.36	(0.15, 0.70)	0.36	(0.16, 0.71)
Fesoterodine	0	2,997	4,768	0.00	(0.00, 0.77)	0.00	Not Est.
Male, aged ≥ 65 years ever treated with							
Any OAB drug	40	22,992	65,253	0.61	(0.44, 0.83)	0.61	(0.44, 0.83)
Oxybutynin	15	9,805	26,195	0.57	(0.32, 0.94)	0.57	(0.32, 0.94)
Tolterodine	22	9,459	31,846	0.69	(0.43, 1.05)	0.69	(0.43, 1.05)
Darifenacin	0	106	240	0.00	(0.00, 15.39)	0.00	Not Est.
Solifenacin	12	7,891	17,498	0.69	(0.35, 1.20)	0.70	(0.36, 1.22)
Trospium	2	2,248	6,738	0.30	(0.04, 1.07)	0.31	(0.04, 1.12)
Fesoterodine	0	918	1,344	0.00	(0.00, 2.74)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	55	44,606	139,296	0.39	(0.30, 0.51)	0.39	(0.30, 0.51)
Oxybutynin	19	19,505	56,690	0.34	(0.20, 0.52)	0.33	(0.20, 0.51)
Tolterodine	32	18,604	68,679	0.47	(0.32, 0.66)	0.47	(0.32, 0.66)
Darifenacin	0	281	698	0.00	(0.00, 5.28)	0.00	Not Est.
Solifenacin	18	18,400	45,867	0.39	(0.23, 0.62)	0.40	(0.23, 0.63)
Trospium	6	4,690	15,636	0.38	(0.14, 0.84)	0.38	(0.14, 0.84)
Fesoterodine	0	2,079	3,425	0.00	(0.00, 1.08)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, ever treated with							
Any OAB drug	144	119,859	399,365	0.36	(0.30, 0.42)	0.36	(0.30, 0.42)
Oxybutynin	52	50,446	155,883	0.33	(0.25, 0.44)	0.33	(0.24, 0.43)
Tolterodine	81	46,649	191,057	0.42	(0.34, 0.53)	0.41	(0.33, 0.51)
Darifenacin	2	648	1,696	1.18	(0.14, 4.26)	1.31	(0.16, 4.76)
Solifenacin	34	48,759	126,880	0.27	(0.19, 0.37)	0.29	(0.20, 0.40)
Trospium	15	11,097	40,636	0.37	(0.21, 0.61)	0.36	(0.20, 0.60)
Fesoterodine	3	5,889	9,881	0.30	(0.06, 0.89)	0.34	(0.07, 1.01)
Male, ever treated with							
Any OAB drug	63	36,157	113,294	0.56	(0.43, 0.71)	0.56	(0.43, 0.71)
Oxybutynin	19	15,599	45,873	0.41	(0.25, 0.65)	0.42	(0.25, 0.65)
Tolterodine	38	14,149	54,167	0.70	(0.50, 0.96)	0.69	(0.48, 0.94)
Darifenacin	2	155	372	5.37	(0.65, 19.41)	4.63	(0.55, 16.78)
Solifenacin	17	12,512	29,851	0.57	(0.33, 0.91)	0.56	(0.33, 0.90)
Trospium	10	3,179	10,647	0.94	(0.45, 1.73)	0.89	(0.43, 1.65)
Fesoterodine	2	1,494	2,298	0.87	(0.11, 3.14)	0.83	(0.10, 3.02)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, ever treated with							
Any OAB drug	81	83,702	286,071	0.28	(0.22, 0.35)	0.28	(0.22, 0.35)
Oxybutynin	33	34,847	110,011	0.30	(0.21, 0.42)	0.29	(0.20, 0.41)
Tolterodine	43	32,500	136,889	0.31	(0.23, 0.42)	0.31	(0.22, 0.41)
Darifenacin	0	493	1,324	0.00	(0.00, 2.79)	0.00	Not Est.
Solifenacin	17	36,247	97,029	0.18	(0.10, 0.28)	0.18	(0.10, 0.29)
Trospium	5	7,918	29,989	0.17	(0.05, 0.39)	0.15	(0.05, 0.36)
Fesoterodine	1	4,395	7,583	0.13	(0.00, 0.73)	0.15	(0.00, 0.84)
Overall, aged < 65 years ever treated with							
Any OAB drug	26	61,567	194,816	0.13	(0.09, 0.20)	0.13	(0.09, 0.20)
Oxybutynin	11	24,666	72,998	0.15	(0.08, 0.27)	0.15	(0.07, 0.27)
Tolterodine	13	23,128	90,532	0.14	(0.08, 0.25)	0.14	(0.07, 0.23)
Darifenacin	0	312	758	0.00	(0.00, 4.87)	0.00	Not Est.
Solifenacin	3	25,490	63,516	0.05	(0.01, 0.14)	0.05	(0.01, 0.16)
Trospium	4	5,120	18,262	0.22	(0.06, 0.56)	0.20	(0.05, 0.51)
Fesoterodine	0	3,142	5,112	0.00	(0.00, 0.72)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years ever treated with							
Any OAB drug	11	16,149	48,041	0.23	(0.11, 0.41)	0.23	(0.11, 0.41)
Oxybutynin	4	6,953	19,678	0.20	(0.06, 0.52)	0.21	(0.06, 0.54)
Tolterodine	7	6,136	22,321	0.31	(0.13, 0.65)	0.30	(0.12, 0.62)
Darifenacin	0	60	132	0.00	(0.00, 27.86)	0.00	Not Est.
Solifenacin	2	5,426	12,353	0.16	(0.02, 0.58)	0.16	(0.02, 0.57)
Trospium	1	1,201	3,909	0.26	(0.01, 1.43)	0.25	(0.01, 1.37)
Fesoterodine	0	642	954	0.00	(0.00, 3.87)	0.00	Not Est.
Female, aged < 65 years ever treated with							
Any OAB drug	15	45,418	146,775	0.10	(0.06, 0.17)	0.10	(0.06, 0.17)
Oxybutynin	7	17,713	53,321	0.13	(0.05, 0.27)	0.13	(0.05, 0.27)
Tolterodine	6	16,992	68,211	0.09	(0.03, 0.19)	0.08	(0.03, 0.18)
Darifenacin	0	252	626	0.00	(0.00, 5.90)	0.00	Not Est.
Solifenacin	1	20,064	51,163	0.02	(0.00, 0.11)	0.02	(0.00, 0.11)
Trospium	3	3,919	14,354	0.21	(0.04, 0.61)	0.18	(0.04, 0.53)
Fesoterodine	0	2,500	4,158	0.00	(0.00, 0.89)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years ever treated with							
Any OAB drug	118	67,598	204,549	0.58	(0.48, 0.69)	0.58	(0.48, 0.69)
Oxybutynin	41	29,310	82,885	0.49	(0.35, 0.67)	0.50	(0.36, 0.68)
Tolterodine	68	28,063	100,525	0.68	(0.53, 0.86)	0.68	(0.52, 0.86)
Darifenacin	2	387	938	2.13	(0.26, 7.70)	2.57	(0.30, 9.29)
Solifenacin	31	26,291	63,364	0.49	(0.33, 0.69)	0.51	(0.35, 0.73)
Trospium	11	6,938	22,374	0.49	(0.25, 0.88)	0.52	(0.26, 0.94)
Fesoterodine	3	2,997	4,768	0.63	(0.13, 1.84)	0.67	(0.14, 1.97)
Male, aged ≥ 65 years ever treated with							
Any OAB drug	52	22,992	65,253	0.80	(0.60, 1.05)	0.80	(0.60, 1.05)
Oxybutynin	15	9,805	26,195	0.57	(0.32, 0.94)	0.57	(0.32, 0.94)
Tolterodine	31	9,459	31,846	0.97	(0.66, 1.38)	0.97	(0.66, 1.38)
Darifenacin	2	106	240	8.34	(1.01, 30.14)	8.05	(0.95, 29.13)
Solifenacin	15	7,891	17,498	0.86	(0.48, 1.41)	0.86	(0.48, 1.42)
Trospium	9	2,248	6,738	1.34	(0.61, 2.54)	1.37	(0.63, 2.61)
Fesoterodine	2	918	1,344	1.49	(0.18, 5.38)	1.45	(0.17, 5.24)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N3.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Ever Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years ever treated with							
Any OAB drug	66	44,606	139,296	0.47	(0.37, 0.60)	0.47	(0.37, 0.60)
Oxybutynin	26	19,505	56,690	0.46	(0.30, 0.67)	0.46	(0.30, 0.68)
Tolterodine	37	18,604	68,679	0.54	(0.38, 0.74)	0.54	(0.38, 0.74)
Darifenacin	0	281	698	0.00	(0.00, 5.28)	0.00	Not Est.
Solifenacin	16	18,400	45,867	0.35	(0.20, 0.57)	0.35	(0.20, 0.56)
Trospium	2	4,690	15,636	0.13	(0.02, 0.46)	0.13	(0.02, 0.45)
Fesoterodine	1	2,079	3,425	0.29	(0.01, 1.63)	0.31	(0.01, 1.72)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	943	41,836	109,884	8.58	(8.04, 9.15)	8.59	(8.05, 9.15)
Oxybutynin	280	12,679	30,934	9.05	(8.02, 10.18)	8.82	(7.81, 9.92)
Tolterodine	333	11,315	38,514	8.65	(7.74, 9.63)	8.51	(7.62, 9.48)
Darifenacin	2	142	234	8.54	(1.03, 30.86)	7.91	(0.95, 28.59)
Solifenacin	167	9,807	21,327	7.83	(6.69, 9.11)	8.39	(7.16, 9.77)
Trospium	129	5,633	15,781	8.17	(6.82, 9.71)	7.98	(6.66, 9.49)
Fesoterodine	32	2,260	3,094	10.34	(7.08, 14.60)	10.89	(7.38, 15.47)
Male, single treated with							
Any OAB drug	450	12,929	33,074	13.61	(12.38, 14.92)	13.80	(12.55, 15.13)
Oxybutynin	153	4,170	10,075	15.19	(12.88, 17.79)	15.96	(13.53, 18.71)
Tolterodine	148	3,602	11,867	12.47	(10.54, 14.65)	12.37	(10.46, 14.53)
Darifenacin	1	42	80	12.44	(0.31, 69.29)	13.07	(0.33, 72.84)
Solifenacin	73	2,671	5,489	13.30	(10.43, 16.72)	13.72	(10.75, 17.25)
Trospium	60	1,759	4,656	12.89	(9.83, 16.59)	12.45	(9.49, 16.04)
Fesoterodine	15	685	907	16.54	(9.26, 27.28)	17.31	(9.65, 28.60)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	493	28,907	76,811	6.42	(5.86, 7.01)	6.52	(5.96, 7.12)
Oxybutynin	127	8,509	20,859	6.09	(5.08, 7.24)	5.99	(4.99, 7.13)
Tolterodine	185	7,713	26,647	6.94	(5.98, 8.02)	6.99	(6.02, 8.07)
Darifenacin	1	100	154	6.51	(0.16, 36.25)	5.84	(0.15, 32.52)
Solifenacin	94	7,136	15,839	5.93	(4.80, 7.26)	6.27	(5.06, 7.69)
Trospium	69	3,874	11,126	6.20	(4.83, 7.85)	6.21	(4.83, 7.86)
Fesoterodine	17	1,575	2,187	7.77	(4.53, 12.45)	8.35	(4.76, 13.53)
Overall, aged < 65 years single treated with							
Any OAB drug	223	21,367	54,459	4.09	(3.58, 4.67)	4.17	(3.64, 4.75)
Oxybutynin	58	6,299	14,817	3.91	(2.97, 5.06)	4.03	(3.05, 5.22)
Tolterodine	83	5,694	18,849	4.40	(3.51, 5.46)	4.34	(3.46, 5.38)
Darifenacin	1	64	87	11.55	(0.29, 64.35)	7.72	(0.20, 43.03)
Solifenacin	44	5,340	11,423	3.85	(2.80, 5.17)	4.03	(2.92, 5.42)
Trospium	26	2,691	7,584	3.43	(2.24, 5.02)	3.44	(2.25, 5.05)
Fesoterodine	11	1,279	1,700	6.47	(3.23, 11.58)	7.01	(3.46, 12.59)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	84	5,718	14,286	5.88	(4.69, 7.28)	6.10	(4.86, 7.55)
Oxybutynin	28	1,925	4,580	6.11	(4.06, 8.84)	6.89	(4.58, 9.96)
Tolterodine	24	1,564	5,005	4.80	(3.07, 7.13)	4.64	(2.97, 6.91)
Darifenacin	1	16	23	43.34	(1.10, 241.46)	30.83	(0.78, 171.77)
Solifenacin	17	1,231	2,476	6.87	(4.00, 10.99)	7.06	(4.11, 11.31)
Trospium	10	672	1,802	5.55	(2.66, 10.21)	5.77	(2.76, 10.60)
Fesoterodine	4	310	400	10.00	(2.73, 25.61)	10.67	(2.91, 27.31)
Female, aged < 65 years single treated with							
Any OAB drug	139	15,649	40,172	3.46	(2.91, 4.09)	3.53	(2.97, 4.17)
Oxybutynin	30	4,374	10,237	2.93	(1.98, 4.18)	3.10	(2.09, 4.42)
Tolterodine	59	4,130	13,844	4.26	(3.24, 5.50)	4.24	(3.23, 5.47)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	27	4,109	8,947	3.02	(1.99, 4.39)	3.04	(2.00, 4.43)
Trospium	16	2,019	5,782	2.77	(1.58, 4.49)	2.68	(1.53, 4.36)
Fesoterodine	7	969	1,300	5.39	(2.17, 11.10)	5.81	(2.28, 12.07)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	720	22,936	55,426	12.99	(12.06, 13.97)	12.79	(11.87, 13.76)
Oxybutynin	222	7,016	16,117	13.77	(12.02, 15.71)	13.38	(11.67, 15.27)
Tolterodine	250	6,543	19,666	12.71	(11.19, 14.39)	12.49	(10.98, 14.14)
Darifenacin	1	87	148	6.78	(0.17, 37.77)	8.08	(0.20, 45.00)
Solifenacin	123	4,926	9,904	12.42	(10.32, 14.82)	12.53	(10.41, 14.96)
Trospium	103	3,306	8,197	12.57	(10.26, 15.24)	12.30	(10.03, 14.93)
Fesoterodine	21	1,058	1,394	15.07	(9.33, 23.03)	14.59	(8.92, 22.47)
Male, aged ≥ 65 years single treated with							
Any OAB drug	366	8,051	18,787	19.48	(17.54, 21.58)	19.46	(17.52, 21.56)
Oxybutynin	125	2,473	5,495	22.75	(18.94, 27.10)	22.64	(18.84, 26.99)
Tolterodine	124	2,362	6,862	18.07	(15.03, 21.55)	18.06	(15.02, 21.53)
Darifenacin	0	29	57	0.00	(0.00, 64.34)	0.00	Not Est.
Solifenacin	56	1,585	3,012	18.59	(14.04, 24.14)	18.62	(14.06, 24.18)
Trospium	50	1,200	2,854	17.52	(13.00, 23.10)	17.37	(12.88, 22.91)
Fesoterodine	11	402	507	21.70	(10.83, 38.83)	22.19	(11.00, 39.83)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a1. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 1 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	354	14,885	36,638	9.66	(8.68, 10.72)	9.67	(8.69, 10.73)
Oxybutynin	97	4,543	10,622	9.13	(7.41, 11.14)	9.04	(7.32, 11.04)
Tolterodine	126	4,181	12,804	9.84	(8.20, 11.72)	9.88	(8.23, 11.76)
Darifenacin	1	58	90	11.09	(0.28, 61.77)	11.86	(0.30, 66.08)
Solifenacin	67	3,341	6,892	9.72	(7.53, 12.35)	9.68	(7.50, 12.30)
Trospium	53	2,106	5,343	9.92	(7.43, 12.97)	9.93	(7.43, 12.98)
Fesoterodine	10	656	887	11.27	(5.41, 20.73)	11.03	(5.14, 20.54)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 1 comprised all CONF-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	973	41,836	109,905	8.85	(8.31, 9.43)	8.85	(8.30, 9.42)
Oxybutynin	289	12,679	30,941	9.34	(8.29, 10.48)	9.08	(8.05, 10.20)
Tolterodine	342	11,315	38,518	8.88	(7.96, 9.87)	8.73	(7.82, 9.70)
Darifenacin	2	142	234	8.54	(1.03, 30.86)	7.91	(0.95, 28.59)
Solifenacin	175	9,807	21,327	8.21	(7.03, 9.52)	8.79	(7.53, 10.20)
Trospium	132	5,633	15,790	8.36	(6.99, 9.91)	8.16	(6.82, 9.68)
Fesoterodine	33	2,260	3,094	10.67	(7.34, 14.98)	11.25	(7.68, 15.89)
Male, single treated with							
Any OAB drug	469	12,929	33,083	14.18	(12.92, 15.52)	14.36	(13.09, 15.72)
Oxybutynin	158	4,170	10,077	15.68	(13.33, 18.32)	16.42	(13.95, 19.19)
Tolterodine	156	3,602	11,870	13.14	(11.16, 15.37)	13.03	(11.06, 15.24)
Darifenacin	1	42	80	12.44	(0.31, 69.29)	13.07	(0.33, 72.84)
Solifenacin	77	2,671	5,489	14.03	(11.07, 17.53)	14.47	(11.42, 18.09)
Trospium	61	1,759	4,660	13.09	(10.01, 16.82)	12.63	(9.65, 16.25)
Fesoterodine	16	685	907	17.64	(10.08, 28.65)	18.57	(10.57, 30.21)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	504	28,907	76,822	6.56	(6.00, 7.16)	6.67	(6.10, 7.27)
Oxybutynin	131	8,509	20,864	6.28	(5.25, 7.45)	6.17	(5.15, 7.33)
Tolterodine	186	7,713	26,649	6.98	(6.01, 8.06)	7.02	(6.05, 8.11)
Darifenacin	1	100	154	6.51	(0.16, 36.25)	5.84	(0.15, 32.52)
Solifenacin	98	7,136	15,838	6.19	(5.02, 7.54)	6.54	(5.30, 7.97)
Trospium	71	3,874	11,130	6.38	(4.98, 8.05)	6.39	(4.99, 8.06)
Fesoterodine	17	1,575	2,187	7.77	(4.53, 12.45)	8.35	(4.76, 13.53)
Overall, aged < 65 years single treated with							
Any OAB drug	226	21,367	54,467	4.15	(3.63, 4.73)	4.22	(3.69, 4.81)
Oxybutynin	58	6,299	14,824	3.91	(2.97, 5.06)	4.05	(3.06, 5.24)
Tolterodine	84	5,694	18,849	4.46	(3.55, 5.52)	4.40	(3.51, 5.44)
Darifenacin	1	64	87	11.55	(0.29, 64.35)	7.72	(0.20, 43.03)
Solifenacin	46	5,340	11,422	4.03	(2.95, 5.37)	4.20	(3.07, 5.62)
Trospium	26	2,691	7,584	3.43	(2.24, 5.02)	3.44	(2.25, 5.05)
Fesoterodine	11	1,279	1,700	6.47	(3.23, 11.58)	7.01	(3.46, 12.59)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	83	5,718	14,289	5.81	(4.63, 7.20)	6.02	(4.80, 7.47)
Oxybutynin	27	1,925	4,583	5.89	(3.88, 8.57)	6.63	(4.37, 9.65)
Tolterodine	24	1,564	5,005	4.80	(3.07, 7.13)	4.64	(2.97, 6.91)
Darifenacin	1	16	23	43.34	(1.10, 241.46)	30.83	(0.78, 171.77)
Solifenacin	17	1,231	2,476	6.87	(4.00, 10.99)	7.06	(4.11, 11.31)
Trospium	10	672	1,802	5.55	(2.66, 10.21)	5.76	(2.76, 10.60)
Fesoterodine	4	310	400	10.00	(2.73, 25.61)	10.67	(2.91, 27.31)
Female, aged < 65 years single treated with							
Any OAB drug	143	15,649	40,178	3.56	(3.00, 4.19)	3.63	(3.06, 4.28)
Oxybutynin	31	4,374	10,242	3.03	(2.06, 4.30)	3.20	(2.17, 4.54)
Tolterodine	60	4,130	13,844	4.33	(3.31, 5.58)	4.32	(3.29, 5.56)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	29	4,109	8,946	3.24	(2.17, 4.66)	3.27	(2.18, 4.70)
Trospium	16	2,019	5,782	2.77	(1.58, 4.49)	2.68	(1.53, 4.36)
Fesoterodine	7	969	1,300	5.39	(2.17, 11.10)	5.81	(2.28, 12.07)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	747	22,937	55,438	13.47	(12.53, 14.48)	13.25	(12.32, 14.24)
Oxybutynin	231	7,017	16,117	14.33	(12.54, 16.31)	13.87	(12.13, 15.79)
Tolterodine	258	6,543	19,669	13.12	(11.57, 14.82)	12.85	(11.33, 14.52)
Darifenacin	1	87	148	6.78	(0.17, 37.77)	8.08	(0.20, 45.00)
Solifenacin	129	4,926	9,905	13.02	(10.87, 15.47)	13.15	(10.98, 15.63)
Trospium	106	3,306	8,206	12.92	(10.58, 15.62)	12.65	(10.35, 15.31)
Fesoterodine	22	1,058	1,394	15.78	(9.89, 23.89)	15.29	(9.47, 23.31)
Male, aged ≥ 65 years single treated with							
Any OAB drug	386	8,052	18,794	20.54	(18.54, 22.69)	20.50	(18.50, 22.65)
Oxybutynin	131	2,474	5,494	23.84	(19.93, 28.29)	23.62	(19.74, 28.04)
Tolterodine	132	2,362	6,865	19.23	(16.09, 22.80)	19.20	(16.06, 22.77)
Darifenacin	0	29	57	0.00	(0.00, 64.34)	0.00	Not Est.
Solifenacin	60	1,585	3,013	19.92	(15.20, 25.64)	19.93	(15.21, 25.65)
Trospium	51	1,200	2,858	17.85	(13.29, 23.46)	17.69	(13.16, 23.27)
Fesoterodine	12	402	507	23.66	(12.23, 41.34)	24.39	(12.52, 42.72)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a2. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 2 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	361	14,885	36,644	9.85	(8.86, 10.92)	9.86	(8.87, 10.93)
Oxybutynin	100	4,543	10,622	9.41	(7.66, 11.45)	9.30	(7.56, 11.33)
Tolterodine	126	4,181	12,804	9.84	(8.20, 11.72)	9.87	(8.23, 11.76)
Darifenacin	1	58	90	11.09	(0.28, 61.77)	11.86	(0.30, 66.08)
Solifenacin	69	3,341	6,892	10.01	(7.79, 12.67)	9.98	(7.76, 12.63)
Trospium	55	2,106	5,348	10.28	(7.75, 13.39)	10.29	(7.75, 13.39)
Fesoterodine	10	656	887	11.27	(5.41, 20.73)	11.03	(5.14, 20.54)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 2 comprised all PROV-1 cases in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	3,104	117,077	301,139	10.31	(9.95, 10.68)	10.36	(10.00, 10.73)
Oxybutynin	1,074	40,084	95,010	11.30	(10.64, 12.00)	11.07	(10.41, 11.75)
Tolterodine	1,201	36,902	120,060	10.00	(9.45, 10.59)	9.90	(9.35, 10.48)
Darifenacin	3	142	233	12.85	(2.65, 37.56)	9.81	(1.68, 29.51)
Solifenacin	633	32,056	67,032	9.44	(8.72, 10.21)	10.29	(9.50, 11.13)
Trospium	159	5,633	15,711	10.12	(8.61, 11.82)	9.92	(8.43, 11.59)
Fesoterodine	34	2,260	3,093	10.99	(7.61, 15.36)	11.54	(7.92, 16.21)
Male, single treated with							
Any OAB drug	1,521	35,446	89,265	17.04	(16.19, 17.92)	17.30	(16.45, 18.20)
Oxybutynin	577	12,990	30,766	18.75	(17.26, 20.35)	19.61	(18.04, 21.27)
Tolterodine	561	11,578	36,400	15.41	(14.16, 16.74)	15.40	(14.15, 16.73)
Darifenacin	2	42	80	25.10	(3.04, 90.65)	19.75	(1.51, 73.99)
Solifenacin	296	8,392	16,484	17.96	(15.97, 20.12)	18.25	(16.23, 20.46)
Trospium	68	1,759	4,630	14.69	(11.41, 18.62)	14.22	(11.03, 18.05)
Fesoterodine	17	685	906	18.77	(10.93, 30.05)	19.57	(11.36, 31.41)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	1,583	81,631	211,874	7.47	(7.11, 7.85)	7.61	(7.24, 8.00)
Oxybutynin	497	27,094	64,244	7.74	(7.07, 8.45)	7.69	(7.02, 8.40)
Tolterodine	640	25,324	83,661	7.65	(7.07, 8.27)	7.72	(7.13, 8.34)
Darifenacin	1	100	154	6.51	(0.16, 36.25)	5.84	(0.15, 32.52)
Solifenacin	337	23,664	50,548	6.67	(5.97, 7.42)	7.14	(6.39, 7.95)
Trospium	91	3,874	11,081	8.21	(6.61, 10.08)	8.22	(6.62, 10.09)
Fesoterodine	17	1,575	2,187	7.77	(4.53, 12.45)	8.36	(4.76, 13.53)
Overall, aged < 65 years single treated with							
Any OAB drug	706	60,443	150,834	4.68	(4.34, 5.04)	4.73	(4.39, 5.10)
Oxybutynin	220	19,982	46,198	4.76	(4.15, 5.43)	4.92	(4.28, 5.62)
Tolterodine	265	18,779	59,348	4.47	(3.94, 5.04)	4.38	(3.87, 4.95)
Darifenacin	1	64	87	11.55	(0.29, 64.35)	7.72	(0.20, 43.03)
Solifenacin	175	17,648	35,940	4.87	(4.17, 5.65)	5.12	(4.38, 5.94)
Trospium	34	2,691	7,562	4.50	(3.11, 6.28)	4.48	(3.10, 6.26)
Fesoterodine	11	1,279	1,700	6.47	(3.23, 11.58)	7.01	(3.46, 12.60)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	244	15,878	38,852	6.28	(5.52, 7.12)	6.37	(5.59, 7.22)
Oxybutynin	85	5,955	13,935	6.10	(4.87, 7.54)	6.67	(5.32, 8.24)
Tolterodine	83	5,134	15,523	5.35	(4.26, 6.63)	5.17	(4.11, 6.40)
Darifenacin	1	16	23	43.34	(1.10, 241.46)	30.83	(0.78, 171.77)
Solifenacin	60	3,791	7,180	8.36	(6.38, 10.76)	8.22	(6.27, 10.58)
Trospium	11	672	1,791	6.14	(3.07, 10.99)	6.40	(3.19, 11.44)
Fesoterodine	4	310	400	10.00	(2.73, 25.61)	10.67	(2.91, 27.31)
Female, aged < 65 years single treated with							
Any OAB drug	462	44,565	111,982	4.13	(3.76, 4.52)	4.20	(3.83, 4.60)
Oxybutynin	135	14,027	32,263	4.18	(3.51, 4.95)	4.34	(3.64, 5.14)
Tolterodine	182	13,645	43,825	4.15	(3.57, 4.80)	4.13	(3.55, 4.77)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	115	13,857	28,760	4.00	(3.30, 4.80)	4.10	(3.39, 4.93)
Trospium	23	2,019	5,771	3.99	(2.53, 5.98)	3.85	(2.44, 5.78)
Fesoterodine	7	969	1,300	5.39	(2.17, 11.10)	5.81	(2.28, 12.07)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	2,398	63,589	150,305	15.95	(15.32, 16.61)	15.72	(15.10, 16.37)
Oxybutynin	854	22,179	48,812	17.50	(16.34, 18.71)	16.93	(15.81, 18.11)
Tolterodine	936	20,971	60,712	15.42	(14.44, 16.44)	15.15	(14.20, 16.16)
Darifenacin	2	87	147	13.62	(1.65, 49.21)	11.78	(0.73, 44.60)
Solifenacin	458	15,989	31,092	14.73	(13.41, 16.14)	15.22	(13.86, 16.69)
Trospium	125	3,305	8,149	15.34	(12.77, 18.28)	15.11	(12.57, 18.01)
Fesoterodine	23	1,058	1,393	16.51	(10.47, 24.78)	15.85	(9.93, 23.95)
Male, aged ≥ 65 years single treated with							
Any OAB drug	1,277	21,941	50,413	25.33	(23.96, 26.76)	25.36	(23.99, 26.79)
Oxybutynin	492	7,798	16,831	29.23	(26.71, 31.93)	29.13	(26.61, 31.83)
Tolterodine	478	7,449	20,877	22.90	(20.89, 25.04)	22.93	(20.92, 25.09)
Darifenacin	1	29	57	17.66	(0.45, 98.40)	11.60	(0.29, 64.62)
Solifenacin	236	5,063	9,304	25.37	(22.23, 28.82)	25.64	(22.47, 29.13)
Trospium	57	1,200	2,839	20.08	(15.21, 26.01)	19.99	(15.13, 25.91)
Fesoterodine	13	402	506	25.70	(13.68, 43.95)	26.13	(13.83, 44.82)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a4. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 4 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	1,121	41,648	99,892	11.22	(10.57, 11.90)	11.21	(10.57, 11.89)
Oxybutynin	362	14,381	31,981	11.32	(10.18, 12.55)	11.21	(10.08, 12.43)
Tolterodine	458	13,522	39,836	11.50	(10.47, 12.60)	11.51	(10.48, 12.61)
Darifenacin	1	58	90	11.09	(0.28, 61.77)	11.86	(0.30, 66.08)
Solifenacin	222	10,926	21,788	10.19	(8.89, 11.62)	10.35	(9.02, 11.80)
Trospium	68	2,105	5,310	12.80	(9.94, 16.23)	12.82	(9.95, 16.25)
Fesoterodine	10	656	887	11.27	(5.41, 20.73)	11.03	(5.14, 20.54)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 4 comprised all PROV-1, CONF-1, CONF-2, and CONF-4 cases.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	3,095	117,077	301,139	10.28	(9.92, 10.65)	10.33	(9.97, 10.70)
Oxybutynin	1,072	40,084	95,010	11.28	(10.62, 11.98)	11.05	(10.40, 11.74)
Tolterodine	1,199	36,902	120,060	9.99	(9.43, 10.57)	9.88	(9.33, 10.46)
Darifenacin	3	142	233	12.85	(2.65, 37.56)	9.81	(1.68, 29.51)
Solifenacin	629	32,056	67,032	9.38	(8.66, 10.15)	10.23	(9.44, 11.06)
Trospium	159	5,633	15,711	10.12	(8.61, 11.82)	9.92	(8.43, 11.59)
Fesoterodine	33	2,260	3,093	10.67	(7.35, 14.99)	11.18	(7.63, 15.79)
Male, single treated with							
Any OAB drug	1,514	35,446	89,265	16.96	(16.12, 17.84)	17.22	(16.37, 18.11)
Oxybutynin	576	12,990	30,766	18.72	(17.22, 20.32)	19.57	(18.01, 21.24)
Tolterodine	559	11,578	36,400	15.36	(14.11, 16.68)	15.34	(14.10, 16.67)
Darifenacin	2	42	80	25.10	(3.04, 90.65)	19.75	(1.51, 73.99)
Solifenacin	293	8,392	16,484	17.77	(15.80, 19.93)	18.07	(16.06, 20.26)
Trospium	68	1,759	4,630	14.69	(11.41, 18.62)	14.22	(11.03, 18.05)
Fesoterodine	16	685	906	17.66	(10.10, 28.69)	18.31	(10.42, 29.80)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	1,581	81,631	211,874	7.46	(7.10, 7.84)	7.60	(7.23, 7.99)
Oxybutynin	496	27,094	64,244	7.72	(7.06, 8.43)	7.67	(7.01, 8.38)
Tolterodine	640	25,324	83,661	7.65	(7.07, 8.27)	7.72	(7.13, 8.34)
Darifenacin	1	100	154	6.51	(0.16, 36.25)	5.84	(0.15, 32.52)
Solifenacin	336	23,664	50,548	6.65	(5.96, 7.40)	7.12	(6.37, 7.93)
Trospium	91	3,874	11,081	8.21	(6.61, 10.08)	8.22	(6.62, 10.09)
Fesoterodine	17	1,575	2,187	7.77	(4.53, 12.45)	8.36	(4.76, 13.53)
Overall, aged < 65 years single treated with							
Any OAB drug	706	60,443	150,834	4.68	(4.34, 5.04)	4.73	(4.39, 5.10)
Oxybutynin	220	19,982	46,198	4.76	(4.15, 5.43)	4.92	(4.28, 5.62)
Tolterodine	265	18,779	59,348	4.47	(3.94, 5.04)	4.38	(3.87, 4.95)
Darifenacin	1	64	87	11.55	(0.29, 64.35)	7.72	(0.20, 43.03)
Solifenacin	175	17,648	35,940	4.87	(4.17, 5.65)	5.12	(4.38, 5.94)
Trospium	34	2,691	7,562	4.50	(3.11, 6.28)	4.48	(3.10, 6.26)
Fesoterodine	11	1,279	1,700	6.47	(3.23, 11.58)	7.01	(3.46, 12.60)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	244	15,878	38,852	6.28	(5.52, 7.12)	6.37	(5.59, 7.22)
Oxybutynin	85	5,955	13,935	6.10	(4.87, 7.54)	6.67	(5.32, 8.24)
Tolterodine	83	5,134	15,523	5.35	(4.26, 6.63)	5.17	(4.11, 6.40)
Darifenacin	1	16	23	43.34	(1.10, 241.46)	30.83	(0.78, 171.77)
Solifenacin	60	3,791	7,180	8.36	(6.38, 10.76)	8.22	(6.27, 10.58)
Trospium	11	672	1,791	6.14	(3.07, 10.99)	6.40	(3.19, 11.44)
Fesoterodine	4	310	400	10.00	(2.73, 25.61)	10.67	(2.91, 27.31)
Female, aged < 65 years single treated with							
Any OAB drug	462	44,565	111,982	4.13	(3.76, 4.52)	4.20	(3.83, 4.60)
Oxybutynin	135	14,027	32,263	4.18	(3.51, 4.95)	4.34	(3.64, 5.14)
Tolterodine	182	13,645	43,825	4.15	(3.57, 4.80)	4.13	(3.55, 4.77)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	115	13,857	28,760	4.00	(3.30, 4.80)	4.10	(3.39, 4.93)
Trospium	23	2,019	5,771	3.99	(2.53, 5.98)	3.85	(2.44, 5.78)
Fesoterodine	7	969	1,300	5.39	(2.17, 11.10)	5.81	(2.28, 12.07)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	2,389	63,589	150,305	15.89	(15.26, 16.54)	15.67	(15.04, 16.31)
Oxybutynin	852	22,179	48,812	17.45	(16.30, 18.67)	16.89	(15.77, 18.07)
Tolterodine	934	20,971	60,712	15.38	(14.41, 16.40)	15.12	(14.17, 16.13)
Darifenacin	2	87	147	13.62	(1.65, 49.21)	11.78	(0.73, 44.60)
Solifenacin	454	15,989	31,092	14.60	(13.29, 16.01)	15.09	(13.73, 16.55)
Trospium	125	3,305	8,149	15.34	(12.77, 18.28)	15.11	(12.57, 18.01)
Fesoterodine	22	1,058	1,393	15.80	(9.90, 23.91)	15.15	(9.37, 23.10)
Male, aged ≥ 65 years single treated with							
Any OAB drug	1,270	21,941	50,413	25.19	(23.83, 26.62)	25.22	(23.85, 26.65)
Oxybutynin	491	7,798	16,831	29.17	(26.65, 31.87)	29.08	(26.56, 31.77)
Tolterodine	476	7,449	20,877	22.80	(20.80, 24.94)	22.84	(20.83, 24.99)
Darifenacin	1	29	57	17.66	(0.45, 98.40)	11.60	(0.29, 64.62)
Solifenacin	233	5,063	9,304	25.04	(21.93, 28.47)	25.32	(22.17, 28.79)
Trospium	57	1,200	2,839	20.08	(15.21, 26.01)	19.99	(15.13, 25.91)
Fesoterodine	12	402	506	23.72	(12.26, 41.44)	23.94	(12.28, 41.94)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.a5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	1,119	41,648	99,892	11.20	(10.56, 11.88)	11.19	(10.55, 11.87)
Oxybutynin	361	14,381	31,981	11.29	(10.15, 12.51)	11.18	(10.05, 12.40)
Tolterodine	458	13,522	39,836	11.50	(10.47, 12.60)	11.51	(10.48, 12.61)
Darifenacin	1	58	90	11.09	(0.28, 61.77)	11.86	(0.30, 66.08)
Solifenacin	221	10,926	21,788	10.14	(8.85, 11.57)	10.30	(8.98, 11.75)
Trospium	68	2,105	5,310	12.80	(9.94, 16.23)	12.82	(9.95, 16.25)
Fesoterodine	10	656	887	11.27	(5.41, 20.73)	11.03	(5.14, 20.54)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	407	117,077	301,139	1.35	(1.22, 1.49)	1.37	(1.24, 1.51)
Oxybutynin	138	40,084	95,010	1.45	(1.22, 1.72)	1.43	(1.20, 1.69)
Tolterodine	164	36,902	120,060	1.37	(1.16, 1.59)	1.36	(1.16, 1.58)
Darifenacin	1	142	233	4.28	(0.11, 23.87)	4.17	(0.11, 23.23)
Solifenacin	75	32,056	67,032	1.12	(0.88, 1.40)	1.28	(1.00, 1.60)
Trospium	27	5,633	15,711	1.72	(1.13, 2.50)	1.68	(1.11, 2.45)
Fesoterodine	2	2,260	3,093	0.65	(0.08, 2.34)	0.63	(0.08, 2.29)
Male, single treated with							
Any OAB drug	189	35,446	89,265	2.12	(1.83, 2.44)	2.16	(1.86, 2.49)
Oxybutynin	64	12,990	30,766	2.08	(1.60, 2.66)	2.18	(1.68, 2.78)
Tolterodine	76	11,578	36,400	2.09	(1.65, 2.61)	2.09	(1.65, 2.62)
Darifenacin	0	42	80	0.00	(0.00, 46.29)	0.00	Not Est.
Solifenacin	37	8,392	16,484	2.24	(1.58, 3.09)	2.34	(1.65, 3.23)
Trospium	11	1,759	4,630	2.38	(1.19, 4.25)	2.20	(1.10, 3.95)
Fesoterodine	1	685	906	1.10	(0.03, 6.15)	1.13	(0.03, 6.30)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	218	81,631	211,874	1.03	(0.90, 1.17)	1.06	(0.92, 1.21)
Oxybutynin	74	27,094	64,244	1.15	(0.90, 1.45)	1.14	(0.89, 1.43)
Tolterodine	88	25,324	83,661	1.05	(0.84, 1.30)	1.07	(0.86, 1.32)
Darifenacin	1	100	154	6.51	(0.16, 36.25)	5.84	(0.15, 32.52)
Solifenacin	38	23,664	50,548	0.75	(0.53, 1.03)	0.85	(0.60, 1.17)
Trospium	16	3,874	11,081	1.44	(0.83, 2.34)	1.47	(0.84, 2.39)
Fesoterodine	1	1,575	2,187	0.46	(0.01, 2.55)	0.44	(0.01, 2.43)
Overall, aged < 65 years single treated with							
Any OAB drug	47	60,443	150,834	0.31	(0.23, 0.41)	0.31	(0.23, 0.42)
Oxybutynin	18	19,982	46,198	0.39	(0.23, 0.62)	0.40	(0.23, 0.63)
Tolterodine	22	18,779	59,348	0.37	(0.23, 0.56)	0.36	(0.22, 0.54)
Darifenacin	0	64	87	0.00	(0.00, 42.60)	0.00	Not Est.
Solifenacin	6	17,648	35,940	0.17	(0.06, 0.36)	0.17	(0.06, 0.38)
Trospium	0	2,691	7,562	0.00	(0.00, 0.49)	0.00	Not Est.
Fesoterodine	1	1,279	1,700	0.59	(0.01, 3.28)	0.66	(0.02, 3.66)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	22	15,878	38,852	0.57	(0.35, 0.86)	0.58	(0.36, 0.87)
Oxybutynin	9	5,955	13,935	0.65	(0.30, 1.23)	0.71	(0.32, 1.35)
Tolterodine	11	5,134	15,523	0.71	(0.35, 1.27)	0.68	(0.34, 1.22)
Darifenacin	0	16	23	0.00	(0.00, 159.87)	0.00	Not Est.
Solifenacin	1	3,791	7,180	0.14	(0.00, 0.78)	0.14	(0.00, 0.76)
Trospium	0	672	1,791	0.00	(0.00, 2.06)	0.00	Not Est.
Fesoterodine	1	310	400	2.50	(0.06, 13.93)	2.67	(0.07, 14.86)
Female, aged < 65 years single treated with							
Any OAB drug	25	44,565	111,982	0.22	(0.14, 0.33)	0.23	(0.15, 0.34)
Oxybutynin	9	14,027	32,263	0.28	(0.13, 0.53)	0.30	(0.14, 0.56)
Tolterodine	11	13,645	43,825	0.25	(0.13, 0.45)	0.25	(0.12, 0.45)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	5	13,857	28,760	0.17	(0.06, 0.41)	0.18	(0.06, 0.43)
Trospium	0	2,019	5,771	0.00	(0.00, 0.64)	0.00	Not Est.
Fesoterodine	0	969	1,300	0.00	(0.00, 2.84)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	360	63,589	150,305	2.40	(2.15, 2.66)	2.37	(2.13, 2.63)
Oxybutynin	120	22,179	48,812	2.46	(2.04, 2.94)	2.42	(2.00, 2.89)
Tolterodine	142	20,971	60,712	2.34	(1.97, 2.76)	2.31	(1.95, 2.73)
Darifenacin	1	87	147	6.81	(0.17, 37.95)	8.08	(0.20, 45.00)
Solifenacin	69	15,989	31,092	2.22	(1.73, 2.81)	2.33	(1.81, 2.95)
Trospium	27	3,305	8,149	3.31	(2.18, 4.82)	3.28	(2.16, 4.78)
Fesoterodine	1	1,058	1,393	0.72	(0.02, 4.00)	0.61	(0.02, 3.40)
Male, aged ≥ 65 years single treated with							
Any OAB drug	167	21,941	50,413	3.31	(2.83, 3.85)	3.32	(2.83, 3.86)
Oxybutynin	55	7,798	16,831	3.27	(2.46, 4.25)	3.26	(2.45, 4.24)
Tolterodine	65	7,449	20,877	3.11	(2.40, 3.97)	3.13	(2.41, 3.99)
Darifenacin	0	29	57	0.00	(0.00, 65.15)	0.00	Not Est.
Solifenacin	36	5,063	9,304	3.87	(2.71, 5.36)	3.97	(2.78, 5.49)
Trospium	11	1,200	2,839	3.87	(1.93, 6.93)	3.83	(1.91, 6.85)
Fesoterodine	0	402	506	0.00	(0.00, 7.29)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.b5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Colorectal Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	193	41,648	99,892	1.93	(1.67, 2.22)	1.93	(1.67, 2.22)
Oxybutynin	65	14,381	31,981	2.03	(1.57, 2.59)	2.02	(1.56, 2.58)
Tolterodine	77	13,522	39,836	1.93	(1.53, 2.42)	1.93	(1.53, 2.42)
Darifenacin	1	58	90	11.09	(0.28, 61.77)	11.86	(0.30, 66.08)
Solifenacin	33	10,926	21,788	1.51	(1.04, 2.13)	1.56	(1.07, 2.19)
Trospium	16	2,105	5,310	3.01	(1.72, 4.89)	3.02	(1.73, 4.91)
Fesoterodine	1	656	887	1.13	(0.03, 6.28)	0.90	(0.02, 4.99)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	98	117,077	301,139	0.33	(0.26, 0.40)	0.33	(0.27, 0.40)
Oxybutynin	34	40,084	95,010	0.36	(0.25, 0.50)	0.35	(0.24, 0.49)
Tolterodine	40	36,902	120,060	0.33	(0.24, 0.45)	0.34	(0.24, 0.46)
Darifenacin	0	142	233	0.00	(0.00, 15.80)	0.00	Not Est.
Solifenacin	20	32,056	67,032	0.30	(0.18, 0.46)	0.32	(0.20, 0.50)
Trospium	3	5,633	15,711	0.19	(0.04, 0.56)	0.18	(0.04, 0.54)
Fesoterodine	1	2,260	3,093	0.32	(0.01, 1.80)	0.47	(0.01, 2.62)
Male, single treated with							
Any OAB drug	37	35,446	89,265	0.41	(0.29, 0.57)	0.42	(0.30, 0.58)
Oxybutynin	17	12,990	30,766	0.55	(0.32, 0.88)	0.58	(0.34, 0.93)
Tolterodine	13	11,578	36,400	0.36	(0.19, 0.61)	0.36	(0.19, 0.61)
Darifenacin	0	42	80	0.00	(0.00, 46.29)	0.00	Not Est.
Solifenacin	6	8,392	16,484	0.36	(0.13, 0.79)	0.37	(0.13, 0.80)
Trospium	1	1,759	4,630	0.22	(0.01, 1.20)	0.18	(0.00, 1.00)
Fesoterodine	0	685	906	0.00	(0.00, 4.07)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	61	81,631	211,874	0.29	(0.22, 0.37)	0.29	(0.23, 0.38)
Oxybutynin	17	27,094	64,244	0.26	(0.15, 0.42)	0.26	(0.15, 0.41)
Tolterodine	27	25,324	83,661	0.32	(0.21, 0.47)	0.33	(0.22, 0.48)
Darifenacin	0	100	154	0.00	(0.00, 24.00)	0.00	Not Est.
Solifenacin	14	23,664	50,548	0.28	(0.15, 0.46)	0.31	(0.17, 0.52)
Trospium	2	3,874	11,081	0.18	(0.02, 0.65)	0.18	(0.02, 0.67)
Fesoterodine	1	1,575	2,187	0.46	(0.01, 2.55)	0.66	(0.02, 3.65)
Overall, aged < 65 years single treated with							
Any OAB drug	15	60,443	150,834	0.10	(0.06, 0.16)	0.10	(0.06, 0.17)
Oxybutynin	5	19,982	46,198	0.11	(0.04, 0.25)	0.12	(0.04, 0.28)
Tolterodine	5	18,779	59,348	0.08	(0.03, 0.20)	0.08	(0.03, 0.19)
Darifenacin	0	64	87	0.00	(0.00, 42.60)	0.00	Not Est.
Solifenacin	4	17,648	35,940	0.11	(0.03, 0.28)	0.12	(0.03, 0.31)
Trospium	1	2,691	7,562	0.13	(0.00, 0.74)	0.14	(0.00, 0.77)
Fesoterodine	0	1,279	1,700	0.00	(0.00, 2.17)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	4	15,878	38,852	0.10	(0.03, 0.26)	0.10	(0.03, 0.27)
Oxybutynin	1	5,955	13,935	0.07	(0.00, 0.40)	0.08	(0.00, 0.44)
Tolterodine	2	5,134	15,523	0.13	(0.02, 0.47)	0.12	(0.02, 0.45)
Darifenacin	0	16	23	0.00	(0.00, 159.87)	0.00	Not Est.
Solifenacin	1	3,791	7,180	0.14	(0.00, 0.78)	0.14	(0.00, 0.76)
Trospium	0	672	1,791	0.00	(0.00, 2.06)	0.00	Not Est.
Fesoterodine	0	310	400	0.00	(0.00, 9.22)	0.00	Not Est.
Female, aged < 65 years single treated with							
Any OAB drug	11	44,565	111,982	0.10	(0.05, 0.18)	0.10	(0.05, 0.18)
Oxybutynin	4	14,027	32,263	0.12	(0.03, 0.32)	0.13	(0.04, 0.34)
Tolterodine	3	13,645	43,825	0.07	(0.01, 0.20)	0.07	(0.01, 0.20)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	3	13,857	28,760	0.10	(0.02, 0.30)	0.11	(0.02, 0.33)
Trospium	1	2,019	5,771	0.17	(0.00, 0.97)	0.18	(0.00, 1.02)
Fesoterodine	0	969	1,300	0.00	(0.00, 2.84)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	83	63,589	150,305	0.55	(0.44, 0.68)	0.55	(0.44, 0.68)
Oxybutynin	29	22,179	48,812	0.59	(0.40, 0.85)	0.57	(0.38, 0.82)
Tolterodine	35	20,971	60,712	0.58	(0.40, 0.80)	0.58	(0.40, 0.80)
Darifenacin	0	87	147	0.00	(0.00, 25.13)	0.00	Not Est.
Solifenacin	16	15,989	31,092	0.51	(0.29, 0.84)	0.52	(0.30, 0.85)
Trospium	2	3,305	8,149	0.25	(0.03, 0.89)	0.23	(0.03, 0.82)
Fesoterodine	1	1,058	1,393	0.72	(0.02, 4.00)	0.92	(0.02, 5.11)
Male, aged ≥ 65 years single treated with							
Any OAB drug	33	21,941	50,413	0.65	(0.45, 0.92)	0.66	(0.45, 0.92)
Oxybutynin	16	7,798	16,831	0.95	(0.54, 1.54)	0.95	(0.54, 1.54)
Tolterodine	11	7,449	20,877	0.53	(0.26, 0.94)	0.53	(0.26, 0.94)
Darifenacin	0	29	57	0.00	(0.00, 65.15)	0.00	Not Est.
Solifenacin	5	5,063	9,304	0.54	(0.17, 1.25)	0.54	(0.17, 1.26)
Trospium	1	1,200	2,839	0.35	(0.01, 1.96)	0.31	(0.01, 1.73)
Fesoterodine	0	402	506	0.00	(0.00, 7.29)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.c5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Pancreatic Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	50	41,648	99,892	0.50	(0.37, 0.66)	0.50	(0.37, 0.66)
Oxybutynin	13	14,381	31,981	0.41	(0.22, 0.70)	0.39	(0.21, 0.67)
Tolterodine	24	13,522	39,836	0.60	(0.39, 0.90)	0.60	(0.39, 0.90)
Darifenacin	0	58	90	0.00	(0.00, 40.90)	0.00	Not Est.
Solifenacin	11	10,926	21,788	0.50	(0.25, 0.90)	0.51	(0.25, 0.92)
Trospium	1	2,105	5,310	0.19	(0.00, 1.05)	0.19	(0.00, 1.03)
Fesoterodine	1	656	887	1.13	(0.03, 6.28)	1.35	(0.03, 7.50)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	364	117,077	301,139	1.21	(1.09, 1.34)	1.22	(1.10, 1.36)
Oxybutynin	138	40,084	95,010	1.45	(1.22, 1.72)	1.42	(1.19, 1.68)
Tolterodine	136	36,902	120,060	1.13	(0.95, 1.34)	1.13	(0.95, 1.34)
Darifenacin	0	142	233	0.00	(0.00, 15.80)	0.00	Not Est.
Solifenacin	71	32,056	67,032	1.06	(0.83, 1.34)	1.15	(0.90, 1.46)
Trospium	18	5,633	15,711	1.15	(0.68, 1.81)	1.13	(0.67, 1.79)
Fesoterodine	1	2,260	3,093	0.32	(0.01, 1.80)	0.36	(0.01, 2.00)
Male, single treated with							
Any OAB drug	162	35,446	89,265	1.81	(1.55, 2.12)	1.85	(1.58, 2.16)
Oxybutynin	71	12,990	30,766	2.31	(1.80, 2.91)	2.41	(1.88, 3.04)
Tolterodine	56	11,578	36,400	1.54	(1.16, 2.00)	1.54	(1.17, 2.01)
Darifenacin	0	42	80	0.00	(0.00, 46.29)	0.00	Not Est.
Solifenacin	27	8,392	16,484	1.64	(1.08, 2.38)	1.70	(1.12, 2.48)
Trospium	7	1,759	4,630	1.51	(0.61, 3.12)	1.51	(0.60, 3.12)
Fesoterodine	1	685	906	1.10	(0.03, 6.15)	1.27	(0.03, 7.06)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	202	81,631	211,874	0.95	(0.83, 1.09)	0.97	(0.84, 1.12)
Oxybutynin	67	27,094	64,244	1.04	(0.81, 1.32)	1.03	(0.80, 1.31)
Tolterodine	80	25,324	83,661	0.96	(0.76, 1.19)	0.97	(0.77, 1.21)
Darifenacin	0	100	154	0.00	(0.00, 24.00)	0.00	Not Est.
Solifenacin	44	23,664	50,548	0.87	(0.63, 1.17)	0.94	(0.68, 1.26)
Trospium	11	3,874	11,081	0.99	(0.50, 1.78)	0.98	(0.49, 1.76)
Fesoterodine	0	1,575	2,187	0.00	(0.00, 1.69)	0.00	Not Est.
Overall, aged < 65 years single treated with							
Any OAB drug	64	60,443	150,834	0.42	(0.33, 0.54)	0.44	(0.34, 0.56)
Oxybutynin	23	19,982	46,198	0.50	(0.32, 0.75)	0.54	(0.34, 0.82)
Tolterodine	18	18,779	59,348	0.30	(0.18, 0.48)	0.30	(0.18, 0.48)
Darifenacin	0	64	87	0.00	(0.00, 42.60)	0.00	Not Est.
Solifenacin	15	17,648	35,940	0.42	(0.23, 0.69)	0.42	(0.23, 0.69)
Trospium	8	2,691	7,562	1.06	(0.46, 2.08)	1.05	(0.45, 2.08)
Fesoterodine	0	1,279	1,700	0.00	(0.00, 2.17)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	10	15,878	38,852	0.26	(0.12, 0.47)	0.26	(0.12, 0.48)
Oxybutynin	4	5,955	13,935	0.29	(0.08, 0.73)	0.31	(0.08, 0.80)
Tolterodine	2	5,134	15,523	0.13	(0.02, 0.47)	0.13	(0.02, 0.46)
Darifenacin	0	16	23	0.00	(0.00, 159.87)	0.00	Not Est.
Solifenacin	2	3,791	7,180	0.28	(0.03, 1.01)	0.27	(0.03, 0.99)
Trospium	2	672	1,791	1.12	(0.14, 4.03)	1.16	(0.14, 4.18)
Fesoterodine	0	310	400	0.00	(0.00, 9.22)	0.00	Not Est.
Female, aged < 65 years single treated with							
Any OAB drug	54	44,565	111,982	0.48	(0.36, 0.63)	0.50	(0.37, 0.65)
Oxybutynin	19	14,027	32,263	0.59	(0.35, 0.92)	0.62	(0.37, 0.97)
Tolterodine	16	13,645	43,825	0.37	(0.21, 0.59)	0.36	(0.21, 0.59)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	13	13,857	28,760	0.45	(0.24, 0.77)	0.47	(0.25, 0.80)
Trospium	6	2,019	5,771	1.04	(0.38, 2.26)	1.02	(0.37, 2.22)
Fesoterodine	0	969	1,300	0.00	(0.00, 2.84)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	300	63,589	150,305	2.00	(1.78, 2.24)	1.97	(1.75, 2.21)
Oxybutynin	115	22,179	48,812	2.36	(1.95, 2.83)	2.26	(1.87, 2.72)
Tolterodine	118	20,971	60,712	1.94	(1.61, 2.33)	1.92	(1.59, 2.30)
Darifenacin	0	87	147	0.00	(0.00, 25.13)	0.00	Not Est.
Solifenacin	56	15,989	31,092	1.80	(1.36, 2.34)	1.85	(1.40, 2.41)
Trospium	10	3,305	8,149	1.23	(0.59, 2.26)	1.21	(0.58, 2.22)
Fesoterodine	1	1,058	1,393	0.72	(0.02, 4.00)	0.70	(0.02, 3.91)
Male, aged ≥ 65 years single treated with							
Any OAB drug	152	21,941	50,413	3.02	(2.55, 3.53)	3.02	(2.56, 3.54)
Oxybutynin	67	7,798	16,831	3.98	(3.09, 5.06)	3.95	(3.06, 5.02)
Tolterodine	54	7,449	20,877	2.59	(1.94, 3.37)	2.59	(1.94, 3.38)
Darifenacin	0	29	57	0.00	(0.00, 65.15)	0.00	Not Est.
Solifenacin	25	5,063	9,304	2.69	(1.74, 3.97)	2.75	(1.78, 4.07)
Trospium	5	1,200	2,839	1.76	(0.57, 4.11)	1.77	(0.57, 4.14)
Fesoterodine	1	402	506	1.98	(0.05, 11.01)	2.20	(0.06, 12.25)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.d5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of the Lung and Bronchus Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	148	41,648	99,892	1.48	(1.25, 1.74)	1.48	(1.25, 1.74)
Oxybutynin	48	14,381	31,981	1.50	(1.11, 1.99)	1.47	(1.08, 1.95)
Tolterodine	64	13,522	39,836	1.61	(1.24, 2.05)	1.61	(1.24, 2.06)
Darifenacin	0	58	90	0.00	(0.00, 40.90)	0.00	Not Est.
Solifenacin	31	10,926	21,788	1.42	(0.97, 2.02)	1.43	(0.97, 2.03)
Trospium	5	2,105	5,310	0.94	(0.31, 2.20)	0.94	(0.31, 2.20)
Fesoterodine	0	656	887	0.00	(0.00, 4.16)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	136	117,077	301,139	0.45	(0.38, 0.53)	0.46	(0.38, 0.54)
Oxybutynin	44	40,084	95,010	0.46	(0.34, 0.62)	0.46	(0.33, 0.62)
Tolterodine	49	36,902	120,060	0.41	(0.30, 0.54)	0.41	(0.30, 0.54)
Darifenacin	0	142	233	0.00	(0.00, 15.80)	0.00	Not Est.
Solifenacin	36	32,056	67,032	0.54	(0.38, 0.74)	0.57	(0.40, 0.79)
Trospium	4	5,633	15,711	0.25	(0.07, 0.65)	0.25	(0.07, 0.64)
Fesoterodine	3	2,260	3,093	0.97	(0.20, 2.84)	1.24	(0.24, 3.67)
Male, single treated with							
Any OAB drug	38	35,446	89,265	0.43	(0.30, 0.58)	0.43	(0.31, 0.59)
Oxybutynin	16	12,990	30,766	0.52	(0.30, 0.84)	0.54	(0.31, 0.88)
Tolterodine	13	11,578	36,400	0.36	(0.19, 0.61)	0.36	(0.19, 0.61)
Darifenacin	0	42	80	0.00	(0.00, 46.29)	0.00	Not Est.
Solifenacin	7	8,392	16,484	0.42	(0.17, 0.87)	0.43	(0.17, 0.90)
Trospium	1	1,759	4,630	0.22	(0.01, 1.20)	0.20	(0.01, 1.12)
Fesoterodine	1	685	906	1.10	(0.03, 6.15)	1.27	(0.03, 7.06)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	98	81,631	211,874	0.46	(0.38, 0.56)	0.46	(0.38, 0.57)
Oxybutynin	28	27,094	64,244	0.44	(0.29, 0.63)	0.43	(0.28, 0.62)
Tolterodine	36	25,324	83,661	0.43	(0.30, 0.60)	0.43	(0.30, 0.60)
Darifenacin	0	100	154	0.00	(0.00, 24.00)	0.00	Not Est.
Solifenacin	29	23,664	50,548	0.57	(0.38, 0.82)	0.62	(0.41, 0.90)
Trospium	3	3,874	11,081	0.27	(0.06, 0.79)	0.27	(0.05, 0.78)
Fesoterodine	2	1,575	2,187	0.91	(0.11, 3.30)	1.24	(0.13, 4.51)
Overall, aged < 65 years single treated with							
Any OAB drug	45	60,443	150,834	0.30	(0.22, 0.40)	0.30	(0.22, 0.41)
Oxybutynin	12	19,982	46,198	0.26	(0.13, 0.45)	0.28	(0.14, 0.48)
Tolterodine	18	18,779	59,348	0.30	(0.18, 0.48)	0.31	(0.18, 0.48)
Darifenacin	0	64	87	0.00	(0.00, 42.60)	0.00	Not Est.
Solifenacin	13	17,648	35,940	0.36	(0.19, 0.62)	0.35	(0.18, 0.60)
Trospium	1	2,691	7,562	0.13	(0.00, 0.74)	0.12	(0.00, 0.68)
Fesoterodine	1	1,279	1,700	0.59	(0.01, 3.28)	0.75	(0.02, 4.20)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	4	15,878	38,852	0.10	(0.03, 0.26)	0.10	(0.03, 0.27)
Oxybutynin	1	5,955	13,935	0.07	(0.00, 0.40)	0.08	(0.00, 0.44)
Tolterodine	2	5,134	15,523	0.13	(0.02, 0.47)	0.13	(0.02, 0.46)
Darifenacin	0	16	23	0.00	(0.00, 159.87)	0.00	Not Est.
Solifenacin	1	3,791	7,180	0.14	(0.00, 0.78)	0.13	(0.00, 0.73)
Trospium	0	672	1,791	0.00	(0.00, 2.06)	0.00	Not Est.
Fesoterodine	0	310	400	0.00	(0.00, 9.22)	0.00	Not Est.
Female, aged < 65 years single treated with							
Any OAB drug	41	44,565	111,982	0.37	(0.26, 0.50)	0.37	(0.26, 0.50)
Oxybutynin	11	14,027	32,263	0.34	(0.17, 0.61)	0.34	(0.17, 0.61)
Tolterodine	16	13,645	43,825	0.37	(0.21, 0.59)	0.36	(0.21, 0.59)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	12	13,857	28,760	0.42	(0.22, 0.73)	0.42	(0.22, 0.73)
Trospium	1	2,019	5,771	0.17	(0.00, 0.97)	0.16	(0.00, 0.91)
Fesoterodine	1	969	1,300	0.77	(0.02, 4.29)	1.00	(0.03, 5.57)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	91	63,589	150,305	0.61	(0.49, 0.74)	0.60	(0.48, 0.74)
Oxybutynin	32	22,179	48,812	0.66	(0.45, 0.93)	0.64	(0.44, 0.90)
Tolterodine	31	20,971	60,712	0.51	(0.35, 0.72)	0.51	(0.35, 0.73)
Darifenacin	0	87	147	0.00	(0.00, 25.13)	0.00	Not Est.
Solifenacin	23	15,989	31,092	0.74	(0.47, 1.11)	0.78	(0.49, 1.17)
Trospium	3	3,305	8,149	0.37	(0.08, 1.08)	0.37	(0.08, 1.07)
Fesoterodine	2	1,058	1,393	1.44	(0.17, 5.19)	1.71	(0.18, 6.25)
Male, aged ≥ 65 years single treated with							
Any OAB drug	34	21,941	50,413	0.67	(0.47, 0.94)	0.68	(0.47, 0.94)
Oxybutynin	15	7,798	16,831	0.89	(0.50, 1.47)	0.89	(0.50, 1.46)
Tolterodine	11	7,449	20,877	0.53	(0.26, 0.94)	0.53	(0.26, 0.95)
Darifenacin	0	29	57	0.00	(0.00, 65.15)	0.00	Not Est.
Solifenacin	6	5,063	9,304	0.64	(0.24, 1.40)	0.66	(0.24, 1.43)
Trospium	1	1,200	2,839	0.35	(0.01, 1.96)	0.35	(0.01, 1.94)
Fesoterodine	1	402	506	1.98	(0.05, 11.01)	2.20	(0.06, 12.25)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.e5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Melanoma of the Skin Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	57	41,648	99,892	0.57	(0.43, 0.74)	0.57	(0.43, 0.74)
Oxybutynin	17	14,381	31,981	0.53	(0.31, 0.85)	0.52	(0.30, 0.84)
Tolterodine	20	13,522	39,836	0.50	(0.31, 0.78)	0.50	(0.31, 0.78)
Darifenacin	0	58	90	0.00	(0.00, 40.90)	0.00	Not Est.
Solifenacin	17	10,926	21,788	0.78	(0.45, 1.25)	0.84	(0.49, 1.34)
Trospium	2	2,105	5,310	0.38	(0.05, 1.36)	0.38	(0.05, 1.36)
Fesoterodine	1	656	887	1.13	(0.03, 6.28)	1.48	(0.04, 8.26)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.f5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Breast Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	641	81,612	211,838	3.03	(2.80, 3.27)	3.07	(2.84, 3.32)
Oxybutynin	192	27,088	64,232	2.99	(2.58, 3.44)	3.00	(2.59, 3.46)
Tolterodine	268	25,320	83,652	3.20	(2.83, 3.61)	3.21	(2.84, 3.62)
Darifenacin	0	100	154	0.00	(0.00, 24.00)	0.00	Not Est.
Solifenacin	134	23,659	50,540	2.65	(2.22, 3.14)	2.77	(2.31, 3.28)
Trospium	37	3,872	11,076	3.34	(2.35, 4.60)	3.32	(2.34, 4.58)
Fesoterodine	10	1,573	2,184	4.58	(2.20, 8.42)	4.36	(2.05, 8.10)
Female, aged < 65 years single treated with							
Any OAB drug	245	44,554	111,961	2.19	(1.92, 2.48)	2.22	(1.95, 2.52)
Oxybutynin	62	14,024	32,255	1.92	(1.47, 2.46)	1.99	(1.53, 2.56)
Tolterodine	108	13,641	43,819	2.46	(2.02, 2.98)	2.45	(2.01, 2.96)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	58	13,854	28,754	2.02	(1.53, 2.61)	2.06	(1.56, 2.67)
Trospium	12	2,019	5,770	2.08	(1.07, 3.63)	2.00	(1.03, 3.49)
Fesoterodine	5	968	1,299	3.85	(1.25, 8.98)	3.82	(1.21, 8.97)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.f5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Breast Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	396	41,639	99,878	3.96	(3.58, 4.38)	3.96	(3.58, 4.37)
Oxybutynin	130	14,378	31,977	4.07	(3.40, 4.83)	4.06	(3.39, 4.83)
Tolterodine	160	13,521	39,833	4.02	(3.42, 4.69)	4.02	(3.42, 4.69)
Darifenacin	0	58	90	0.00	(0.00, 40.90)	0.00	Not Est.
Solifenacin	76	10,924	21,786	3.49	(2.75, 4.37)	3.51	(2.76, 4.39)
Trospium	25	2,103	5,306	4.71	(3.05, 6.95)	4.72	(3.06, 6.97)
Fesoterodine	5	655	885	5.65	(1.83, 13.19)	4.94	(1.55, 11.64)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.g5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Corpus Uteri Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	103	60,743	153,507	0.67	(0.55, 0.81)	0.74	(0.60, 0.90)
Oxybutynin	31	20,642	48,076	0.64	(0.44, 0.92)	0.69	(0.46, 0.98)
Tolterodine	46	18,690	60,301	0.76	(0.56, 1.02)	0.82	(0.60, 1.09)
Darifenacin	0	60	95	0.00	(0.00, 38.94)	0.00	Not Est.
Solifenacin	18	17,421	35,877	0.50	(0.30, 0.79)	0.58	(0.34, 0.91)
Trospium	7	2,719	7,513	0.93	(0.37, 1.92)	0.96	(0.38, 1.98)
Fesoterodine	1	1,211	1,645	0.61	(0.02, 3.39)	0.67	(0.02, 3.72)
Female, aged < 65 years single treated with							
Any OAB drug	30	34,473	84,569	0.35	(0.24, 0.51)	0.42	(0.28, 0.60)
Oxybutynin	8	11,147	25,164	0.32	(0.14, 0.63)	0.39	(0.17, 0.76)
Tolterodine	12	10,354	32,810	0.37	(0.19, 0.64)	0.41	(0.21, 0.71)
Darifenacin	0	27	43	0.00	(0.00, 85.48)	0.00	Not Est.
Solifenacin	10	10,717	21,530	0.46	(0.22, 0.85)	0.59	(0.28, 1.09)
Trospium	0	1,425	3,971	0.00	(0.00, 0.93)	0.00	Not Est.
Fesoterodine	0	803	1,052	0.00	(0.00, 3.51)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.g5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Corpus Uteri Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	73	29,065	68,938	1.06	(0.83, 1.33)	1.07	(0.84, 1.35)
Oxybutynin	23	10,321	22,912	1.00	(0.64, 1.51)	1.00	(0.63, 1.51)
Tolterodine	34	9,468	27,492	1.24	(0.86, 1.73)	1.25	(0.86, 1.75)
Darifenacin	0	37	52	0.00	(0.00, 71.53)	0.00	Not Est.
Solifenacin	8	7,361	14,347	0.56	(0.24, 1.10)	0.56	(0.24, 1.10)
Trospium	7	1,439	3,542	1.98	(0.79, 4.07)	1.97	(0.79, 4.07)
Fesoterodine	1	439	594	1.68	(0.04, 9.38)	1.37	(0.03, 7.64)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.h5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Prostate Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, single treated with							
Any OAB drug	755	35,446	89,265	8.46	(7.87, 9.08)	8.58	(7.98, 9.21)
Oxybutynin	283	12,990	30,766	9.20	(8.16, 10.34)	9.62	(8.53, 10.81)
Tolterodine	275	11,578	36,400	7.56	(6.69, 8.50)	7.53	(6.67, 8.48)
Darifenacin	1	42	80	12.55	(0.32, 69.91)	13.07	(0.33, 72.84)
Solifenacin	149	8,392	16,484	9.04	(7.65, 10.61)	9.10	(7.69, 10.68)
Trospium	38	1,759	4,630	8.21	(5.81, 11.27)	7.87	(5.56, 10.82)
Fesoterodine	9	685	906	9.94	(4.54, 18.86)	10.56	(4.80, 20.09)
Male, aged < 65 years single treated with							
Any OAB drug	146	15,878	38,852	3.76	(3.17, 4.42)	3.81	(3.22, 4.48)
Oxybutynin	49	5,955	13,935	3.52	(2.60, 4.65)	3.85	(2.85, 5.09)
Tolterodine	49	5,134	15,523	3.16	(2.34, 4.17)	3.05	(2.25, 4.03)
Darifenacin	1	16	23	43.34	(1.10, 241.46)	30.83	(0.78, 171.77)
Solifenacin	41	3,791	7,180	5.71	(4.10, 7.75)	5.61	(4.02, 7.61)
Trospium	4	672	1,791	2.23	(0.61, 5.72)	2.32	(0.63, 5.95)
Fesoterodine	2	310	400	5.00	(0.61, 18.07)	5.33	(0.65, 19.26)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.h5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Prostate Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged ≥ 65 years single treated with							
Any OAB drug	609	21,941	50,413	12.08	(11.14, 13.08)	12.08	(11.14, 13.08)
Oxybutynin	234	7,798	16,831	13.90	(12.18, 15.80)	13.87	(12.15, 15.77)
Tolterodine	226	7,449	20,877	10.83	(9.46, 12.33)	10.84	(9.47, 12.35)
Darifenacin	0	29	57	0.00	(0.00, 65.15)	0.00	Not Est.
Solifenacin	108	5,063	9,304	11.61	(9.52, 14.02)	11.66	(9.57, 14.08)
Trospium	34	1,200	2,839	11.98	(8.29, 16.74)	11.96	(8.28, 16.72)
Fesoterodine	7	402	506	13.84	(5.56, 28.51)	14.41	(5.74, 29.78)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	386	117,077	301,139	1.28	(1.16, 1.42)	1.28	(1.15, 1.41)
Oxybutynin	152	40,084	95,010	1.60	(1.36, 1.88)	1.54	(1.30, 1.80)
Tolterodine	126	36,902	120,060	1.05	(0.87, 1.25)	1.02	(0.85, 1.22)
Darifenacin	0	142	233	0.00	(0.00, 15.80)	0.00	Not Est.
Solifenacin	85	32,056	67,032	1.27	(1.01, 1.57)	1.41	(1.12, 1.74)
Trospium	17	5,633	15,711	1.08	(0.63, 1.73)	1.10	(0.64, 1.76)
Fesoterodine	6	2,260	3,093	1.94	(0.71, 4.22)	2.04	(0.71, 4.52)
Male, single treated with							
Any OAB drug	244	35,446	89,265	2.73	(2.40, 3.10)	2.78	(2.44, 3.15)
Oxybutynin	99	12,990	30,766	3.22	(2.62, 3.92)	3.36	(2.73, 4.09)
Tolterodine	84	11,578	36,400	2.31	(1.84, 2.86)	2.31	(1.84, 2.86)
Darifenacin	0	42	80	0.00	(0.00, 46.29)	0.00	Not Est.
Solifenacin	50	8,392	16,484	3.03	(2.25, 4.00)	3.05	(2.26, 4.02)
Trospium	7	1,759	4,630	1.51	(0.61, 3.12)	1.58	(0.63, 3.27)
Fesoterodine	4	685	906	4.42	(1.20, 11.31)	4.08	(1.11, 10.47)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	142	81,631	211,874	0.67	(0.56, 0.79)	0.68	(0.58, 0.81)
Oxybutynin	53	27,094	64,244	0.82	(0.62, 1.08)	0.81	(0.61, 1.07)
Tolterodine	42	25,324	83,661	0.50	(0.36, 0.68)	0.51	(0.37, 0.69)
Darifenacin	0	100	154	0.00	(0.00, 24.00)	0.00	Not Est.
Solifenacin	35	23,664	50,548	0.69	(0.48, 0.96)	0.76	(0.53, 1.06)
Trospium	10	3,874	11,081	0.90	(0.43, 1.66)	0.90	(0.43, 1.66)
Fesoterodine	2	1,575	2,187	0.91	(0.11, 3.30)	1.24	(0.13, 4.51)
Overall, aged < 65 years single treated with							
Any OAB drug	67	60,443	150,834	0.44	(0.34, 0.56)	0.44	(0.34, 0.56)
Oxybutynin	26	19,982	46,198	0.56	(0.37, 0.82)	0.56	(0.36, 0.82)
Tolterodine	16	18,779	59,348	0.27	(0.15, 0.44)	0.26	(0.15, 0.42)
Darifenacin	0	64	87	0.00	(0.00, 42.60)	0.00	Not Est.
Solifenacin	17	17,648	35,940	0.47	(0.28, 0.76)	0.52	(0.30, 0.83)
Trospium	6	2,691	7,562	0.79	(0.29, 1.73)	0.82	(0.30, 1.79)
Fesoterodine	2	1,279	1,700	1.18	(0.14, 4.25)	1.41	(0.17, 5.11)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	37	15,878	38,852	0.95	(0.67, 1.31)	0.97	(0.68, 1.33)
Oxybutynin	13	5,955	13,935	0.93	(0.50, 1.60)	1.02	(0.54, 1.74)
Tolterodine	9	5,134	15,523	0.58	(0.27, 1.10)	0.56	(0.26, 1.07)
Darifenacin	0	16	23	0.00	(0.00, 159.87)	0.00	Not Est.
Solifenacin	10	3,791	7,180	1.39	(0.67, 2.56)	1.37	(0.66, 2.51)
Trospium	4	672	1,791	2.23	(0.61, 5.72)	2.33	(0.64, 5.97)
Fesoterodine	1	310	400	2.50	(0.06, 13.93)	2.67	(0.07, 14.86)
Female, aged < 65 years single treated with							
Any OAB drug	30	44,565	111,982	0.27	(0.18, 0.38)	0.27	(0.18, 0.39)
Oxybutynin	13	14,027	32,263	0.40	(0.21, 0.69)	0.41	(0.22, 0.70)
Tolterodine	7	13,645	43,825	0.16	(0.06, 0.33)	0.16	(0.06, 0.33)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	7	13,857	28,760	0.24	(0.10, 0.50)	0.24	(0.10, 0.50)
Trospium	2	2,019	5,771	0.35	(0.04, 1.25)	0.33	(0.04, 1.18)
Fesoterodine	1	969	1,300	0.77	(0.02, 4.29)	1.00	(0.03, 5.57)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	319	63,589	150,305	2.12	(1.90, 2.37)	2.07	(1.85, 2.32)
Oxybutynin	126	22,179	48,812	2.58	(2.15, 3.07)	2.47	(2.05, 2.94)
Tolterodine	110	20,971	60,712	1.81	(1.49, 2.18)	1.75	(1.44, 2.11)
Darifenacin	0	87	147	0.00	(0.00, 25.13)	0.00	Not Est.
Solifenacin	68	15,989	31,092	2.19	(1.70, 2.77)	2.26	(1.75, 2.86)
Trospium	11	3,305	8,149	1.35	(0.67, 2.42)	1.36	(0.68, 2.43)
Fesoterodine	4	1,058	1,393	2.87	(0.78, 7.35)	2.64	(0.63, 6.96)
Male, aged ≥ 65 years single treated with							
Any OAB drug	207	21,941	50,413	4.11	(3.57, 4.71)	4.11	(3.57, 4.71)
Oxybutynin	86	7,798	16,831	5.11	(4.09, 6.31)	5.09	(4.07, 6.28)
Tolterodine	75	7,449	20,877	3.59	(2.83, 4.50)	3.60	(2.83, 4.51)
Darifenacin	0	29	57	0.00	(0.00, 65.15)	0.00	Not Est.
Solifenacin	40	5,063	9,304	4.30	(3.07, 5.85)	4.29	(3.06, 5.84)
Trospium	3	1,200	2,839	1.06	(0.22, 3.09)	1.03	(0.21, 3.01)
Fesoterodine	3	402	506	5.93	(1.22, 17.33)	5.13	(1.06, 14.98)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.i5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Urinary Bladder Cancer Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	112	41,648	99,892	1.12	(0.92, 1.35)	1.12	(0.92, 1.35)
Oxybutynin	40	14,381	31,981	1.25	(0.89, 1.70)	1.24	(0.88, 1.69)
Tolterodine	35	13,522	39,836	0.88	(0.61, 1.22)	0.88	(0.61, 1.22)
Darifenacin	0	58	90	0.00	(0.00, 40.90)	0.00	Not Est.
Solifenacin	28	10,926	21,788	1.29	(0.85, 1.86)	1.31	(0.87, 1.89)
Trospium	8	2,105	5,310	1.51	(0.65, 2.97)	1.51	(0.65, 2.98)
Fesoterodine	1	656	887	1.13	(0.03, 6.28)	1.48	(0.04, 8.26)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	95	117,077	301,139	0.32	(0.26, 0.39)	0.32	(0.26, 0.39)
Oxybutynin	25	40,084	95,010	0.26	(0.17, 0.39)	0.25	(0.16, 0.37)
Tolterodine	40	36,902	120,060	0.33	(0.24, 0.45)	0.33	(0.24, 0.45)
Darifenacin	0	142	233	0.00	(0.00, 15.80)	0.00	Not Est.
Solifenacin	28	32,056	67,032	0.42	(0.28, 0.60)	0.45	(0.30, 0.66)
Trospium	2	5,633	15,711	0.13	(0.02, 0.46)	0.13	(0.02, 0.47)
Fesoterodine	0	2,260	3,093	0.00	(0.00, 1.19)	0.00	Not Est.
Male, single treated with							
Any OAB drug	44	35,446	89,265	0.49	(0.36, 0.66)	0.50	(0.36, 0.67)
Oxybutynin	14	12,990	30,766	0.46	(0.25, 0.76)	0.47	(0.26, 0.79)
Tolterodine	18	11,578	36,400	0.49	(0.29, 0.78)	0.50	(0.29, 0.78)
Darifenacin	0	42	80	0.00	(0.00, 46.29)	0.00	Not Est.
Solifenacin	12	8,392	16,484	0.73	(0.38, 1.27)	0.75	(0.39, 1.31)
Trospium	0	1,759	4,630	0.00	(0.00, 0.80)	0.00	Not Est.
Fesoterodine	0	685	906	0.00	(0.00, 4.07)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	51	81,631	211,874	0.24	(0.18, 0.32)	0.25	(0.18, 0.32)
Oxybutynin	11	27,094	64,244	0.17	(0.09, 0.31)	0.17	(0.08, 0.30)
Tolterodine	22	25,324	83,661	0.26	(0.16, 0.40)	0.27	(0.17, 0.41)
Darifenacin	0	100	154	0.00	(0.00, 24.00)	0.00	Not Est.
Solifenacin	16	23,664	50,548	0.32	(0.18, 0.51)	0.34	(0.19, 0.55)
Trospium	2	3,874	11,081	0.18	(0.02, 0.65)	0.18	(0.02, 0.66)
Fesoterodine	0	1,575	2,187	0.00	(0.00, 1.69)	0.00	Not Est.
Overall, aged < 65 years single treated with							
Any OAB drug	25	60,443	150,834	0.17	(0.11, 0.24)	0.17	(0.11, 0.24)
Oxybutynin	7	19,982	46,198	0.15	(0.06, 0.31)	0.15	(0.06, 0.30)
Tolterodine	8	18,779	59,348	0.13	(0.06, 0.27)	0.13	(0.06, 0.26)
Darifenacin	0	64	87	0.00	(0.00, 42.60)	0.00	Not Est.
Solifenacin	10	17,648	35,940	0.28	(0.13, 0.51)	0.30	(0.14, 0.55)
Trospium	0	2,691	7,562	0.00	(0.00, 0.49)	0.00	Not Est.
Fesoterodine	0	1,279	1,700	0.00	(0.00, 2.17)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	12	15,878	38,852	0.31	(0.16, 0.54)	0.31	(0.16, 0.54)
Oxybutynin	5	5,955	13,935	0.36	(0.12, 0.84)	0.39	(0.13, 0.91)
Tolterodine	3	5,134	15,523	0.19	(0.04, 0.56)	0.19	(0.04, 0.55)
Darifenacin	0	16	23	0.00	(0.00, 159.87)	0.00	Not Est.
Solifenacin	4	3,791	7,180	0.56	(0.15, 1.43)	0.56	(0.15, 1.45)
Trospium	0	672	1,791	0.00	(0.00, 2.06)	0.00	Not Est.
Fesoterodine	0	310	400	0.00	(0.00, 9.22)	0.00	Not Est.
Female, aged < 65 years single treated with							
Any OAB drug	13	44,565	111,982	0.12	(0.06, 0.20)	0.12	(0.06, 0.20)
Oxybutynin	2	14,027	32,263	0.06	(0.01, 0.22)	0.07	(0.01, 0.24)
Tolterodine	5	13,645	43,825	0.11	(0.04, 0.27)	0.11	(0.04, 0.26)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	6	13,857	28,760	0.21	(0.08, 0.45)	0.21	(0.08, 0.46)
Trospium	0	2,019	5,771	0.00	(0.00, 0.64)	0.00	Not Est.
Fesoterodine	0	969	1,300	0.00	(0.00, 2.84)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	70	63,589	150,305	0.47	(0.36, 0.59)	0.46	(0.36, 0.58)
Oxybutynin	18	22,179	48,812	0.37	(0.22, 0.58)	0.36	(0.21, 0.56)
Tolterodine	32	20,971	60,712	0.53	(0.36, 0.74)	0.52	(0.36, 0.74)
Darifenacin	0	87	147	0.00	(0.00, 25.13)	0.00	Not Est.
Solifenacin	18	15,989	31,092	0.58	(0.34, 0.91)	0.60	(0.36, 0.95)
Trospium	2	3,305	8,149	0.25	(0.03, 0.89)	0.26	(0.03, 0.92)
Fesoterodine	0	1,058	1,393	0.00	(0.00, 2.65)	0.00	Not Est.
Male, aged ≥ 65 years single treated with							
Any OAB drug	32	21,941	50,413	0.63	(0.43, 0.90)	0.64	(0.43, 0.90)
Oxybutynin	9	7,798	16,831	0.53	(0.24, 1.02)	0.54	(0.24, 1.02)
Tolterodine	15	7,449	20,877	0.72	(0.40, 1.19)	0.72	(0.40, 1.19)
Darifenacin	0	29	57	0.00	(0.00, 65.15)	0.00	Not Est.
Solifenacin	8	5,063	9,304	0.86	(0.37, 1.69)	0.89	(0.38, 1.75)
Trospium	0	1,200	2,839	0.00	(0.00, 1.30)	0.00	Not Est.
Fesoterodine	0	402	506	0.00	(0.00, 7.29)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.j5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Cancer of Kidney and Renal System Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	38	41,648	99,892	0.38	(0.27, 0.52)	0.38	(0.27, 0.52)
Oxybutynin	9	14,381	31,981	0.28	(0.13, 0.53)	0.27	(0.12, 0.52)
Tolterodine	17	13,522	39,836	0.43	(0.25, 0.68)	0.43	(0.25, 0.69)
Darifenacin	0	58	90	0.00	(0.00, 40.90)	0.00	Not Est.
Solifenacin	10	10,926	21,788	0.46	(0.22, 0.84)	0.47	(0.22, 0.87)
Trospium	2	2,105	5,310	0.38	(0.05, 1.36)	0.38	(0.05, 1.36)
Fesoterodine	0	656	887	0.00	(0.00, 4.16)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, single treated with							
Any OAB drug	110	117,077	301,139	0.37	(0.30, 0.44)	0.37	(0.30, 0.45)
Oxybutynin	35	40,084	95,010	0.37	(0.26, 0.51)	0.37	(0.26, 0.52)
Tolterodine	55	36,902	120,060	0.46	(0.35, 0.60)	0.45	(0.34, 0.59)
Darifenacin	1	142	233	4.28	(0.11, 23.87)	1.91	(0.05, 10.64)
Solifenacin	13	32,056	67,032	0.19	(0.10, 0.33)	0.22	(0.12, 0.37)
Trospium	6	5,633	15,711	0.38	(0.14, 0.83)	0.38	(0.14, 0.83)
Fesoterodine	0	2,260	3,093	0.00	(0.00, 1.19)	0.00	Not Est.
Male, single treated with							
Any OAB drug	45	35,446	89,265	0.50	(0.37, 0.67)	0.51	(0.37, 0.68)
Oxybutynin	12	12,990	30,766	0.39	(0.20, 0.68)	0.41	(0.21, 0.71)
Tolterodine	24	11,578	36,400	0.66	(0.42, 0.98)	0.65	(0.42, 0.97)
Darifenacin	1	42	80	12.55	(0.32, 69.91)	6.68	(0.17, 37.22)
Solifenacin	5	8,392	16,484	0.30	(0.10, 0.71)	0.33	(0.11, 0.76)
Trospium	3	1,759	4,630	0.65	(0.13, 1.89)	0.67	(0.14, 1.97)
Fesoterodine	0	685	906	0.00	(0.00, 4.07)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, single treated with							
Any OAB drug	65	81,631	211,874	0.31	(0.24, 0.39)	0.31	(0.24, 0.40)
Oxybutynin	23	27,094	64,244	0.36	(0.23, 0.54)	0.36	(0.22, 0.54)
Tolterodine	31	25,324	83,661	0.37	(0.25, 0.53)	0.38	(0.26, 0.53)
Darifenacin	0	100	154	0.00	(0.00, 24.00)	0.00	Not Est.
Solifenacin	8	23,664	50,548	0.16	(0.07, 0.31)	0.18	(0.08, 0.35)
Trospium	3	3,874	11,081	0.27	(0.06, 0.79)	0.26	(0.05, 0.77)
Fesoterodine	0	1,575	2,187	0.00	(0.00, 1.69)	0.00	Not Est.
Overall, aged < 65 years single treated with							
Any OAB drug	22	60,443	150,834	0.15	(0.09, 0.22)	0.15	(0.09, 0.22)
Oxybutynin	10	19,982	46,198	0.22	(0.10, 0.40)	0.23	(0.11, 0.43)
Tolterodine	9	18,779	59,348	0.15	(0.07, 0.29)	0.14	(0.07, 0.28)
Darifenacin	0	64	87	0.00	(0.00, 42.60)	0.00	Not Est.
Solifenacin	1	17,648	35,940	0.03	(0.00, 0.16)	0.02	(0.00, 0.14)
Trospium	2	2,691	7,562	0.26	(0.03, 0.96)	0.27	(0.03, 0.97)
Fesoterodine	0	1,279	1,700	0.00	(0.00, 2.17)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Male, aged < 65 years single treated with							
Any OAB drug	9	15,878	38,852	0.23	(0.11, 0.44)	0.23	(0.11, 0.45)
Oxybutynin	3	5,955	13,935	0.22	(0.04, 0.63)	0.23	(0.05, 0.68)
Tolterodine	5	5,134	15,523	0.32	(0.10, 0.75)	0.31	(0.10, 0.72)
Darifenacin	0	16	23	0.00	(0.00, 159.87)	0.00	Not Est.
Solifenacin	0	3,791	7,180	0.00	(0.00, 0.51)	0.00	Not Est.
Trospium	1	672	1,791	0.56	(0.01, 3.11)	0.58	(0.01, 3.25)
Fesoterodine	0	310	400	0.00	(0.00, 9.22)	0.00	Not Est.
Female, aged < 65 years single treated with							
Any OAB drug	13	44,565	111,982	0.12	(0.06, 0.20)	0.12	(0.06, 0.21)
Oxybutynin	7	14,027	32,263	0.22	(0.09, 0.45)	0.23	(0.09, 0.47)
Tolterodine	4	13,645	43,825	0.09	(0.02, 0.23)	0.09	(0.02, 0.23)
Darifenacin	0	48	64	0.00	(0.00, 58.08)	0.00	Not Est.
Solifenacin	1	13,857	28,760	0.03	(0.00, 0.19)	0.03	(0.00, 0.18)
Trospium	1	2,019	5,771	0.17	(0.00, 0.97)	0.16	(0.00, 0.91)
Fesoterodine	0	969	1,300	0.00	(0.00, 2.84)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Overall, aged ≥ 65 years single treated with							
Any OAB drug	88	63,589	150,305	0.59	(0.47, 0.72)	0.58	(0.47, 0.72)
Oxybutynin	25	22,179	48,812	0.51	(0.33, 0.76)	0.50	(0.33, 0.75)
Tolterodine	46	20,971	60,712	0.76	(0.55, 1.01)	0.75	(0.55, 1.00)
Darifenacin	1	87	147	6.81	(0.17, 37.95)	3.70	(0.09, 20.61)
Solifenacin	12	15,989	31,092	0.39	(0.20, 0.67)	0.40	(0.21, 0.70)
Trospium	4	3,305	8,149	0.49	(0.13, 1.26)	0.49	(0.13, 1.25)
Fesoterodine	0	1,058	1,393	0.00	(0.00, 2.65)	0.00	Not Est.
Male, aged ≥ 65 years single treated with							
Any OAB drug	36	21,941	50,413	0.71	(0.50, 0.99)	0.72	(0.50, 0.99)
Oxybutynin	9	7,798	16,831	0.53	(0.24, 1.02)	0.54	(0.25, 1.02)
Tolterodine	19	7,449	20,877	0.91	(0.55, 1.42)	0.91	(0.55, 1.42)
Darifenacin	1	29	57	17.66	(0.45, 98.40)	11.60	(0.29, 64.62)
Solifenacin	5	5,063	9,304	0.54	(0.17, 1.25)	0.56	(0.18, 1.32)
Trospium	2	1,200	2,839	0.70	(0.09, 2.54)	0.74	(0.09, 2.68)
Fesoterodine	0	402	506	0.00	(0.00, 7.29)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N4.k5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Non-Hodgkin Lymphoma Endpoint Definition 5 for Single Exposed Category, by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Female, aged ≥ 65 years single treated with							
Any OAB drug	52	41,648	99,892	0.52	(0.39, 0.68)	0.52	(0.39, 0.68)
Oxybutynin	16	14,381	31,981	0.50	(0.29, 0.81)	0.49	(0.28, 0.80)
Tolterodine	27	13,522	39,836	0.68	(0.45, 0.99)	0.68	(0.45, 0.98)
Darifenacin	0	58	90	0.00	(0.00, 40.90)	0.00	Not Est.
Solifenacin	7	10,926	21,788	0.32	(0.13, 0.66)	0.33	(0.13, 0.67)
Trospium	2	2,105	5,310	0.38	(0.05, 1.36)	0.37	(0.04, 1.34)
Fesoterodine	0	656	887	0.00	(0.00, 4.16)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Maximum dose (mg)							
≤ 5	529	11,123	27,295	19.38	(17.76, 21.11)	18.54	(16.98, 20.20)
> 5 to 10	248	4,980	14,200	17.46	(15.36, 19.78)	18.52	(16.28, 20.99)
> 10	45	1,127	3,423	13.15	(9.59, 17.59)	17.10	(12.31, 23.07)
Cumulative dose (mg)							
≤ 200	334	15,369	16,464	20.29	(18.17, 22.58)	20.79	(18.62, 23.15)
> 200 to 1,000	308	9,887	17,592	17.51	(15.61, 19.58)	18.09	(16.12, 20.23)
> 1,000	180	4,004	10,863	16.57	(14.24, 19.18)	15.72	(13.50, 18.20)
Number of prescriptions							
1	390	15,369	20,773	18.77	(16.96, 20.73)	20.29	(18.33, 22.41)
2-3	176	8,505	9,457	18.61	(15.96, 21.57)	18.68	(16.02, 21.66)
4-5	75	5,381	3,556	21.09	(16.59, 26.44)	19.70	(15.48, 24.72)
6-9	65	4,138	3,470	18.73	(14.46, 23.88)	17.40	(13.41, 22.19)
10+	116	2,976	7,663	15.14	(12.51, 18.16)	13.86	(11.44, 16.64)
Cumulative duration							
1 - 45 days	387	15,369	20,775	18.63	(16.82, 20.58)	20.14	(18.18, 22.25)
46 - 180 days	271	8,539	13,960	19.41	(17.17, 21.87)	18.94	(16.75, 21.33)
181 - 365 days	70	3,799	4,226	16.56	(12.91, 20.93)	15.04	(11.71, 19.02)
> 365 days	94	2,348	5,956	15.78	(12.75, 19.31)	14.60	(11.79, 17.89)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin (continued)							
Time since first exposure							
1 - 45 days	75	15,369	1,862	40.27	(31.67, 50.48)	41.50	(32.64, 52.02)
46 - 180 days	168	14,825	5,173	32.48	(27.75, 37.78)	33.54	(28.66, 39.01)
181 - 365 days	127	13,271	6,260	20.29	(16.91, 24.14)	20.89	(17.41, 24.85)
> 365 days	452	11,437	31,623	14.29	(13.01, 15.67)	14.24	(12.96, 15.62)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Maximum dose (mg)							
≤ 3.5	67	1,577	3,956	16.94	(13.13, 21.51)	13.86	(10.65, 17.71)
> 3.5	774	12,912	49,897	15.51	(14.44, 16.64)	15.39	(14.33, 16.52)
Cumulative dose (mg)							
≤ 200	347	14,076	21,602	16.06	(14.42, 17.85)	16.85	(15.12, 18.72)
> 200 to 1,300	329	8,589	21,275	15.46	(13.84, 17.23)	15.33	(13.71, 17.08)
> 1,300	165	3,270	10,976	15.03	(12.83, 17.51)	12.72	(10.84, 14.83)
Number of prescriptions							
1	341	14,076	21,559	15.82	(14.18, 17.59)	17.11	(15.34, 19.03)
2-3	172	8,623	10,918	15.75	(13.49, 18.29)	16.10	(13.78, 18.69)
4-5	77	5,910	4,642	16.59	(13.09, 20.73)	16.02	(12.62, 20.05)
6-9	76	4,783	5,091	14.93	(11.76, 18.68)	13.53	(10.65, 16.95)
10+	175	3,520	11,643	15.03	(12.89, 17.43)	12.52	(10.72, 14.54)
Cumulative duration							
1 - 45 days	318	14,076	19,927	15.96	(14.25, 17.81)	17.00	(15.18, 18.98)
46 - 180 days	285	9,035	17,433	16.35	(14.51, 18.36)	16.58	(14.71, 18.62)
181 - 365 days	88	4,651	6,151	14.31	(11.47, 17.63)	12.87	(10.32, 15.86)
> 365 days	150	3,130	10,342	14.50	(12.28, 17.02)	12.18	(10.29, 14.30)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine (continued)							
Time since first exposure							
1 - 45 days	67	14,076	1,717	39.02	(30.24, 49.56)	40.22	(31.14, 51.11)
46 - 180 days	142	13,769	4,918	28.87	(24.32, 34.03)	29.27	(24.65, 34.51)
181 - 365 days	110	12,883	6,253	17.59	(14.46, 21.20)	17.61	(14.47, 21.22)
> 365 days	522	11,791	40,965	12.74	(11.67, 13.88)	12.39	(11.35, 13.50)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Maximum dose (mg)							
≤ 7.5	4	129	227	17.61	(4.80, 45.10)	16.12	(4.01, 42.09)
> 7.5	4	56	136	29.41	(8.01, 75.30)	29.00	(7.84, 74.39)
Cumulative dose (mg)							
≤ 400	2	152	94	21.32	(2.58, 77.02)	24.44	(1.28, 93.25)
> 400 to 1,400	3	108	105	28.46	(5.87, 83.16)	26.29	(5.37, 76.96)
> 1,400	3	64	164	18.31	(3.77, 53.50)	17.76	(3.16, 53.12)
Number of prescriptions							
1	2	152	89	22.56	(2.73, 81.50)	22.22	(2.42, 81.06)
2-3	2	110	77	25.96	(3.14, 93.77)	24.17	(2.41, 88.83)
4-5	2	79	25	78.85	(9.55, 284.85)	73.90	(6.57, 274.04)
6-9	1	65	45	22.22	(0.56, 123.80)	18.77	(0.48, 104.56)
10+	1	46	127	7.87	(0.20, 43.85)	5.66	(0.14, 31.55)
Cumulative duration							
1 - 45 days	3	152	102	29.42	(6.07, 85.97)	32.28	(4.62, 99.27)
46 - 180 days	3	103	109	27.59	(5.69, 80.63)	25.34	(4.71, 75.31)
181 - 365 days	1	58	59	17.07	(0.43, 95.10)	15.81	(0.40, 88.09)
> 365 days	1	34	94	10.66	(0.27, 59.40)	7.18	(0.18, 40.01)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin (continued)							
Time since first exposure							
1 - 45 days	0	152	19	0.00	(0.00, 198.43)	0.00	Not Est.
46 - 180 days	1	147	50	19.97	(0.51, 111.28)	23.31	(0.59, 129.87)
181 - 365 days	1	125	58	17.16	(0.43, 95.62)	12.90	(0.33, 71.89)
> 365 days	6	108	236	25.40	(9.32, 55.29)	22.15	(7.90, 48.63)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Maximum dose (mg)							
≤ 5	369	11,099	20,454	18.04	(16.25, 19.98)	17.79	(16.02, 19.70)
> 5	138	3,898	9,128	15.12	(12.70, 17.86)	14.99	(12.58, 17.73)
Cumulative dose (mg)							
≤ 200	170	12,438	8,217	20.69	(17.69, 24.04)	21.50	(18.39, 24.99)
> 200 to 1,800	237	9,054	13,770	17.21	(15.09, 19.55)	17.25	(15.12, 19.60)
> 1,800	100	3,544	7,594	13.17	(10.71, 16.02)	11.90	(9.68, 14.48)
Number of prescriptions							
1	185	12,438	9,563	19.35	(16.66, 22.34)	20.64	(17.77, 23.84)
2-3	127	8,530	6,202	20.48	(17.07, 24.36)	20.98	(17.48, 24.96)
4-5	38	5,996	2,953	12.87	(9.11, 17.67)	12.75	(9.00, 17.52)
6-9	63	4,800	3,409	18.48	(14.20, 23.64)	17.49	(13.43, 22.39)
10+	94	3,505	7,455	12.61	(10.19, 15.43)	10.95	(8.84, 13.41)
Cumulative duration							
1 - 45 days	193	12,438	9,413	20.50	(17.71, 23.61)	21.41	(18.49, 24.66)
46 - 180 days	163	8,598	9,680	16.84	(14.35, 19.63)	17.11	(14.58, 19.95)
181 - 365 days	71	4,681	4,165	17.05	(13.31, 21.50)	16.04	(12.52, 20.24)
> 365 days	80	3,051	6,324	12.65	(10.03, 15.74)	11.22	(8.89, 13.97)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin (continued)							
Time since first exposure							
1 - 45 days	62	12,438	1,505	41.20	(31.59, 52.82)	42.52	(32.56, 54.56)
46 - 180 days	118	11,946	4,132	28.56	(23.64, 34.20)	28.70	(23.75, 34.39)
181 - 365 days	75	10,494	4,897	15.32	(12.05, 19.20)	15.29	(12.02, 19.17)
> 365 days	252	8,846	19,048	13.23	(11.65, 14.97)	12.94	(11.39, 14.65)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Maximum dose (mg)							
≤ 40	173	2,599	9,991	17.32	(14.83, 20.10)	16.24	(13.91, 18.86)
> 40	8	642	637	12.55	(5.42, 24.73)	12.38	(5.27, 24.51)
Cumulative dose (mg)							
≤ 1,150	39	3,173	1,686	23.13	(16.45, 31.62)	22.35	(15.88, 30.57)
> 1,150 to 8,000	106	2,774	6,250	16.96	(13.89, 20.51)	16.35	(13.37, 19.79)
> 8,000	36	884	2,692	13.37	(9.37, 18.51)	11.60	(8.08, 16.12)
Number of prescriptions							
1	86	3,173	4,390	19.59	(15.67, 24.19)	19.08	(15.25, 23.57)
2-3	36	1,945	2,150	16.75	(11.73, 23.19)	16.70	(11.68, 23.15)
4-5	17	1,269	925	18.38	(10.71, 29.43)	16.94	(9.81, 27.21)
6-9	11	987	1,040	10.58	(5.28, 18.92)	9.47	(4.67, 17.05)
10+	31	681	2,123	14.60	(9.92, 20.72)	12.21	(8.20, 17.45)
Cumulative duration							
1 - 45 days	84	3,173	4,220	19.90	(15.88, 24.64)	19.35	(15.43, 23.96)
46 - 180 days	59	1,966	3,499	16.86	(12.84, 21.75)	16.04	(12.19, 20.72)
181 - 365 days	17	908	1,135	14.98	(8.73, 23.98)	13.60	(7.87, 21.85)
> 365 days	21	580	1,774	11.84	(7.33, 18.10)	10.13	(6.20, 15.60)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium (continued)							
Time since first exposure							
1 - 45 days	13	3,173	385	33.79	(17.99, 57.78)	32.19	(17.10, 55.10)
46 - 180 days	30	3,054	1,061	28.28	(19.08, 40.37)	27.40	(18.46, 39.14)
181 - 365 days	23	2,708	1,284	17.91	(11.35, 26.87)	16.91	(10.71, 25.40)
> 365 days	115	2,375	7,898	14.56	(12.02, 17.48)	13.57	(11.19, 16.31)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Maximum dose (mg)							
4	30	1,315	1,608	18.66	(12.59, 26.63)	18.13	(12.23, 25.88)
> 4	10	453	669	14.94	(7.16, 27.47)	13.64	(6.50, 25.15)
Cumulative dose (mg)							
≤ 200	18	1,487	760	23.68	(14.04, 37.43)	23.11	(13.68, 36.55)
> 200 to 1,000	14	1,014	951	14.71	(8.04, 24.69)	15.21	(8.18, 25.72)
> 1,000	8	440	566	14.14	(6.10, 27.86)	13.33	(5.74, 26.29)
Number of prescriptions							
1	15	1,487	779	19.25	(10.78, 31.75)	19.21	(10.75, 31.70)
2-3	11	998	559	19.67	(9.82, 35.20)	20.10	(9.90, 36.17)
4-5	5	674	274	18.26	(5.93, 42.62)	15.06	(4.82, 35.30)
6-9	4	499	263	15.20	(4.14, 38.92)	13.21	(3.60, 33.83)
10+	5	315	402	12.43	(4.04, 29.01)	11.84	(3.84, 27.63)
Cumulative duration							
1 - 45 days	16	1,487	808	19.81	(11.32, 32.16)	19.38	(11.07, 31.49)
46 - 180 days	16	982	854	18.74	(10.71, 30.44)	19.45	(10.88, 31.93)
181 - 365 days	3	474	320	9.37	(1.93, 27.38)	8.57	(1.76, 25.05)
> 365 days	5	267	296	16.91	(5.49, 39.47)	15.91	(5.15, 37.15)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Males by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine (continued)							
Time since first exposure							
1 - 45 days	5	1,487	179	27.95	(9.08, 65.23)	27.34	(8.87, 63.81)
46 - 180 days	15	1,409	479	31.32	(17.53, 51.66)	30.34	(16.98, 50.05)
181 - 365 days	7	1,191	538	13.01	(5.23, 26.81)	13.38	(5.32, 27.69)
> 365 days	13	936	1,082	12.02	(6.40, 20.55)	11.68	(6.20, 19.99)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin							
Maximum dose (mg)							
≤ 5	605	26,278	71,660	8.44	(7.78, 9.14)	7.92	(7.29, 8.58)
> 5 to 10	242	9,750	28,913	8.37	(7.35, 9.49)	8.52	(7.48, 9.67)
> 10	47	2,226	6,923	6.79	(4.99, 9.03)	7.97	(5.70, 10.79)
Cumulative dose (mg)							
≤ 200	370	34,278	44,358	8.34	(7.51, 9.24)	8.25	(7.43, 9.13)
> 200 to 1,000	299	20,777	39,252	7.62	(6.78, 8.53)	7.54	(6.71, 8.44)
> 1,000	225	8,282	23,885	9.42	(8.23, 10.73)	8.53	(7.44, 9.75)
Number of prescriptions							
1	397	34,278	50,616	7.84	(7.09, 8.65)	8.08	(7.30, 8.92)
2-3	194	18,775	22,262	8.71	(7.53, 10.03)	8.56	(7.40, 9.86)
4-5	64	11,805	8,355	7.66	(5.90, 9.78)	7.11	(5.47, 9.09)
6-9	76	9,186	8,347	9.10	(7.17, 11.40)	8.42	(6.61, 10.56)
10+	163	6,554	17,915	9.10	(7.76, 10.61)	7.93	(6.72, 9.29)
Cumulative duration							
1 - 45 days	399	34,278	50,716	7.87	(7.11, 8.68)	8.06	(7.29, 8.89)
46 - 180 days	273	18,768	33,106	8.25	(7.30, 9.28)	7.96	(7.04, 8.97)
181 - 365 days	102	8,309	9,855	10.35	(8.44, 12.56)	9.73	(7.90, 11.84)
> 365 days	120	5,084	13,818	8.68	(7.20, 10.38)	7.28	(5.99, 8.75)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Oxybutynin (continued)							
Time since first exposure							
1 - 45 days	37	34,278	4,174	8.87	(6.24, 12.22)	8.85	(6.22, 12.22)
46 - 180 days	123	33,371	11,768	10.45	(8.69, 12.47)	10.50	(8.72, 12.54)
181 - 365 days	122	30,407	14,403	8.47	(7.03, 10.11)	8.43	(6.99, 10.07)
> 365 days	612	26,375	77,151	7.93	(7.32, 8.59)	7.59	(7.00, 8.22)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine							
Maximum Dose (mg)							
≤ 3.5	96	4,000	11,496	8.35	(6.76, 10.20)	7.44	(5.96, 9.16)
> 3.5	985	29,317	124,501	7.91	(7.43, 8.42)	7.85	(7.37, 8.36)
Cumulative dose (mg)							
≤ 200	455	32,298	58,052	7.84	(7.13, 8.59)	7.93	(7.22, 8.69)
> 200 to 1,300	390	19,047	52,218	7.47	(6.75, 8.25)	7.46	(6.74, 8.24)
> 1,300	236	7,234	25,726	9.17	(8.04, 10.42)	8.15	(7.12, 9.28)
Number of prescriptions							
1	439	32,298	57,658	7.61	(6.92, 8.36)	7.95	(7.22, 8.73)
2-3	220	19,253	27,398	8.03	(7.00, 9.16)	8.09	(7.05, 9.23)
4-5	75	13,031	11,358	6.60	(5.19, 8.28)	6.44	(5.07, 8.08)
6-9	95	10,535	11,723	8.10	(6.56, 9.91)	7.81	(6.31, 9.55)
10+	252	7,909	27,860	9.05	(7.96, 10.23)	7.79	(6.84, 8.83)
Cumulative duration							
1 - 45 days	405	32,298	53,694	7.54	(6.83, 8.31)	7.72	(6.99, 8.51)
46 - 180 days	340	20,136	43,646	7.79	(6.98, 8.66)	7.85	(7.04, 8.73)
181 - 365 days	114	10,260	14,274	7.99	(6.59, 9.59)	7.53	(6.21, 9.05)
> 365 days	222	6,969	24,383	9.10	(7.95, 10.38)	8.02	(6.97, 9.17)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Tolterodine (continued)							
Time since first exposure							
1 - 45 days	46	32,298	3,953	11.64	(8.52, 15.52)	11.94	(8.74, 15.93)
46 - 180 days	97	31,810	11,453	8.47	(6.87, 10.33)	8.60	(6.97, 10.49)
181 - 365 days	107	30,229	14,762	7.25	(5.94, 8.76)	7.29	(5.97, 8.81)
> 365 days	831	28,065	105,829	7.85	(7.33, 8.40)	7.61	(7.10, 8.15)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin							
Maximum dose (mg)							
≤ 7.5	5	437	863	5.79	(1.88, 13.52)	5.26	(1.70, 12.30)
> 7.5	3	165	441	6.80	(1.40, 19.87)	8.74	(0.94, 27.63)
Cumulative dose (mg)							
≤ 400	1	487	403	2.48	(0.06, 13.83)	2.20	(0.06, 12.27)
> 400 to 1,400	4	333	485	8.25	(2.25, 21.12)	8.17	(2.19, 21.01)
> 1,400	3	159	417	7.20	(1.49, 21.05)	8.55	(1.71, 25.14)
Number of prescriptions							
1	1	487	414	2.42	(0.06, 13.46)	2.11	(0.05, 11.77)
2-3	4	326	337	11.86	(3.23, 30.36)	13.89	(2.96, 37.31)
4-5	0	205	168	0.00	(0.00, 21.97)	0.00	Not Est.
6-9	1	145	145	6.91	(0.18, 38.52)	6.06	(0.15, 33.76)
10+	2	96	240	8.32	(1.01, 30.06)	8.11	(0.98, 29.30)
Cumulative duration							
1 - 45 days	1	487	421	2.38	(0.06, 13.24)	1.98	(0.05, 11.03)
46 - 180 days	4	328	525	7.62	(2.08, 19.52)	7.39	(2.00, 18.95)
181 - 365 days	3	133	169	17.73	(3.66, 51.81)	17.48	(3.60, 51.10)
> 365 days	0	76	190	0.00	(0.00, 19.46)	0.00	Not Est.

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Darifenacin (continued)							
Time since first exposure							
1 - 45 days	0	487	59	0.00	(0.00, 62.50)	0.00	Not Est.
46 - 180 days	1	467	164	6.08	(0.15, 33.89)	5.79	(0.15, 32.24)
181 - 365 days	2	415	196	10.21	(1.24, 36.90)	9.50	(1.15, 34.33)
> 365 days	5	356	885	5.65	(1.83, 13.18)	5.58	(1.80, 13.04)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin							
Maximum dose (mg)							
≤ 5	526	33,304	70,252	7.49	(6.86, 8.16)	7.54	(6.91, 8.22)
> 5	192	9,979	25,709	7.47	(6.45, 8.60)	7.91	(6.81, 9.14)
Cumulative dose (mg)							
≤ 200	227	35,946	29,964	7.58	(6.62, 8.63)	8.09	(7.07, 9.22)
> 200 to 1,800	312	25,193	42,759	7.30	(6.51, 8.15)	7.52	(6.71, 8.40)
> 1,800	179	10,022	23,238	7.70	(6.62, 8.92)	7.20	(6.18, 8.35)
Number of prescriptions							
1	253	35,946	33,674	7.51	(6.62, 8.50)	8.22	(7.23, 9.31)
2-3	130	23,843	19,771	6.58	(5.49, 7.81)	6.87	(5.74, 8.17)
4-5	68	16,802	9,498	7.16	(5.56, 9.08)	7.34	(5.69, 9.32)
6-9	98	13,501	10,188	9.62	(7.81, 11.72)	9.50	(7.70, 11.59)
10+	169	9,946	22,829	7.40	(6.33, 8.61)	6.71	(5.73, 7.81)
Cumulative duration							
1 - 45 days	243	35,946	32,827	7.40	(6.50, 8.39)	7.96	(6.99, 9.03)
46 - 180 days	218	24,272	31,132	7.00	(6.10, 8.00)	7.30	(6.36, 8.35)
181 - 365 days	107	13,154	12,589	8.50	(6.97, 10.27)	8.37	(6.85, 10.12)
> 365 days	150	8,670	19,413	7.73	(6.54, 9.07)	7.07	(5.97, 8.30)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Solifenacin (continued)							
Time since first exposure							
1 - 45 days	40	35,946	4,375	9.14	(6.53, 12.45)	9.59	(6.84, 13.08)
46 - 180 days	99	34,933	12,290	8.06	(6.55, 9.81)	8.57	(6.96, 10.45)
181 - 365 days	113	31,635	14,930	7.57	(6.24, 9.10)	7.91	(6.51, 9.52)
> 365 days	466	27,286	64,366	7.24	(6.60, 7.93)	7.28	(6.63, 7.97)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium							
Maximum dose (mg)							
≤ 40	225	6,662	28,307	7.95	(6.94, 9.06)	7.56	(6.60, 8.62)
> 40	15	1,461	1,616	9.28	(5.19, 15.31)	8.95	(4.98, 14.82)
Cumulative dose (mg)							
≤ 1,150	31	7,908	4,373	7.09	(4.82, 10.06)	7.17	(4.86, 10.19)
> 1,150 to 8,000	142	7,006	18,604	7.63	(6.43, 9.00)	7.36	(6.20, 8.68)
> 8,000	67	2,123	6,946	9.65	(7.47, 12.25)	8.71	(6.73, 11.09)
Number of prescriptions							
1	91	7,908	13,178	6.91	(5.56, 8.48)	6.84	(5.50, 8.40)
2-3	49	4,643	6,228	7.87	(5.82, 10.40)	7.56	(5.59, 10.00)
4-5	24	3,002	2,529	9.49	(6.08, 14.12)	9.29	(5.91, 13.88)
6-9	20	2,337	2,421	8.26	(5.05, 12.76)	7.59	(4.63, 11.74)
10+	56	1,721	5,568	10.06	(7.60, 13.06)	9.04	(6.79, 11.79)
Cumulative duration							
1 - 45 days	98	7,908	13,041	7.51	(6.10, 9.16)	7.36	(5.97, 8.98)
46 - 180 days	71	4,621	9,407	7.55	(5.90, 9.52)	7.33	(5.72, 9.25)
181 - 365 days	28	2,170	2,922	9.58	(6.37, 13.85)	9.00	(5.94, 13.06)
> 365 days	43	1,417	4,554	9.44	(6.83, 12.72)	8.16	(5.90, 11.00)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Trospium (continued)							
Time since first exposure							
1 - 45 days	8	7,908	963	8.31	(3.59, 16.38)	8.40	(3.61, 16.59)
46 - 180 days	24	7,674	2,712	8.85	(5.67, 13.17)	8.71	(5.57, 12.98)
181 - 365 days	25	7,035	3,388	7.38	(4.78, 10.89)	7.12	(4.60, 10.51)
> 365 days	183	6,358	22,861	8.00	(6.89, 9.25)	7.56	(6.50, 8.74)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine							
Maximum dose (mg)							
4	40	3,829	5,187	7.71	(5.51, 10.50)	8.11	(5.76, 11.09)
> 4	9	1,381	2,287	3.93	(1.80, 7.47)	4.35	(1.86, 8.46)
Cumulative dose (mg)							
≤ 200	19	4,342	2,608	7.28	(4.39, 11.38)	7.59	(4.52, 11.92)
> 200 to 1,000	21	2,931	3,019	6.96	(4.31, 10.63)	7.65	(4.61, 11.86)
> 1,000	9	1,283	1,847	4.87	(2.23, 9.25)	5.31	(2.37, 10.17)
Number of prescriptions							
1	25	4,342	2,799	8.93	(5.78, 13.19)	9.10	(5.82, 13.54)
2-3	10	2,822	1,737	5.76	(2.76, 10.59)	6.94	(3.15, 13.04)
4-5	3	1,865	765	3.92	(0.81, 11.46)	5.60	(0.83, 17.15)
6-9	4	1,444	869	4.60	(1.25, 11.78)	5.01	(1.31, 12.95)
10+	7	949	1,305	5.37	(2.16, 11.05)	5.18	(2.05, 10.72)
Cumulative duration							
1 - 45 days	21	4,342	2,789	7.53	(4.66, 11.51)	7.86	(4.80, 12.10)
46 - 180 days	14	2,846	2,700	5.18	(2.83, 8.70)	5.76	(3.04, 9.84)
181 - 365 days	9	1,363	1,028	8.76	(4.00, 16.63)	9.75	(4.36, 18.67)
> 365 days	5	758	957	5.22	(1.70, 12.19)	4.85	(1.55, 11.37)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N5. Person-time, Frequency, and Incidence Rates (per 1,000 Person-years) of Composite Cancer Endpoint Definition 5 for Females by Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)[a]	Standardized Incidence Rate[b]	(95% CI)[c]
Fesoterodine (continued)							
Time since first exposure							
1 - 45 days	3	4,342	526	5.71	(1.18, 16.68)	5.06	(1.04, 14.81)
46 - 180 days	10	4,168	1,434	6.98	(3.34, 12.83)	6.87	(3.27, 12.67)
181 - 365 days	9	3,628	1,657	5.43	(2.48, 10.31)	6.42	(2.84, 12.35)
> 365 days	27	2,897	3,858	7.00	(4.61, 10.18)	7.51	(4.89, 11.00)

CI = confidence interval; Not Est. = not estimable; OAB = overactive bladder.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

[b] Overall results were standardized to the sex and age distribution of the study cohort person-years; sex-specific results were standardized to the sex-specific age distribution of the study cohort person-years.

[c] Confidence intervals for the standardized incidence rates were calculated using the methods described in Dobson et al. Stat Med. 1991;10:457-62. As these are exact confidence limits based on a Poisson count, an estimate for variance does not exist when no events are observed.

Table N Additional 1. Number of Cases and Incidence Rates (per 1,000 Person-years) for Each Study Cancer Endpoint Definition 5, by Months Since Cohort Entry

	Colon and Rectum			Pancreas			Lung and Bronchus		
Time Since Cohort Entry (Months)	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 6	79	1.39	(1.10, 1.74)	15	0.26	(0.15, 0.44)	79	1.39	(1.10, 1.74)
> 6 to 12	56	1.11	(0.84, 1.44)	16	0.32	(0.18, 0.51)	60	1.19	(0.91, 1.53)
> 12 to 18	63	1.41	(1.08, 1.80)	15	0.34	(0.19, 0.55)	46	1.03	(0.75, 1.37)
> 18 to 24	44	1.12	(0.81, 1.50)	18	0.46	(0.27, 0.72)	40	1.01	(0.72, 1.38)
> 24 to 30	51	1.47	(1.09, 1.93)	10	0.29	(0.14, 0.53)	47	1.35	(1.00, 1.80)
> 30 to 36	44	1.45	(1.05, 1.94)	6	0.20	(0.07, 0.43)	42	1.38	(0.99, 1.86)
> 36 to 42	47	1.77	(1.30, 2.35)	14	0.53	(0.29, 0.88)	35	1.31	(0.92, 1.83)
> 42 to 48	23	1.00	(0.63, 1.50)	6	0.26	(0.10, 0.57)	29	1.26	(0.84, 1.81)
> 48 to 54	25	1.26	(0.81, 1.85)	5	0.25	(0.08, 0.59)	21	1.05	(0.65, 1.61)
> 54 to 60	34	2.00	(1.38, 2.79)	10	0.59	(0.28, 1.08)	20	1.17	(0.72, 1.81)
> 60 to 66	24	1.67	(1.07, 2.48)	6	0.42	(0.15, 0.91)	17	1.18	(0.69, 1.89)
> 66 to 72	17	1.42	(0.83, 2.28)	3	0.25	(0.05, 0.73)	17	1.42	(0.83, 2.28)
> 72 to 78	15	1.55	(0.87, 2.55)	3	0.31	(0.06, 0.90)	9	0.93	(0.42, 1.76)
> 78 to 84	11	1.43	(0.72, 2.56)	4	0.52	(0.14, 1.33)	7	0.91	(0.37, 1.88)
> 84 to 90	4	0.70	(0.19, 1.80)	2	0.35	(0.04, 1.27)	12	2.11	(1.09, 3.68)
> 90 to 96	7	1.80	(0.72, 3.71)	3	0.77	(0.16, 2.26)	7	1.80	(0.72, 3.71)
> 96 to 102	1	0.45	(0.01, 2.51)	2	0.90	(0.11, 3.25)	4	1.80	(0.49, 4.61)
> 102 to 108	0	0.00	(0.00, 4.96)	0	0.00	(0.00, 4.96)	3	4.03	(0.83, 11.79)
Total	545	1.36	(1.25, 1.48)	138	0.35	(0.29, 0.41)	495	1.24	(1.13, 1.35)

CI = confidence interval.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Table N Additional 1. Number of Cases and Incidence Rates (per 1,000 Person-years) for Each Study Cancer Endpoint Definition 5, by Months Since Cohort Entry

	Melanoma of the Skin			Breast (Female)			Corpus Uteri (Female)		
Time Since Cohort Entry (Months)	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 6	26	0.46	(0.30, 0.67)	134	3.37	(2.82, 3.99)	32	1.09	(0.74, 1.54)
> 6 to 12	26	0.51	(0.34, 0.75)	114	3.20	(2.64, 3.84)	21	0.81	(0.50, 1.23)
> 12 to 18	21	0.47	(0.29, 0.72)	102	3.22	(2.62, 3.91)	14	0.61	(0.33, 1.02)
> 18 to 24	14	0.35	(0.19, 0.60)	84	2.99	(2.39, 3.70)	11	0.54	(0.27, 0.97)
> 24 to 30	18	0.52	(0.31, 0.82)	64	2.58	(1.98, 3.29)	12	0.68	(0.35, 1.18)
> 30 to 36	15	0.49	(0.28, 0.81)	75	3.42	(2.69, 4.29)	15	0.96	(0.54, 1.59)
> 36 to 42	11	0.41	(0.21, 0.74)	61	3.17	(2.42, 4.07)	6	0.44	(0.16, 0.96)
> 42 to 48	10	0.43	(0.21, 0.80)	51	3.05	(2.27, 4.01)	7	0.60	(0.24, 1.23)
> 48 to 54	4	0.20	(0.05, 0.51)	39	2.70	(1.92, 3.69)	3	0.30	(0.06, 0.87)
> 54 to 60	7	0.41	(0.17, 0.85)	42	3.39	(2.44, 4.58)	3	0.35	(0.07, 1.02)
> 60 to 66	13	0.90	(0.48, 1.54)	37	3.52	(2.48, 4.85)	4	0.55	(0.15, 1.41)
> 66 to 72	5	0.42	(0.14, 0.98)	17	1.95	(1.13, 3.11)	2	0.33	(0.04, 1.21)
> 72 to 78	2	0.21	(0.02, 0.74)	28	3.93	(2.61, 5.68)	3	0.62	(0.13, 1.81)
> 78 to 84	2	0.26	(0.03, 0.94)	9	1.59	(0.73, 3.03)	1	0.26	(0.01, 1.46)
> 84 to 90	5	0.88	(0.29, 2.05)	16	3.81	(2.18, 6.19)	1	0.35	(0.01, 1.97)
> 90 to 96	2	0.51	(0.06, 1.86)	6	2.10	(0.77, 4.57)	0	0.00	(0.00, 1.92)
> 96 to 102	0	0.00	(0.00, 1.66)	6	3.67	(1.35, 8.00)	1	0.92	(0.02, 5.12)
> 102 to 108	1	1.34	(0.03, 7.49)	1	1.81	(0.05, 10.07)	0	0.00	(0.00, 9.98)
Total	182	0.46	(0.39, 0.53)	886	3.10	(2.90, 3.31)	136	0.67	(0.56, 0.79)

CI = confidence interval.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Table N Additional 1. Number of Cases and Incidence Rates (per 1,000 Person-years) for Each Study Cancer Endpoint Definition 5, by Months Since Cohort Entry

	Prostate (Male)			Urinary Bladder		
Time Since Cohort Entry (Months)	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 6	327	19.34	(17.30, 21.55)	194	3.42	(2.96, 3.94)
> 6 to 12	123	8.28	(6.88, 9.88)	76	1.51	(1.19, 1.88)
> 12 to 18	100	7.69	(6.26, 9.36)	53	1.19	(0.89, 1.55)
> 18 to 24	66	5.80	(4.49, 7.38)	45	1.14	(0.83, 1.53)
> 24 to 30	64	6.50	(5.01, 8.30)	33	0.95	(0.65, 1.34)
> 30 to 36	47	5.52	(4.06, 7.35)	25	0.82	(0.53, 1.21)
> 36 to 42	54	7.32	(5.50, 9.55)	26	0.98	(0.64, 1.43)
> 42 to 48	26	4.09	(2.67, 6.00)	22	0.95	(0.60, 1.44)
> 48 to 54	33	6.05	(4.17, 8.50)	19	0.95	(0.57, 1.49)
> 54 to 60	24	5.17	(3.31, 7.70)	7	0.41	(0.17, 0.85)
> 60 to 66	15	3.86	(2.16, 6.37)	8	0.56	(0.24, 1.09)
> 66 to 72	18	5.60	(3.32, 8.86)	6	0.50	(0.18, 1.09)
> 72 to 78	15	5.83	(3.26, 9.61)	8	0.82	(0.36, 1.63)
> 78 to 84	6	2.96	(1.09, 6.45)	5	0.65	(0.21, 1.52)
> 84 to 90	7	4.70	(1.89, 9.69)	1	0.18	(0.00, 0.98)
> 90 to 96	4	3.89	(1.06, 9.95)	2	0.51	(0.06, 1.86)
> 96 to 102	3	5.12	(1.06, 14.96)	3	1.35	(0.28, 3.95)
> 102 to 108	0	0.00	(0.00, 19.41)	1	1.34	(0.03, 7.49)
Total	932	8.23	(7.71, 8.77)	534	1.34	(1.23, 1.46)

CI = confidence interval.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Table N Additional 1. Number of Cases and Incidence Rates (per 1,000 Person-years) for Each Study Cancer Endpoint Definition 5, by Months Since Cohort Entry

	Kidney and Renal Pelvis			Non-Hodgkin Lymphoma		
Time Since Cohort Entry (Months)	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 6	20	0.35	(0.22, 0.54)	26	0.46	(0.30, 0.67)
> 6 to 12	18	0.36	(0.21, 0.56)	17	0.34	(0.20, 0.54)
> 12 to 18	9	0.20	(0.09, 0.38)	15	0.34	(0.19, 0.55)
> 18 to 24	13	0.33	(0.18, 0.56)	18	0.46	(0.27, 0.72)
> 24 to 30	5	0.14	(0.05, 0.34)	7	0.20	(0.08, 0.42)
> 30 to 36	12	0.39	(0.20, 0.69)	11	0.36	(0.18, 0.65)
> 36 to 42	12	0.45	(0.23, 0.79)	11	0.41	(0.21, 0.74)
> 42 to 48	5	0.22	(0.07, 0.51)	5	0.22	(0.07, 0.51)
> 48 to 54	8	0.40	(0.17, 0.79)	7	0.35	(0.14, 0.72)
> 54 to 60	3	0.18	(0.04, 0.51)	4	0.23	(0.06, 0.60)
> 60 to 66	6	0.42	(0.15, 0.91)	1	0.07	(0.00, 0.39)
> 66 to 72	2	0.17	(0.02, 0.60)	7	0.59	(0.24, 1.21)
> 72 to 78	7	0.72	(0.29, 1.49)	5	0.52	(0.17, 1.20)
> 78 to 84	2	0.26	(0.03, 0.94)	4	0.52	(0.14, 1.33)
> 84 to 90	2	0.35	(0.04, 1.27)	3	0.53	(0.11, 1.54)
> 90 to 96	0	0.00	(0.00, 0.95)	1	0.26	(0.01, 1.43)
> 96 to 102	1	0.45	(0.01, 2.51)	2	0.90	(0.11, 3.25)
> 102 to 108	0	0.00	(0.00, 4.96)	0	0.00	(0.00, 4.96)
Total	125	0.31	(0.26, 0.37)	144	0.36	(0.30, 0.42)

CI = confidence interval.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Table N Additional 2. Number of Cases and Incidence Rates (per 1,000 Person-years) for Each Study Cancer Endpoint Definition 5, by Years Since Cohort Entry

	Colon and Rectum			Pancreas			Lung and Bronchus		
Time Since Cohort Entry (Years)	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 1	135	1.26	(1.06, 1.49)	31	0.29	(0.20, 0.41)	139	1.30	(1.09, 1.53)
> 1 to 2	107	1.27	(1.04, 1.54)	33	0.39	(0.27, 0.55)	86	1.02	(0.82, 1.26)
> 2 to 3	95	1.46	(1.18, 1.78)	16	0.25	(0.14, 0.40)	89	1.37	(1.10, 1.68)
> 3 to 4	70	1.41	(1.10, 1.78)	20	0.40	(0.25, 0.62)	64	1.29	(0.99, 1.64)
> 4 to 5	59	1.60	(1.22, 2.06)	15	0.41	(0.23, 0.67)	41	1.11	(0.80, 1.51)
> 5 to 6	41	1.56	(1.12, 2.11)	9	0.34	(0.16, 0.65)	34	1.29	(0.89, 1.80)
> 6 to 7	26	1.50	(0.98, 2.19)	7	0.40	(0.16, 0.83)	16	0.92	(0.53, 1.50)
> 7 to 8	11	1.15	(0.57, 2.06)	5	0.52	(0.17, 1.22)	19	1.98	(1.19, 3.10)
> 8 to 9	1	0.34	(0.01, 1.88)	2	0.67	(0.08, 2.44)	7	2.36	(0.95, 4.87)
Total	545	1.36	(1.25, 1.48)	138	0.35	(0.29, 0.41)	495	1.24	(1.13, 1.35)

CI = confidence interval.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Table N Additional 2. Number of Cases and Incidence Rates (per 1,000 Person-years) for Each Study Cancer Endpoint Definition 5, by Years Since Cohort Entry

	Melanoma of the Skin			Breast (Female)			Corpus Uteri (Female)		
Time Since Cohort Entry (Years)	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 1	52	0.49	(0.36, 0.64)	248	3.29	(2.89, 3.73)	53	0.95	(0.72, 1.25)
> 1 to 2	35	0.42	(0.29, 0.58)	186	3.11	(2.68, 3.59)	25	0.58	(0.37, 0.85)
> 2 to 3	33	0.51	(0.35, 0.71)	139	2.97	(2.50, 3.51)	27	0.81	(0.53, 1.18)
> 3 to 4	21	0.42	(0.26, 0.65)	112	3.12	(2.56, 3.75)	13	0.51	(0.27, 0.88)
> 4 to 5	11	0.30	(0.15, 0.53)	81	3.02	(2.40, 3.75)	6	0.32	(0.12, 0.70)
> 5 to 6	18	0.68	(0.40, 1.08)	54	2.80	(2.11, 3.66)	6	0.45	(0.17, 0.99)
> 6 to 7	4	0.23	(0.06, 0.59)	37	2.90	(2.04, 3.99)	4	0.46	(0.13, 1.18)
> 7 to 8	7	0.73	(0.29, 1.51)	22	3.12	(1.95, 4.72)	1	0.21	(0.01, 1.17)
> 8 to 9	1	0.34	(0.01, 1.88)	7	3.20	(1.29, 6.60)	1	0.69	(0.02, 3.82)
Total	182	0.46	(0.39, 0.53)	886	3.10	(2.90, 3.31)	136	0.67	(0.56, 0.79)

CI = confidence interval.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Table N Additional 2. Number of Cases and Incidence Rates (per 1,000 Person-years) for Each Study Cancer Endpoint Definition 5, by Years Since Cohort Entry

	Prostate (Male)			Urinary Bladder		
Time Since Cohort Entry (Years)	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 1	450	14.17	(12.89, 15.54)	270	2.52	(2.23, 2.84)
> 1 to 2	166	6.81	(5.81, 7.93)	98	1.16	(0.95, 1.42)
> 2 to 3	111	6.05	(4.98, 7.28)	58	0.89	(0.68, 1.15)
> 3 to 4	80	5.83	(4.62, 7.25)	48	0.97	(0.71, 1.28)
> 4 to 5	57	5.65	(4.28, 7.32)	26	0.70	(0.46, 1.03)
> 5 to 6	33	4.65	(3.20, 6.53)	14	0.53	(0.29, 0.89)
> 6 to 7	21	4.57	(2.83, 6.98)	13	0.75	(0.40, 1.28)
> 7 to 8	11	4.37	(2.18, 7.82)	3	0.31	(0.06, 0.92)
> 8 to 9	3	3.87	(0.80, 11.30)	4	1.35	(0.37, 3.46)
Total	932	8.23	(7.71, 8.77)	534	1.34	(1.23, 1.46)

CI = confidence interval.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Table N Additional 2. Number of Cases and Incidence Rates (per 1,000 Person-years) for Each Study Cancer Endpoint Definition 5, by Years Since Cohort Entry

	Kidney and Renal Pelvis			Non-Hodgkin Lymphoma		
Time Since Cohort Entry (Years)	Events	Crude Incidence Rate	(95% CI)[a]	Events	Crude Incidence Rate	(95% CI)[a]
0 to 1	38	0.35	(0.25, 0.49)	43	0.40	(0.29, 0.54)
> 1 to 2	22	0.26	(0.16, 0.40)	33	0.39	(0.27, 0.55)
> 2 to 3	17	0.26	(0.15, 0.42)	18	0.28	(0.16, 0.44)
> 3 to 4	17	0.34	(0.20, 0.55)	16	0.32	(0.18, 0.52)
> 4 to 5	11	0.30	(0.15, 0.53)	11	0.30	(0.15, 0.53)
> 5 to 6	8	0.30	(0.13, 0.60)	8	0.30	(0.13, 0.60)
> 6 to 7	9	0.52	(0.24, 0.98)	9	0.52	(0.24, 0.98)
> 7 to 8	2	0.21	(0.03, 0.75)	4	0.42	(0.11, 1.07)
> 8 to 9	1	0.34	(0.01, 1.88)	2	0.67	(0.08, 2.44)
Total	125	0.31	(0.26, 0.37)	144	0.36	(0.30, 0.42)

CI = confidence interval.

Note: Cancer definition 5 comprised all CONF-1, CONF-2, and CONF-4 cases; PROV-1 cases were included except for those from linked practices in the validation cohort.

[a] Confidence intervals for the crude incidence rates were calculated using exact Poisson methods.

Table N Additional 3. Extrapolation of Cancer Event Counts in the Validation Sample

Cancer	Number of Observed CONF-1 Events[a]	Scaling Factor	Extrapolated Event Count[b]
Colon and rectum	185	1.55	288
Pancreas	43	2.10	91
Lung and bronchus	148	2.12	314
Melanoma of the skin	59	1.56	92
Breast (female only)	354	1.11	393
Corpus uteri (female only)	43	1.75	76
Prostate (male only)	320	1.26	403
Urinary bladder	170	1.61	275
Kidney and renal pelvis	29	2.80	82
Non-Hodgkin lymphoma	46	1.53	71
Composite	1,397	1.46	2,045

[a] CONF-1 cancer was the first confirmed cancer in the CPRD GOLD database.
[b] For non-integer values, the ceiling function was applied.