Post-Authorization Safety Program—Validation of the Danish Data Resources 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 Danish Study Report

ISN/Protocol No.178-CL-119:

A long-term observational study in the Danish Data Resources 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 2.0, April 22, 2015

ISN/Protocol Number 178-CL-119

NDA Number: 202611

EU MAH: Astellas

EU PAS register no: ENCEPP/SDPP/8441

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Title	Post-Authorization Safety Program—Validation of the Danish Data Resources for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder
Version identifier of the final study report	2.0
Date of last version of the final study report	Version 1.0: March 26, 2015
EU PAS register number	ENCEPP/SDPP/8441
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 for overactive bladder (OAB) (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium). ▪ Describe the patterns of use of OAB medications, including duration of treatments, drug switching, and use of medications as add-on therapy. ▪ Estimate the incidence rates of cardiovascular endpoints in new users of OAB medications by individual OAB medication and overall. ▪ Estimate the incidence rate ratio of cardiovascular endpoints in users of each of the OAB medications compared with tolterodine, a frequently used OAB medication. ▪ Estimate the incidence of an overall composite cancer endpoint (10 cancers, both men and women) and two sex-specific composite 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.
Country(-ies) of study	Denmark
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Marketing authorization holder(s)

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Final Report
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Study #178-CL-119

Report date: April 22, 2015

The following people have reviewed this document and given their approval:

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MD, PhD

Date

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Date

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Astellas (US)

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Global Pharmacovigilance

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1 Abstract

Title: Post-Authorization Safety Program—Validation of the Danish Data Resources for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder

Keywords: cancer, cardiovascular safety, Denmark, pharmacoepidemiology, OAB medications

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 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 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: To describe drug use patterns among users of antimuscarinic drugs, to calculate background rates of cardiovascular and cancer outcomes in this population, and to estimate adjusted measures of association between antimuscarinic drugs and cardiovascular outcomes.

Study design: This was a cohort study conducted with data from multiple Danish registries for patients newly exposed to specified medications to treat OAB: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium.

Setting: This study used information prospectively collected in a set of Danish national registries, linked within Statistics Denmark through the Danish Person Registry number.

Subjects and study size, including dropouts: Patients had at least 12 months of residence in Denmark, 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 and the patient was aged 18 years or older. Patients were excluded if they had a diagnosis of cancer other than non-melanoma skin cancer. The study included all eligible patients and their eligible follow-up time during the study period.

Variables and data sources: Person-time was classified based on prescriptions for individual OAB medications. Exposure was ascertained from the Danish National Prescription Registry, and outcomes were ascertained from the Danish National Registry of Patients and the Danish Cancer Registry.

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

Three composite cancer endpoints were evaluated: an overall composite cancer endpoint (10 cancers, both men and women) and two sex-specific composite cancer endpoints (one for men and one for women). 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:

- Overall composite cancer endpoint: lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, pancreas, prostate, female breast, corpus uteri
- Sex-specific composite cancer endpoint for males: prostate, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, and pancreas
- Sex-specific composite cancer endpoint for 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, characteristics that define elevated cardiovascular and cancer risk, relevant diagnoses related to OAB, health care utilization, and use of other medications were evaluated.

Results: The study population included 72,917 patients; 60% were female. The mean age at cohort entry was 66 years, 9% of the patients were aged 18-44 years, and 59% were aged 65 years or older. The most common index prescriptions for OAB medications were for solifenacin (42%), tolterodine (33%), and trospium (12%). Fesoterodine was the index medication in 8% of the population, darifenacin in 4%, and oxybutynin in 1%. Less than 1% entered the cohort with multiple OAB medications.

The mean duration of therapy episodes ranged between 5.0 months (fesoterodine) and 6.9 months (darifenacin). Around half of the episodes were for a single prescription (from 43% for darifenacin to 54% for tolterodine). For all drugs, approximately 20% of episodes involved two prescriptions, and most of the remaining multiple-prescription episodes involved five or more prescriptions.

Of all episodes, 4% ended with a switch and 3% with an add-on. The most common drug switched to or added was solifenacin. For solifenacin drug episodes, the most common drug switched to or added was tolterodine.

Of the 72,917 patients in the study, 1,698 had an AMI, 637 had a stroke, and 3,488 died of cardiovascular causes. A total of 5,074 patients experienced an event in the MACE definition, and 11,044 died of any cause.

Compared with the overall cohort, 62% of the study population without cardiovascular outcomes was female, and more than 53% was aged 65 years or older. Patients with any of the cardiovascular endpoints were older, and the proportion of males was greater among those with a cardiovascular endpoint than among those without a cardiovascular endpoint.

For current use of any OAB medication, the standardized incidence rate (SIR) (95% confidence interval [CI]) per 1,000 person-years for AMI was 2.7 (2.5-2.9) cases, for

stroke was 1.3 (1.2-1.5), for all-cause mortality was 15.2 (14.8-15.6) and for MACE was 7.8 (7.5-8.1). We did not observe an increased risk of any of the cardiovascular endpoints for any of the individual OAB medications with the age- and sex-adjusted incidence rate ratios (IRRs) or in the multivariate analyses. The same fact was observed when the adjustment was performed with propensity scores.

Overall, 3,475 patients developed study cancers during their follow-up time (1,832 in males and 1,643 in females). The most commonly occurring study cancers were prostate (881; 25.4% of all study cancers), breast (658; 18.9%), lung (534; 15.4%), colorectal (434; 12.5%), and bladder (369; 10.6%). The 3,475 cancer outcomes occurred during 259,072 person-years of follow-up (crude incidence rate, 13.4; 95% CI, 13.0-13.9). The SIR (95% CI) per 1,000 person-years for all study cancers combined for ever exposure to any study OAB medication was 5.4 (5.3-5.6) and was 4.6 (4.4-4.9) among females and 6.2 (6.0-6.5) among males. The SIR (95% CI) per 1,000 person-years for any study cancer ranged from 5.2 (5.0-5.5) for ever use of tolterodine to 6.0 for both fesoterodine (5.4-6.7) and oxybutynin (5.0-7.2). In females, the SIR (95% CI) for the sex-specific composite cancer endpoint ranged from 4.6 (4.3-4.9) for tolterodine to 5.3 (4.5-6.2) for fesoterodine. In males, the SIR (95% CI) for the sex-specific composite cancer endpoint ranged from 5.9 (5.5-6.3) for tolterodine to 6.8 for both darifenacin (5.5-8.3) and fesoterodine (5.7-7.9).

In analyses of individual cancer types, the SIR (95% CI) for prostate cancer in males ever exposed to fesoterodine (6.3; 5.2-7.4) was higher than for those ever exposed to solifenacin (3.4; 3.1-3.7), tolterodine (3.1; 2.8-3.4), or trospium (3.9; 3.3-4.5). The SIR (95% CI) for breast cancer in females ever exposed to fesoterodine (3.2; 2.6-3.9) was higher than that for tolterodine (2.2; 1.9-2.4). In males and females combined, the SIR (95% CI) for colorectal cancer was higher in patients ever exposed to fesoterodine (1.2; 0.9-1.5) than for solifenacin (0.7; 0.6-0.8) and tolterodine (0.7; 0.6-0.8). However, SIRs were again generally similar for patients with single exposure to the various study drugs.

There was no trend of increasing cancer risk with increasing cumulative dose or duration of single exposure for any of the study OAB medications. In general, SIRs tended to decrease over time since time of first exposure and time of last exposure to a single study OAB medication. Taken together, these results do not suggest a cancer-causing effect, which would typically increase with increasing cumulative exposure. The tendency for a decrease in risk to be observed with increasing time since first or last exposure to a single OAB medication suggests a higher risk early during exposure, which could be related to protopathic or detection bias.

Discussion: In this cohort of patients with at least one prescription for an OAB medication, the majority were elderly females using one drug during follow-up. The observed exposure patterns are well suited to detecting acute adverse events for individual OAB medications. For effects potentially driven by moderate to long-term exposure or lag time for clinical manifestation, the ability will depend on the length of drug use and follow-up for each individual OAB medication.

The risk of the targeted cardiovascular endpoints was similar among individual OAB medications and does not suggest a consistently increased risk for any specific OAB medication.

Although some of the analyses suggest a higher risk of composite cancer endpoints among patients receiving fesoterodine prescriptions, results from the single-exposure analysis do not confirm this finding. For the composite endpoint, an increased risk was found during the early exposure period, which could suggest a protopathic bias for some cancers, i.e., a prescription for an OAB medication was used to treat symptoms that were actually early symptoms of cancer, leading to earlier detection.

Marketing Authorization Holder and Program Sponsor: Astellas Pharma Global Development, Inc

Names and affiliations of principal investigators:

[redacted]

2 List of Abbreviations

AMI	acute myocardial infarction
BRCA1	breast cancer 1, early onset gene
BRCA2	breast cancer 2, early onset gene
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
DAMD	Danish General Practice Database
DDD	defined daily dose
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
GP	general practitioner
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HIV	human immunodeficiency virus
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
ICD-8	*International Classification of Diseases, 8th Revision*
IRR	incidence rate ratios
ISPE	International Society for Pharmacoepidemiology
MACE	major adverse cardiac events
NSAID	nonsteroidal anti-inflammatory drug
OAB	overactive bladder

PASS	post-authorization safety study
PPV	positive predictive value
Q*n*	quarter of a calendar year
RTI-HS	RTI Health Solutions, a business unit of RTI International
SD	standard deviation
SDU	University of Southern Denmark (Syddansk University)
SIR	standardized incidence rate
US	United States of America

3 Investigators

The University of Southern Denmark (SDU) is responsible for conducting the study in the Danish data resources.

4 Other Responsible Parties

RTI Health Solutions coordinates the European studies and supports SDU:

- Principal Investigator for the Mirabegron program and coordinator: [redacted], MD MPH, [redacted]
- [redacted], MD, ScD, [redacted]
- [redacted], MD, PhD, MPH, [redacted]

5 Milestones

Milestone	Planned Date	Actual Date	Comments
Submission of study protocol to FDA	Q3 2014 (end of)	February 27, 2015	Version 2.0, dated February 23, 2015
SDU ethics approval	—	Not applicable	See note[a]
Registration of protocol version 2.0 in the EU PAS Register[b]	Q4 2014	March 4, 2015	
Development of statistical analysis plan	October 2014	February 24, 2015	
Submission to FDA of statistical analysis plan	October 2014 (end of)	February 27, 2015	
Start of data collection[c]	Q4 2014	January 2015	
End of data collection[d]	Q4 2014	March 2015	
Final report of validation study results (regulatory milestone)	March 31, 2015		

FDA = Food and Drug Administration; RTI-HS = RTI Health Solutions; SDU = University of Southern Denmark.

[a] Retrospective registry studies do not require ethics committee notification, since they do not fall under the Danish definition of health science research.

[b] The EU PAS Register is a publicly available registry of non-interventional postauthorization safety studies maintained by the European Medicines Agency (http://www.encepp.eu/encepp_studies/indexRegister.shtml).

[c] Start of data extraction.

[d] Analytic data set was completely available.

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 authorizations for mirabegron on June 28, 2012, in the United States and on December 20, 2012, in the European Union. The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) included a postapproval requirement to evaluate cardiovascular safety. The FDA also required a postapproval commitment to evaluate cancer risks. To prepare for a postapproval safety assessment of cardiovascular and cancer risk, a validation study has been designed to describe drug utilization patterns among users of antimuscarinic drugs and calculate background rates of cardiovascular and cancer endpoints among antimuscarinic drug users in the Danish data sources.

This is part of a multinational research program in Denmark, Sweden, the United Kingdom, and the United States.

6.1 Literature Review

6.1.1 Drug Utilization

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

In a study using reimbursed prescriptions from [redacted], Denmark, 66.2% of the individuals prescribed OAB medications were women (mean age, 68.0 years) and 33.8% were men (mean age, 69.0 years).[1] 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.

6.1.2 Cardiovascular Risk Factors in OAB Medication Users

In a study performed in the HealthCore Integrated Research Database and GE Healthcare Database in the US, baseline cardiovascular comorbidity was higher in patients with an OAB diagnosis or treated with OAB antimuscarinic drugs (39%) than in age- and sex-matched patients without codes for either OAB or OAB antimuscarinic treatment (21%).[2] Cardiovascular comorbidities 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 medications with antimuscarinic effect was also higher in the OAB group: 33% vs. 17% for patients without codes for OAB or OAB antimuscarinic treatment. Prevalence of cardiovascular comorbidity was similar in patients with OAB treated with OAB antimuscarinic drugs (39%) and age- and sex-matched patients with OAB with no such treatment (38%). The use of non-OAB medications with antimuscarinic effect was higher in patients treated with OAB antimuscarinic drugs (37% vs. 29% for untreated patients with OAB).

A related study, also in the US (GE Healthcare database), found that patients with OAB treated with OAB antimuscarinics had baseline heart rate distributions similar to those with no such treatment.[3] In this study, treated patients with OAB had a higher proportion of cardiovascular comorbidity (59% vs. 54% for untreated patients), 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).

6.1.3 Outcome Identification and Validation in the Data Sources

Several studies have reported predictive values of codes and algorithms used to identify the endpoints of interest in Danish databases.

Acute Myocardial Infarction

A recent validation study on AMI diagnoses was conducted on the Danish Aarhus University Hospital Database, which comprises a prescription registry, a registry of hospital discharge records, a death registry and various others, which can be linked.[4] AMI was defined as the first occurrence of any ICD-10 code for acute myocardial infarction (code I21) in hospital discharge records in years 1996-2009. Of 200 randomly selected cases, medical charts of 148 cases could be accessed and reviewed; the remaining 52 could not be accessed due to the absence of institutional agreements that would have permitted access to the medical charts. All cases were confirmed (positive predictive value [PPV] = 100%).

A validation study sought to validate codes for acute coronary syndrome in the Danish National Registry of Patients.[5] Cases were patients enrolled in the prospective cohort "Diet, Cancer and Health" aged 50-64 years who had hospital discharge codes for acute coronary syndrome in the primary or secondary positions in years 1993-2003, with no cancer or acute coronary syndrome diagnoses prior to cohort entry. A total of 1,654 potential cases of acute coronary syndrome were identified, of which, medical records for 1,577 were available for review. Of the subset of patients with AMI discharge diagnoses, 1,072 medical charts were reviewed and AMI diagnoses were confirmed in 878 (PPV = 81.9%).

Another study validated cases of hospitalization for AMI in the county of Funen in Denmark.[6] Potential cases were patients with an AMI discharge record in the Hospital Discharge Registry in years 1994-1999 (ICD-10 codes I21-I22, acute and subsequent myocardial infarction). Hospital discharge letters of a random sample of 500 cases were reviewed for validation of the AMI diagnosis, yielding a PPV of 94%.

Another validation study sought to validate fatal AMIs and AMI hospitalizations from the Danish National Registry of Patients, Registry of Cause of Death, and the National Heart Registry, which combines information from the other two.[7] The reference was the DANMONICA study, a multicenter study that monitored AMI incidence, risk factors, and therapy in 1982-1991. Potential cases were AMIs (identified from ICD-8[1] codes) that occurred in those years in inhabitants of a Copenhagen suburb aged 25-74 years. For AMI as the primary discharge diagnosis or underlying cause of death, the PPV was 93.6%. For AMI as primary or secondary discharge diagnosis, or underlying or contributory cause of death, the PPV was 92.4%.

Stroke

A validation study explored the validity of the diagnosis of stroke in the Danish National Registry of Patients.[8] Potential stroke cases were identified as those with ICD-10 codes I61, I63, and I64 (intracerebral hemorrhage, cerebral infarction, and stroke not specified as hemorrhage or infarction, respectively) in patients aged 18 years or older hospitalized in 2009. Of 10,015 potential cases, 7,877 were confirmed against medical records, yielding a PPV of 79%.

[1] ICD-8 - *International Classification of Diseases, 8th Revision.*

Another validation study explored the validity of first-ever stroke in patients enrolled in the prospective Copenhagen City Heart Study.[9] Potential cases were patients with ICD-10 codes I60, I61, I63, or I64 (subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and stroke not specified as hemorrhage or infarction, respectively) in the Danish National Register of Patients in years 1998-1999. Hospital discharge letters, medical records, computed tomography, magnetic resonance imaging, angiography, and autopsy reports were reviewed by two reviewers. Of 164 potential stroke cases, one reviewer confirmed 132 (PPV = 80.5%) and the other reviewer confirmed 141 (PPV = 86.0%).

Another validation study investigated the PPV of stroke diagnoses from the Danish National Registry of Patients in patients enrolled in the prospective cohort study "Diet, Cancer and Health."[10] Potential cases were patients without prior hospitalizations for cardiovascular or cerebrovascular conditions aged 50-64 years with ICD-10 codes I60, I61, I63, or I64 (see description of codes provided previously) in the primary or secondary positions in the National Patient Registry in years 1993-1998 (Copenhagen) or 1993-1999 (Aarhus). Case confirmation was based on review of medical records (including reports from imaging studies and laboratory test results) and hospital discharge letters. The PPV was 79.3% for the 377 potential cases identified.

In a study looking at subarachnoid hemorrhage in relatives of patients who had a subarachnoid hemorrhage in Funen County in years 1977-1995,[11] potential cases identified in the National Patient Registry (ICD-10 codes I60 and analogous ICD-8 codes) were confirmed through review of medical records, discharge abstracts, and autopsy reports. Patients with concurrent codes for arteriovenous malformations were excluded. The authors reported misclassification of less than 20% in the 191 incident events identified, with differences depending on the type of ward from which the patient was discharged (neurosurgery, neurology, or others).

A study that explored the risk of stroke in twins validated stroke diagnoses in the National Discharge Registry against discharge abstracts.[12] Potential cases were twins registered in the Danish Twin Registry and living in Funen County who had codes for stroke in the National Discharge Registry (I61, I63 and I64 ICD-10 codes, and analogous ICD-8 codes) in years 1977-1998. Of 333 potential events identified, records for 288 were accessible, with a PPV of 85%.

Neoplasm Endpoints

One study validated the diagnosis of female breast cancer in the Danish Cancer Registry in residents of Aarhus County.[13] Potential cases were patients with breast cancer records in the Danish Cancer Registry, the Danish Breast Cancer Cooperative Group (which collects information related to breast cancer in clinical trials), and the local oncology department registry (which provided administrative information) in years 1983-1989. Exclusion criteria for validation were information from the death certificate as the sole source; no clinical information; no histopathological diagnosis; previous history of invasive cancer; benign tumors or carcinoma in situ; surgery outside the county; unknown primary tumor; and tumors other than carcinoma. From the 1,749 potential cases, the percentage of clinical information correctly identified in the registry was 99%.

Another study ascertained the validity of brain tumors in a pediatric population in the Danish Cancer Registry for the period 1980-1996.[14] By manual review of medical records for 640 cases reported to the Danish Cancer Registry, 98% of the brain tumors could be verified. The recorded histopathological classification in the Danish Cancer Registry was correct in 82% of cases for which a histopathological diagnosis was available. This proportion varied by histopathological diagnosis and was 84% for astrocytomas, 88% for ependymomas, and 95% for medulloblastomas. Other, more rare tumors had a lower level of accuracy.

A study from 1985 ascertained the coverage (sensitivity) of the Danish Cancer Registry, by cross-referencing all records from 1977 with all cancer diagnoses found in the Danish National Registry of Patients.[15] No case validation was carried out. Of 23,228 cancer cases that were found in either registry, 21,740 (94%) could be found in the Danish Cancer Registry. It should be noted that since 2004, all cancers in the Danish National Registry of Patients are routinely reported to the Danish Cancer Registry.

7 Research Question and Objectives

- Characterize users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) with respect to selected covariates.
- Describe the patterns of use of OAB medications, including duration of treatments, drug switching, and use of medications as add-on therapy.
- Estimate the incidence rates of cardiovascular endpoints in new users of OAB medications by individual OAB medication and overall.
- Estimate the incidence rate ratio of cardiovascular endpoints in users of each of the OAB medications compared with tolterodine, a frequently used OAB medication.
- Estimate the incidence of an overall composite cancer endpoint (10 cancers, both men and women) and two sex-specific composite 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.

8 Amendments and Updates

Version Number	Date	Section(s) of Study Report	Amendment or Update	Reason
Final Study Report, Version 2.0	April 22, 2015	Annex 4. Analysis Results Tables	Updated Table CV5b. Crude and Standardized Incidence Rate Ratios for Stroke, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure	Version 1.0 contained a duplicate of Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure
Final Study Report, Version 1.0	March 26, 2015	This was the original Study Report		

9 Research Methods

To meet the objectives mentioned in Section 7, this study had the following parts, which are detailed in later sections:

- Drug utilization study
  - Characterization of users of OAB medications
  - Description of utilization patterns for OAB medications
- Study of cardiovascular endpoints
- Study of cancer endpoints

9.1 Study Design

This was a retrospective cohort study of adults newly exposed to drugs used to treat OAB conducted on the Danish population in the period of January 1, 2004, through December 31, 2012. The study drugs are oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine. The study had three components: a drug utilization study, a study of cardiovascular endpoints, and a study of cancer endpoints. With this design, we are able to observe the use of the study medications and the development of the endpoints as they occurred and were recorded during routine clinical practice. Data were collected prospectively (even though the study was conducted retrospectively on data already collected), thus eliminating the risk of recall bias. The new user design reduces problems related to depletion of susceptibles.[16]

9.2 Setting

This study used routine health care information from Danish residents collected in a set of registries. The study period was January 1, 2004, through December 31, 2012. Six different national data sources were employed:

- Danish National Registry of Patients
- Danish National Prescription Registry
- Danish Person Registry
- Taxation Registry
- Cause of Death Registry
- Danish Cancer Registry

9.2.1 Linkage Process

All data sources were linked using the Danish Person Registry number, a unique identifier assigned to all Danish residents since 1968 that encodes sex and date of birth. All linkages occur within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes. The first four registries in this list are hosted in Statistics Denmark (data from the other data sources were transferred to Statistics Denmark for linkage for the purpose of this study). Confidentiality is ensured by several layers of password-protected sign-in, use of a real-time password assigned by a remote token, use of de-identified data, and the fact that researchers cannot extract data from Statistics Denmark, only the output of their analyses.[17]

9.3 Subjects

9.3.1 Inclusion Criteria

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

- Have at least 12 months of continuous enrollment in the database, followed by a prescription for oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine, provided that the 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 one or more prescriptions for a different OAB medication at any time prior to the index prescription and may have had one or more prescriptions for the same OAB medication more than 12 months prior to the index prescription.
- Be aged 18 years or older at the time of the index prescription.

9.3.2 Exclusion Criteria

Patients were excluded if they had a diagnosis of cancer other than non-melanoma skin cancer at any time prior to the potential index prescription date.

9.3.3 Considerations When Applying Inclusion/Exclusion Criteria

The first prescription for a study OAB medication found during the study period may or may not be the same as the first prescription that met all of the inclusion/exclusion criteria. For example, a patient may have been aged less than 18 years on the date of that first prescription. If this is the case, subsequent prescriptions were evaluated according to the inclusion/exclusion criteria until finding one that met all criteria. The date of such a qualifying index prescription was defined as the cohort entry date for that patient.

9.3.4 Follow-up

The cohort entry date was defined by the date of the qualifying index prescription for one of the six study medications. Follow-up of eligible patients started on the cohort entry date and finished at the earliest of the following dates:

- End of the study period (i.e., December 31, 2012)
- Death
- Disenrollment from the database (i.e., patient emigrated from Denmark)

In the cardiovascular analysis, person-time allocation was assigned differently for the composite MACE outcome and for sequential targeted events occurring in the same individual. Allocation of person-time for the composite MACE outcome terminated at the date of occurrence of the first targeted cardiovascular event. However, for sequential targeted cardiovascular endpoints occurring in the same individual, person-time at risk continued to accumulate until the date of occurrence of a subsequent targeted cardiovascular event.

For all cancer analyses (for all three composite cancer endpoints), only the first incident targeted cancer was considered; subsequent or sequential targeted cancer events occurring in the same individual were ignored, and person-time was truncated at the occurrence of the first targeted cancer event.

9.4 Variables

9.4.1 Exposure

The study drugs were oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine. These medications were available only as prescription medications during the study period.

9.4.2 Endpoints/Outcomes

9.4.2.1 Cardiovascular Endpoints

Each of the following individual study endpoints was evaluated:

- Acute myocardial infarction (AMI), including out-of-hospital coronary heart disease deaths
- Stroke, including out-of-hospital stroke-related deaths
- Cardiovascular mortality: coronary heart disease death and cerebrovascular disease death
- Composite endpoint, major adverse cardiac events (MACE): nonfatal AMI, nonfatal stroke, and cardiovascular mortality
- All-cause mortality

Cases were identified through hospitalization discharge or outpatient hospital clinic diagnoses in any position in the National Danish Patient Registry. Codes used to identify cardiovascular endpoints are provided in Annex 2.

9.4.2.2 Cancer Endpoints

The cancer cases observed in the mirabegron clinical development program were those that occur commonly in the general population; therefore, the present study focused on composites involving the 10 most commonly occurring malignancies. Because some of these cancers occur exclusively (or nearly exclusively) in either males or females, two sex-specific composite cancer endpoints were evaluated in addition to an overall endpoint. The types of cancer in each composite cancer endpoint are detailed in Table 1. Cases were identified through the Danish Cancer Registry. Codes to identify cancer endpoints are located in Annex 3.

Table 1. Composite Cancer Endpoints

Type of Cancer	Overall	Males	Females
Colon and rectum	Y	Y	Y
Pancreas	Y	Y	Y
Lung & bronchus	Y	Y	Y
Melanoma of the skin	Y	Y	Y
Breast (female only)	Y	N	Y
Corpus uteri	Y	N	Y
Prostate	Y	Y	N
Urinary bladder	Y	Y	Y
Kidney and renal pelvis	Y	Y	Y
Non-Hodgkin lymphoma	Y	Y	Y

9.4.2.3 Covariates

Demographic and enrollment-related covariates were ascertained from the Danish Person Registry, cause of death from the Cause of Death Registry, and income from the Taxation Registry. Prescription-related information was ascertained from dispensed prescriptions in the Danish National Prescription Registry, and diagnoses were based on hospitalization discharge or outpatient hospital clinic diagnoses in any position in the Danish National Registry of Patients.

Some lifestyle factors are relevant for the risk of cardiovascular and cancer outcomes, in particular, smoking, alcohol, and obesity. None of these were expected to be recorded consistently and in a timely manner for all patients. Secondary care diagnoses or recorded drug use were used as proxies for lifestyle factors. For smoking, a diagnosis of chronic obstructive pulmonary disease (COPD) or use of an inhaled anticholinergic or a smoking cessation drug were used. Hospital diagnoses of obesity were used as proxies for obesity; however, use of prescribed weight-loss products were not used as proxies for obesity, as they are likely to have a low positive predictive value. For alcoholism, the included proxies were diagnoses indicating alcohol dependence, as well as organ damage indicated as alcohol related (liver, pancreas, brain, peripheral nerves) and use of drugs to support alcohol abstinence (disulfiram, acamprosate, naltrexone). Finally, adjusting for income may to some extent adjust for potential confounding by lifestyle factors in the analysis. For the diagnosis of OAB, the following ICD-10 codes were used: R32, Unspecified urinary incontinence; N39.3, Stress incontinence; N39.4, Other specified urinary incontinence; R35, Polyuria; and N32.8, Other specified disorders of bladder.

The full list of covariates with the data source, time window for assessment, and some comments is provided in Table 2.

Table 2. Description of Patient Characteristic Variables Available in the Danish Data Resources

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source
Birth or immigration, cohort entry, cohort exit, death or emigration dates	Date	Specific date	Danish Person Registry
Cause of death	ICD-10 codes	Specific date	Cause of Death Registry
Duration of registration prior to cohort entry (days)	Number	Specific period	Danish Person Registry, Danish National Prescription Registry
Duration of follow-up (days)	Number (date of cohort exit minus the date of cohort entry)	Specific period	Danish National Prescription Registry and others, depending on the reason for stopping follow-up
Demographics: age, sex	Age: numerical Sex: binary	Baseline	Danish Person Registry

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source
Socioeconomic characteristics: income	Categorical: specific categories depend on the data structure	Baseline (any time before the cohort entry date)	Taxation Registry
Genes: *BRCA1* and *BRCA2* mutations	—	—	This information is not captured
Functional stage (capabilities for living a normal daily life); proxy for frailty	—	—	This information is not captured
Smoking proxy	Binary	Baseline (any time before the cohort entry date)	Danish National Registry of Patients; Danish National Prescription Registry
Obesity proxy	Obesity: binary	Baseline (any time before the cohort entry date)	Danish National Registry of Patients
Hypertension	Binary	Baseline (any time before the cohort entry date)	Danish National Registry of Patients; Danish National Prescription Registry
Dyslipidemia	Binary	Baseline (any time before the cohort entry date)	Danish National Prescription Registry, based on prescribed treatment
History of AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, pulmonary artery disease	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Diabetes	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients; Danish National Prescription Registry
Family history of the individual cancers: Colon and rectum Pancreas Lung and bronchus Melanoma of the skin Breast (female) Corpus uteri Prostate Urinary bladder Kidney and renal pelvis Non-Hodgkin lymphoma	—	—	This information is not captured

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source
Comorbidities			
Alcohol abuse and related conditions	Binary	Baseline (any time before the cohort entry date) and time varying	The Danish National Registry of Patients, Danish Prescription Registry
Drug abuse	—	—	This information is not captured
Comorbidities included in the Charlson Index	Each comorbidity: binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Renal impairment	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Dialysis	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Fractures	Binary	Time varying and proxy of frailty	The Danish National Registry of Patients
Gout	Binary	Baseline (any time before the cohort entry date)	Danish National Prescription Registry, based on prescribed treatment
Arthritis	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Overactive bladder	—	—	This information is not captured from primary care, only hospital diagnosis
Organ transplantation	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Polycystic ovary syndrome	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Endometrial polyps or other benign growths of the uterine lining	Binary	Baseline (any time before the cohort entry date)	The Danish National Registry of Patients
Prescriptions Hormone-replacement therapy Tamoxifen use Thyroid hormone replacement	Binary	Baseline (any time before the cohort entry date)	Danish Prescription Registry All prescription drugs are fully covered; however, NSAIDs are available over the counter; 83% by volume (DDDs) is recorded

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source
Nitrates, digoxin, antidiabetic drugs, statins Non-aspirin NSAIDs Low-dose aspirin Antiplatelets (including aspirin in low doses) Immunosuppressive agents			in the Danish National Prescription Registry. Low-dose aspirin is also available over the counter; coverage in the Danish National Prescription Registry is 91%
Health services utilization			
Outpatient visits			This information is not captured
Hospitalizations	Numerical	Baseline (12 months)	The Danish National Registry of Patients
Nursing home stay	—	—	This information is not identified although data from nursing homes is captured in the registries
Sigmoidoscopies	Numerical	Baseline (12 months)	The Danish National Registry of Patients
Mammograms	Number	Time varying: per year, starting in the baseline period	This information is not captured

AMI = acute myocardial infarction; *BRCA1* = breast cancer 1, early onset gene; *BRCA2* = breast cancer 2, early onset; DDDs = defined daily doses; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; NSAIDs = nonsteroidal anti-inflammatory drugs.

9.5 Data Sources and Measurement

The following linked data sources were used in this study:

- Danish National Registry of Patients
- Danish National Prescription Registry
- Danish Person Registry
- Taxation Registry
- Cause of Death Registry
- Danish Cancer Registry

9.5.1 Danish National Registry of Patients

The Danish National Registry of Patients contains data on all secondary care (hospital) contacts in Denmark since 1977. From 1995 onward, outpatient hospital clinic diagnoses have been included systematically. Discharge diagnoses were coded according to ICD-8 from 1977 through 1993 and have been coded according to ICD-10 since 1994. Virtually all medical care in Denmark is furnished by the public health authorities, whereby this data resource allows true population-based studies covering all inhabitants of Denmark.[18] Primary and secondary diagnoses were used to identify cardiovascular outcomes and covariates.

9.5.2 Danish National Prescription Registry

The Danish National Prescription Registry contains data on all prescription drugs dispensed to Danish citizens since 1995.[19] The data include the dispensed substance, brand name and quantity of the drug, date of dispensing, age and sex of the drug user, and identifiers for the prescribing physician and the dispensing pharmacy, regardless of whether they were prescribed by GPs or specialists or their reimbursement status.

9.5.3 Danish Person Registry

The Danish Person Registry contains data on vital status (dates of birth and death where appropriate) and migrations in and out of Denmark, thus rendering it possible to censor follow-up appropriately.

9.5.4 Taxation Registry

The Taxation Registry was the source of information about socioeconomic status at the individual level. In the Taxation Registry, disposable income is defined as income for a single family member after taxation and adjustment for the number of family members (http://www.dst.dk/en.aspx). For this study, patients were categorized on the basis of quartiles of disposable income at baseline into low (first quartile), medium (second and third quartile), and high (fourth quartile) income categories.[20]

9.5.5 Cause of Death Registry

The Cause of Death Registry collects information on the underlying and contributing causes of death of all residents of Denmark since 1875. Data are retrieved from death certificates, which are completed by physicians. The physician in charge of the patient at the time of death is required to report the cause of death.[21] For patients who are found dead out of a hospital, their GP completes the death certificate, based on what is known about the patient's medical history. If an autopsy is performed, new diagnoses may be added to the death certificate.

9.5.6 Danish Cancer Registry

The Danish Cancer Registry is population based and contains records of all incidences of new malignant neoplasms in the Danish population from 1943. Reporting to the Danish Cancer Registry has been mandatory since 1987.[22] From 2004, reporting has been mediated via the Danish National Registry of Patients: when a cancer is entered into the Danish National Registry of Patients, the Danish Cancer Registry is automatically notified. Information in the Danish Cancer Registry is cross-referenced against several sources (e.g., the Danish Pathology Registry, the Cause of Death Registry) to ensure completeness and remove duplicates. Additional information regarding, for example, mode of diagnosis or stage at diagnosis, is often requested. Less than 1% of cases in the Danish Cancer Registry are based solely on information from death certificates. Finally, there is an internal validity check of consistency, which may occasionally trigger requests for new information.[23] For the majority of cancer groups, approximately 90% of the tumors were histologically verified, including the major groups such as breast cancer, lung cancer, melanoma, and colon cancer.

9.6 Bias

Outcome identification was performed electronically independently of exposure. Analytical measures to minimize bias 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

9.8.1 Exposure Duration

Individual prescription records do not contain information on the duration of the prescription or data to estimate the prescription duration based on information present in the prescription. Therefore, we employed the waiting-time approach described by Pottegård and Hallas.[24] We calculated the prescription duration for each individual OAB medication using calendar year 2011-2012 as the source and used the 80% cutoff described by Pottegård and Hallas. The result of this analysis is a uniform duration assigned to all prescriptions for a given OAB medication. In brief, this analysis uses a fixed time window (e.g., a calendar year) and analyzes the distribution of first occurrences of the drug within that window. The typical waiting-time distribution will have a high plateau in the first months and then level off at a lower rate of first-time prescriptions. Drugs that are dispensed with short intervals tend to have their first occurrence early in the time window and reach their low equilibrium level early. This can be formalized to an actual estimate of the period of usage for a prescription, as described in the referenced paper.

9.9 Statistical Methods

9.9.1 Main Summary Measures

We used mean and standard deviation (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- and sex–standardized incidence rate (SIR) of cardiovascular and cancer endpoints and IRRs for cardiovascular endpoints. The reference for standardization was the entire Danish population from Statistics Denmark as of January 1, 2008.[25]

9.9.2 Main Statistical Methods

9.9.2.1 Drug Utilization Study

Therapy Episodes

We defined two prescriptions of an OAB medication as belonging to the same therapy episode if the period of duration for the former overlapped the date of dispensing for the second. If there was any gap between prescriptions (even 1 day), the second prescription defined the beginning of a new episode. The duration assigned to single prescriptions or to the last prescription in an episode was identical to the uniform duration from the waiting-time approach.

The Danish prescription database does not contain dose instructions or duration information for the single prescription. Instead, the period of usage for each prescription was modelled by use of the waiting-time distribution.[24] Switching and add-ons were then defined by an overlap between treatment episodes for two different OAB medications, prescribed to the same individual. If the formal overlap was between 1 and 60 days, it was considered a switch and if it was greater than 60 days, it was considered an add-on. These limits were chosen arbitrarily, based on considerations of underlying mechanism. If a patient was switched from one OAB medication to another, for example because of intolerance, we found it likely that some of the dispensed amount for the first drug was not used. Since the Danish data source registers only dispensed medication, not actual periods of ingested medication, this would manifest as an apparent overlap between treatment episodes. This overlap would be limited, as the first prescriptions for the first drug would not be renewed. If, on the other hand, the two drugs were intended to be taken concurrently, the formal overlap between treatment episodes would be much larger.

Dose was expressed using the defined daily dose (DDD).[26] The DDD is established by an expert panel of the World Health Organization as the typical daily the dose when the drug is used for its main indication in an adult. One DDD for two related drugs should thus express equipotent amounts. The DDD methodology entails the possibility of aggregating drug amounts for related drugs of different potency. It is widely used in Europe and is included in the Danish prescription databases.

Descriptive Analysis of Patterns of Drug Use

We summarized baseline characteristics of the study population at the time of cohort entry, including demographic information and data on cardiovascular and cancer risk factors. Comorbidities, use of other medications, and health utilization by subgroups determined by use of OAB medication at cohort entry were analyzed. We also described the use of study drugs prior to cohort entry.

We then described therapy episodes in terms of duration of completed and ongoing episodes, by individual drug. Last, we described, for all therapy episodes stratified by individual drug, duration and number of prescriptions per episode, and of episodes that finished in a drug switch or add-on.

9.9.2.2 Cardiovascular Study

Time at Risk and Exposure Classification

In the cardiovascular study, we were mostly interested in current exposure to individual drugs. The time-at-risk assumption was that any cardiovascular effects of OAB medications would present shortly after first exposure, continue during current exposure, and decline shortly after the medication was discontinued. We defined the following exposure categories:

- *Current exposure* was all follow-up that occurred within an OAB medication therapy episode, as previously described.
- *Recent exposure* started the day after the period of current exposure ended and continued for 60 days or until a new episode of current exposure began.
- *Past exposure* began the day after the period of recent exposure ended and included person-time until the end of the follow-up or a subsequent period of current exposure of the same drug, whichever came first.

Each day of exposed person-time was classified in categories based on specific drug exposure and recency of exposure (i.e., for each category of exposure—current, recent, and past—to each of the six study drugs). Patients contributed person-time to multiple drug exposure categories if they switched treatment.

Statistical Analysis in the Cardiovascular Study

Descriptive Analysis

Baseline characteristics of the study population at the time of cohort entry are stratified by whether they experienced AMI, stroke, cardiovascular mortality, or the composite cardiovascular outcome, along with results of a separate analysis of all-cause death.

Incidence Rates

Person-time accumulated separately for each endpoint. This was done for the four cardiovascular endpoints delimiting four different person-time populations: AMI, stroke, cardiovascular mortality, and the composite endpoint (any of these individual endpoints). In

addition, all-cause mortality was evaluated independently. For each endpoint, person-years, event count, and crude and standardized incidence rates (SIRs) and 95% confidence intervals (CIs) were reported, including incidence rates for each exposure category.

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.

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)

All incidence rates and 95% CIs were calculated per 1,000 person-years, using exact confidence limits for the Poisson distribution.

The impact of various intervals of time since exposure, recency of exposure (e.g., recent exposure or past exposure), duration of exposure, dose, and cumulative dose on the incidence rates was evaluated.

Incidence Rate Ratios

Patients were compared in Cox regression models for each of the exposure-outcome combinations (e.g., separate models were constructed to explore the association of current use of solifenacin relative to current use of tolterodine for the outcome stroke, and the association of current use of trospium relative to current use of tolterodine for the same outcome). This allowed the covariates in each model to take different coefficients and thus better address confounding for each exposure-outcome association. Exposure categories were the same ones used as outcomes in the exposure propensity score model.

To compare the risk of cardiovascular outcomes during periods of treatment with OAB medications, we estimated crude incidence rate ratios (IRRs) and IRRs with 95% CIs standardized by age and sex to the Danish population of same age range.

Adjusted IRRs for each of the OAB medications compared with tolterodine were calculated for each endpoint, individual and composite, using Cox regression models. The process for selecting confounders to include in models is described below.

Regression models were used to estimate the multivariable adjusted IRRs of the cardiovascular endpoints with reference to current exposure to tolterodine. First, individual Cox regression models for each covariate and the exposure variable (current OAB medication exposure) were constructed for each endpoint. For each endpoint, the effect (if any) of each individual covariate on the IRR of current OAB medication exposure compared with tolterodine was measured. In addition, the adjusted IRR was estimated for each OAB medication, with unexposed person-time as the reference group. Additional IRRs calculated as the incidence rate within person-time during current exposure to a particular drug divided by the incidence rate during current exposure to any other drug (i.e., excluding all unexposed person-time) were presented.

The selection of candidate variables to be included in multivariable models was based on biological and clinical considerations. The variables included were Charlson items 1-4 (cardiovascular history); any prior hospital diagnosis of renal failure or dialysis, arthritis, diabetes, COPD, obesity, hypertension, or atrial fibrillation; and any prior prescription of NSAIDs, lipid-lowering drugs, low-dose aspirin, antigout drugs, drugs against COPD, nicotine preparations, drugs for alcohol abstinence, antihypertensives, or antidiabetics; and the patient's disposable income as a crude marker of socioeconomic status.

We estimated risks for current and recent drug use. Models were repeated with reference to use of any OAB medication (e.g., for analysis on oxybutynin, the reference was use of any of the other five drugs) and to no use of any OAB medication (i.e., periods of no use). When analyzing for recent use, we excluded all follow-up classified as current use of any OAB medication, in order to avoid having in our reference group follow-up that was currently exposed to an active OAB medication. Due to the observed patterns of use, this restriction actually entailed removing a small portion of the overall follow-up.

Propensity Score Analysis

For each comparison, e.g., current use of darifenacin versus tolterodine, a multivariate logistic regression model was established that had use of darifenacin (i.e., the non-tolterodine OAB medication) as the dependent variable. The independent variables included in the model were all the baseline characteristics listed in Table A6. A new model was established for each pairwise comparison of OAB medications, but the same propensity score model was applied for all outcomes (stroke, AMI, cardiovascular death, composite endpoint all-cause death), given the choice of comparator drugs. New models were also generated for each pairwise comparison of recent OAB medication use. Thus, 12 different propensity score models were constructed representing exposure propensity at cohort entry (six different sets of comparators, for both current and recent use). None of the models included interaction terms of any order.

All models were trimmed using the asymmetrical trimming approach.[27] In brief, two propensity score limits are set, corresponding to the 2.5 percentile of propensity score for the exposed and the 97.5 percentile for the unexposed. All patients with propensity scores

outside the range established by these two limits, whether exposed or unexposed, are excluded from the analysis. The remaining range of the propensity score was divided into 10 equally broad bands ("deciles"), and a conventional stratified analysis was performed, having the propensity score as the only criterion for stratification and using these deciles. Estimates and confidence intervals were calculated by conventional Mantel-Haenszel techniques for stratified cohort studies.

Stratified Analysis

As described previously, strata for stratified analyses were sex, sex and age 65 or more years, increased risk for cardiovascular disease and sex, and increased risk for cardiovascular disease.

9.9.2.3 Cancer Study

Time at Risk and Exposure Classification in Cancer Study

In the cancer study, we did not distinguish between current, recent, and past exposure. The time-at-risk assumption is that effects of OAB medications on the incidence of neoplasms may continue for a long period of time after the medication is discontinued. Cumulative dose and duration of exposure were of interest because effects associated with cancer, which may be present for a long time before cancer is detected, may be associated with cumulative exposure metrics. Time at risk started with the first prescription representing new exposure to any of the OAB medications.

Exposed person-time was categorized as "ever" or "never" exposed to each of the study medications. Once a person started contributing person-time to any category of exposure, all person-time until the end of follow-up was counted as time subsequent to exposure to that drug. Person-time may have been counted as exposure to more than one drug.

There could have been exposure to OAB medications before the cohort entry date. The entire available look-back period was used to identify exposure to other OAB medications before cohort entry for the purpose of creating a variable identifying history of exposure to each OAB medication.

For the construction of cohorts for exposure to single OAB medications in the cancer study, patients who had no previous exposure to OAB medications during the study period and who entered the cohort of exposure to drug A were considered "exposed" to *single* OAB medication A if they had no records of another OAB medication from the start of the prescription registry (1995) until end of follow-up or had a cancer outcomes as defined above.

Among those ever exposed, exposure was further classified into the following categories, for each individual drug:

- *Cumulative dose* categories were 0-199 DDDs, 200-499 DDDs, 500-999 DDDs, and 1,000 DDDs.
- *Cumulative duration of exposure* in patients ever exposed to each individual drug for 0 to 6 months, > 6 to 12 months, or more than 12 months.

- *Time since discontinuation of the medication or last exposure:* 0 to 6 months, > 6 to 12 months, and more than 12 months.
- *Time since first exposure:* 0 to 6 months, > 6 to 12 months, and by number of years (e.g., 1 year, 2 years, 3 years) thereafter.

Statistical Analysis in the Cancer Study

First, counts of events (any target cancer and individual cancers) were stratified by age and by sex. Then, occurrence of the overall and sex-specific composite cancer endpoints was estimated. The study report summarizes for all OAB medications and for each individual drug the number of enrolled patients, person-time, frequency of endpoints, and crude and sex- and age–standardized incidence rates with 95% CIs. Incidence rates for individual cancers were estimated. Except for uterine, female breast, and prostate cancers, incidence rates for individual cancers were analyzed for males and females combined when adequate. Last, we presented the same counts and incidence rates stratified as described in the paragraph below.

Stratified Analysis

We stratified estimations of crude and standardized incidence rates by categories of exposure described previously (i.e., cumulative dose, time since first exposure, time since last exposure, and cumulative duration of exposure).

9.9.3 Missing Values

Handling of the lack of information on days of supply is described in the data transformation section.

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

Data from the Danish General Practice Database were not available for this project.

Exclusion criteria: HIV diagnosis (Section 9.3.2.). The study protocol and SAP had “diagnosis of human immunodeficiency virus (HIV) infection” as an exclusion criterion in order to align this study with the studies in other data sources. That exclusion was driven by the fact that in some health care systems, HIV 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. This is not the case in Denmark, where finding a recorded HIV diagnosis is not expected due to patient protection practice. Therefore, this exclusion

criterion was not applied in Denmark. In the final review of the cohort, 15 patients with an HIV code were identified.

Some of the analyses in the statistical analysis plan were not performed or were presented in a different way:

- Characteristics of patients newly exposed at cohort entry is presented in Table A6. The SAP called for a table with the characteristics of patients newly exposed to each medication at the time of first exposure, which could be after cohort entry. This second table was not created because it was not considered very informative given the large percentage of patients that were users of a single medication.
- Some patterns of prescribing as described in the SAP could not be analyzed because in Denmark the prescribed dose is not available. Number of prescriptions, daily doses, and users broken out by specific OAB medication, formulation, and quantity could not be calculated.
- The results of the analysis of the association between individual OAB medications and the study endpoints did not show any association. Therefore the same analysis stratified by prior exposure to OAB medications to address drug switching over the course of the study was not conducted.
- Individual case validation was not possible in the Danish study population. Therefore the sensitivity analyses with "confirmed or probable" cases could not be conducted and should not have included in the SAP.
- For neoplasm endpoints, the SAP proposed a sensitivity analysis with a lag time of 180 days. Following findings from another study population in which rates of selected neoplasms varied over the follow-up period, we conducted analysis stratified by follow-up period: 0-6 months, 7-12 months, over 1 year up to 2 years, more than 2 years up to 3 years, more than 3 years.

9.10 Quality Control

Analyses were performed using the statistical software Stata for Windows version 13. The study analysis adhered to the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP).*[28]

Quality control of the data management and analysis activities of this study were performed according to University of Southern Denmark internal process guidance. 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 reflected 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

The analysis tables of results are available in Annex 4. Drug utilization results are in Table A1, A2, etc, results from the cardiovascular study are in Tables CV1, CV3a, CV3b, etc and results from the cancer study are in Tables N1, N3a, N3b, etc.

10.1 Participants

The study period was from January 1, 2004, through December 31, 2012. The study population included 72,917 patients (Table A1). The drug utilization study, the cardiovascular study, and the cancer study were conducted in this population. The period covered by the data sources was as follows: data from the Danish National Prescription Registry were available from 1995 onward; data from Danish National Registry of Patients (hospitalizations), from 1994 onward; data from the Danish Cancer Registry, from 1943 onward; and data from the Cause of Death Registry, from 2004 onward.

10.2 Descriptive Data

The most common index prescriptions for OAB medications were for solifenacin (42%), tolterodine (33%), and trospium (12%) (Table A2). Fesoterodine was the index medication in 8% of the population, darifenacin in 4%, and oxybutynin in 1%. Less than 1% entered the cohort with multiple OAB medications.

The three most commonly prescribed drugs in index prescriptions—solifenacin, tolterodine and trospium—were prescribed from the beginning of the study period, 2004. Darifenacin and oxybutynin were first prescribed in 2005, and fesoterodine in 2008 (Table A3). Of the entire cohort, 92% had not been exposed to other study drugs prior to cohort entry (Table A2).

Sixty percent of the study population was female (Table A1). By OAB medication, the percentage of females ranged from 58% (tolterodine) to 81% (oxybutynin) (Table A3). The mean age at cohort entry was 66 years; 9% of the patients were aged 18-44 years at cohort entry, and 59% were aged 65 years or older. The mean age at cohort entry by drug varied between 66 and 69 years. Mean disposable income in the year of cohort entry (defined as the average amount available per adult household member after tax) ranged from 146,000 Danish crowns (for darifenacin) to 159,000 Danish crowns (for fesoterodine) (Table A6).

At cohort entry, 22% of patients had hypertension (based on diagnoses or treatment); 9% had diabetes (based on diagnoses or treatment); 7% had a hospital diagnosis code for obesity (ranging from 6% for tolterodine users to 10% for fesoterodine users); 11% had proxies for smoking; 6% had codes for alcohol abuse or related conditions; and 24% had a history of AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, or pulmonary artery disease (Table A6). Regarding medication use prior to cohort entry, 64% of the women in the study cohort used hormone-replacement therapy; 40% used nitrates, digoxin, statins, or drugs to treat diabetes; more than 80% used non-aspirin NSAIDs; and 37% used low-dose aspirin.

At cohort entry, about 20% of study patients had a prior history of OAB medication use, ranging from 46% in users of oxybutynin to 14% in users of tolterodine.

10.3 Outcome Data

Outcome data for the cardiovascular and cancer components are presented with the main results for each component.

10.4 Main Results

10.4.1 Drug Utilization Study

10.4.1.1 Index Therapy Episodes

There were 72,860 index therapy episodes for individual drugs; 42% were for solifenacin, 33% for tolterodine, 12% for trospium, 8% for fesoterodine, 4% for darifenacin, and 1% for oxybutynin. The mean duration of completed index episodes ranged from 4.9 months (fesoterodine) to 7.3 months (tolterodine) (Table A8). The mean duration of the ongoing therapy episodes ranged from 8.5 months (fesoterodine) to 22.3 months (tolterodine); 10% of index episodes were ongoing at the end of the study. Of the index therapy episodes, 53% of the episodes that were completed or ongoing lasted between 1 and 3 months, and 19% lasted more than 9 months.

10.4.1.2 All Therapy Episodes

There were 224,680 therapy episodes over the entire study period (Table A9). The distribution of therapy episodes by drug was similar to that of index episodes, with the most common drugs being solifenacin (39%) and tolterodine (35%).

The mean duration of therapy episodes ranged between 5.0 months (fesoterodine) and 6.9 months (darifenacin) (Table A8). Most episodes were for a single prescription (from 43% for darifenacin to 54% for tolterodine). For all drugs, approximately 20% of episodes involved two prescriptions, and most of the remaining multiple-prescription episodes involved five or more prescriptions.

Of all episodes, 4% ended with a switch and 3% with an add-on. The most common drug switched to or added was solifenacin. For solifenacin drug episodes, the most common drug switched to or added was tolterodine.

10.4.2 Cardiovascular Results

A total of 72,917 patients qualified for this analysis. Of these patients, 1,698 had an AMI, 637 had a stroke, and 3,488 died of cardiovascular causes. A total of 5,074 patients experienced an event in the MACE definition. Of the 72,917 patients that used one of the OAB medications studied, 11,044 died of any cause.

Table CV1 summarizes the characteristics of the study patients and the prevalence of cardiovascular risk factors according to the presence or absence of the different endpoints. Compared with the overall cohort, 62% of the study population without cardiovascular outcomes was female, and more than 53% was aged 65 years or older. Patients with any of the cardiovascular endpoints were older, and the proportion of males was greater among those with a cardiovascular endpoint than among those without a cardiovascular endpoint.

Tables CV3a-CV3e describe 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, and combinations of these variables. Tables CV4a-CV4e are similar but for recent exposure to each OAB medication.

For AMI (Tables CV3a and CV4a), the SIR (95% CI) was 2.7 (2.5-2.9) cases per 1,000 person-years for current use of any OAB medication and 3.1 (2.6-3.6) for recent use. Of the four most commonly used OAB medications—solifenacin, tolterodine, trospium and fesoterodine—the SIR (95% CI) per 1,000 person-years was lower for current use of fesoterodine, 1.8 (1.3-2.4), and greater for solifenacin, 2.9 (2.6-3.2). The SIR (95% CI) per 1,000 person-years was greater for current use of any OAB medication among patients with high cardiovascular risk, 4.5 (4.1-4.9), than in the overall cohort.

For stroke (Tables CV3b and CV4b), the SIR (95% CI) per 1,000 person-years was 1.3 (1.2-1.5) for current use of any OAB medication and 5.6 (4.2-7.3) for recent use. Of the three most commonly used OAB medications, the SIR (95% CI) per 1,000 person-years was lower for current use of fesoterodine, 0.9 (0.6-1.4), and greater for tolterodine, 1.5 (1.3-1.8). The SIR (95% CI) per 1,000 person-years was greater for current use of any OAB medication among patients with high cardiovascular risk, 2.7 (2.3-3.1), than in the overall cohort.

When analyzing overall mortality (Tables CV3c and CV4c), the SIR (95% CI) per 1,000 person-years for current use of any OAB medication was 15.2 (14.8-15.6) and for recent use 17.2 (16.1-18.4). Among the three most commonly used OAB medications, the SIR (95% CI) per 1,000 person-years was lower for current use of fesoterodine, 11.1 (9.8-12.6), and greater for tolterodine, 17.4 (16.6-18.2). The greatest SIR (95% CI) among all medications was seen for oxybutynin, 34.5 (26.9-43.7). The SIR (95% CI) per 1,000 person-years was greater for current use of any OAB medication among patients with high cardiovascular risk, 26.8 (25.9-27.7), than in the overall cohort.

When analyzing cardiovascular mortality (Tables CV3d and CV4d), the SIR (95% CI) per 1,000 person-years was 4.8 (4.5-5.0) for current use of any OAB medication and 4.4 (3.8-5.0) for recent use. Among the three most commonly used OAB medications, the SIR (95% CI) per 1,000 person-years was lower for current use of fesoterodine, 3.8 (3.1-4.7), and greater for tolterodine, 6.2 (5.8-6.7). The greatest SIR (95% CI) among all medications was seen for oxybutynin, 6.9 (4.5-10.1).

We included the composite endpoint MACE to be analyzed in case the effect of OAB medications was homogeneous on the components of MACE (Tables CV3e and CV4e). The SIR (95% CI) per 1,000 person-years was 7.8 (7.5-8.1) for current use of any OAB medication and 11.8 (10.7-13.1) for recent use. Among the three most commonly used OAB medications, the SIR (95% CI) per 1,000 person-years was lower for current use of fesoterodine, 6.1 (5.1-7.2), and greater for tolterodine, 9.4 (8.8-10). The SIR (95% CI) per 1,000 person-years was greater for current use of any OAB medication among patients with high cardiovascular risk, 13.2 (12.6-13.8), than in the overall cohort.

The effect of exposure to each of the OAB medications compared with current use of tolterodine in the five cardiovascular endpoints studied is shown in the Table CV5 set. Tables CV5a-CV5e show crude and adjusted (by age and sex) IRRs for the different cardiovascular endpoints with tolterodine as the reference for current exposure to OAB medications. Tables CV5f-CV5i show crude and adjusted (by age and sex) IRRs for the different cardiovascular endpoints with tolterodine as the reference for recent exposure to OAB medications. Tables CV6a-CV6f show the multivariate adjusted IRR of exposure to each of the OAB medications studied for the different cardiovascular endpoints, first using current use of tolterodine as the comparator, second using current use of any other OAB medication as the comparator, and third using periods of no or past use of OAB medications as the comparator.

We did not observe an increased risk of any of the main cardiovascular endpoints for any of the individual OAB medications with the age- and sex-adjusted IRRs or in the multivariate analyses. The same fact was observed when the adjustment was performed with propensity scores (Tables CV7a and CV7b).

For coronary heart disease death, the IRRs of current exposure to each study OAB medication was lower than 1.0 when compared to tolterodine, and the 95% CI of the IRR excluded 1.0 for all medications except for oxybutynin (Table CV5f). Patients with current exposure to oxybutynin had an IRR of cerebrovascular death of 1.85 (95% CI, 1.10-3.11) when compared with patients with current exposure to tolterodine (Table CV5g).

10.4.3 Cancer Results

Study cancers were analyzed overall, by ever exposure to study OAB medications and by single exposure to study drugs. For the individual study drugs, the composite cancer endpoint was analyzed in relation to cumulative dose and duration of exposure, as well as time since first and latest exposure.

Cancer incidence rates were standardized to the age distribution of the Danish population to facilitate comparisons among patients exposed to the various OAB study medications. Standardized incidence rates were estimated for all cancers included in the overall composite cancer endpoint (both sexes combined), as well as for each of the two sex-specific composite cancer endpoints and according to individual study cancers (overall and separately by sex). All incidence rates are reported per 1,000 person-years unless otherwise noted.

10.4.3.1 Overall Cancer Events

Overall, 3,475 patients developed study cancers during their follow-up time (1,832 in males and 1,643 in females) and 69,442 did not (Table N1). Over half of patients developing cancers (52.7%) were male, while 60.2% of patients who did not develop cancer were female. Patients developing cancer had an age distribution shifted toward older ages relative to those who did not; for example, 31.3% of those who developed cancer were aged 75-84 years, while 22.8% of those without cancer were aged 75-84 years; 4.4% of patients with cancer were aged 45-54 years, while 11.6% of those without cancer were in that age group.

The most commonly occurring study cancers were prostate (881; 25.4% of all study cancers), breast (658; 18.9%), lung (534; 15.4%), colorectal (434; 12.5%), and bladder (369; 10.6%) (Table N1).

10.4.3.2 Cancer Incidence Rates by Ever Exposure to Study OAB Medications

The 3,475 cancer outcomes occurred during 259,072 person-years of follow-up (crude incidence rate, 13.4; 95% CI, 13.0-13.9) (Table N3_cancer). The SIR (95% CI) for all study cancers combined for ever exposure to any study OAB medication was 5.4 (5.3-5.6) and was 4.6 (4.4-4.9) among females and 6.2 (6.0-6.5) among males. The SIR for any study cancer ranged from 5.2 (5.0-5.5) for ever use of tolterodine to 6.0 for both fesoterodine (5.4-6.7) and oxybutynin (5.0-7.2). In females, SIRs for the sex-specific composite cancer endpoint ranged from 4.6 (4.3-4.9) for tolterodine to 5.3 (4.5-6.2) for fesoterodine. In males, SIRs for the sex-specific composite cancer endpoint ranged from 5.9 (5.5-6.3) for tolterodine to 6.8 for both darifenacin (5.5-8.3) and fesoterodine (5.7-7.9).

In analyses of individual cancer types (Tables N3_Bladder, N3_Breast, etc.), SIRs were generally similar for patients ever exposed to the various study drugs. However, the SIR (95% CI) for prostate cancer in males ever exposed to fesoterodine (6.3; 5.2-7.4) was higher than for those ever exposed to solifenacin (3.4; 3.1-3.7), tolterodine (3.1; 2.8-3.4), or trospium (3.9; 3.3-4.5). The SIR (95% CI) for breast cancer in females ever exposed to fesoterodine (3.2; 2.6-3.9) was higher than that for tolterodine (2.2; 1.9-2.4). In males and females combined, the SIR (95% CI) for colorectal cancer was higher in patients ever exposed to fesoterodine (1.2; 0.9-1.5) than for solifenacin (0.7; 0.6-0.8) and tolterodine (0.7; 0.6-0.8). Although the SIR for bladder cancer in males ever exposed to oxybutynin (2.6; 1.2-4.7) was higher than for the other study OAB medications (next highest was for solifenacin, 1.4; 1.2-1.6), the estimate for oxybutynin is based on only 10 cases and is imprecise.

10.4.3.3 Cancer Incidence Rates by Single Exposure to Study OAB Medications

Overall 2,483 study cancers occurred during 158,716 person-years of follow-up among patients with ever exposure to only a single study OAB medication (crude incidence rate 15.6; 95% CI, 15.0-16.3) (Table N4_Cancer). The SIR (95% CI) for all study cancers combined during follow-up time among those with ever exposure to a single study drug was 6.2 (6.0-6.4) and was 5.3 (4.9-5.6) among females and 7.2 (6.8-7.5) among males. The SIR (95% CI) for any study cancer ranged from 4.8 (2.5-8.5) for single use of oxybutynin to 7.0 (6.2-7.9) for trospium. In females, the SIR (95% CI) for the sex-specific composite cancer endpoint ranged from 2.7 (1.0-6.0) for oxybutynin to 6.0 (4.9-7.2) for trospium. In males, the SIR (95% CI) for the sex-specific composite cancer endpoint ranged from 6.8 (6.3-7.4) for tolterodine to 8.3 (6.1-10.9) for darifenacin.

In analyses of individual cancer types (Tables N4_Bladder, N4_Breast, etc.), SIRs were again generally similar for patients with single exposure to the various study drugs. However, the SIR (95% CI) for lung cancer in males with single exposure to darifenacin (2.7; 1.4-4.7) was higher than that for solifenacin (1.0; 0.8-1.3), tolterodine (0.9; 0.7-1.1), and trospium (0.7; 0.4-1.2).

10.4.3.4 Cancer Incidence Rates by Cumulative Dose and Duration of Exposure

Overall composite cancer incidence rates (both sexes combined) by cumulative dose and duration of exposure for single exposure to each of the study OAB medications are shown in Tables N4-2_Darifenacin, N4-2_Fesoterodine, etc. There was no trend of increasing cancer risk with increasing cumulative dose or duration of single exposure for any of the study OAB medications. In general, SIRs tended to decrease over time since both time of first exposure and time of last exposure to single study OAB medications. Taken together, these results do not suggest a cancer-causing effect, which would typically increase with increasing cumulative exposure. The tendency for a decrease in risk to be observed with increasing time since first or last exposure to single OAB medications suggests a higher risk early during exposure which could be related to protopathic or detection bias; i.e., a prescription for an OAB medication was used to treat symptoms that were actually early symptoms of cancer, leading to earlier detection.

10.5 Other Analyses

Not applicable.

10.6 Adverse Events/Adverse Reactions

For studies in which the research team uses 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."*[29]

Module VIII – Post-Authorisation Safety Studies, of the same document echoes this approach.[30] 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

The study population included 72,917 patients with 72,860 index therapy episodes for individual drugs (42% of index episodes were for solifenacin, 33% for tolterodine, 12% for trospium, 8% for fesoterodine, 4% for darifenacin, and 1% for oxybutynin). The mean duration of completed index episodes ranged from 4.9 months (fesoterodine) to 7.3 months (tolterodine).

A total of 72,917 patients qualified for the cardiovascular analysis. Of these patients, 1,698 had an AMI, 637 had a stroke, and 3,488 died of cardiovascular causes. A total of 5,074 patients experienced an event considered in the MACE definition. In none of the age- and sex–adjusted IRRs, or the multivariate analyses, or the propensity score–adjusted analysis could we observe an increased risk of any of the cardiovascular endpoints for any of the individual OAB medications.

Standardized incidence rates for the sex-specific composite cancer endpoints varied somewhat for person-time ever exposed to the various OAB medications studied. Tolterodine was associated with the lowest rate in both males and females, and fesoterodine was associated with the highest rate in both sexes (with darifenacin also having the same highest rate in males as fesoterodine). However, confidence intervals for the rates for ever exposure to the individual drugs overlapped (within each sex for the sex-specific composite endpoints). Therefore, although the relative positions of these particular study drugs within the observed range of incidence rates suggest the possibility that the true study cancer incidence rates associated with ever exposure to tolterodine are actually lower than those

associated with the other drugs, and that the rates associated with fesoterodine (and, in males, darifenacin) are actually higher than the rates associated with the other drugs, these variations could also plausibly be considered to be chance findings.

Considering SIRs for individual cancers in relation to ever exposure to the various OAB medications studied, fesoterodine was associated with the highest rates for prostate cancer in males, breast cancer in females, and colorectal cancer in both sexes combined, while tolterodine was associated with the lowest rates for these cancers (with the colorectal cancer rate for solifenacin the same as for tolterodine). The confidence intervals for the highest rates (fesoterodine) for these cancers and the corresponding lowest rates (tolterodine, and also solifenacin for colorectal cancer) do not overlap, which seems to make chance less plausible as an explanation for these findings. Evidently, fesoterodine being associated with the highest incidence rates for these three commonly occurring cancers drives (to some extent) the pattern observed for sex-specific composite cancer endpoint rates summarized in the preceding paragraph. We are not aware of any biological distinction between fesoterodine and the other OAB medications that might explain the association between ever use of fesoterodine and the highest SIRs for these three commonly occurring cancers. However, fesoterodine was introduced into the Danish market in 2008, later than the other medications, and median duration of use is shorter than the median duration of use of the other medications. This different pattern of use and the observed tendency for some cancer rates to decrease with increasing time since first exposure to single OAB medications might be a possible explanation for the higher rates observed for fesoterodine.

Besides, the results for single exposure to individual OAB medications do not support fesoterodine exposure being associated with a substantially higher cancer risk than the other OAB medications. The highest rates for the sex-specific composite cancer endpoints were associated with single use of trospium in females and darifenacin in males. Nor was any individual study cancer associated with single use of fesoterodine at a particularly higher rate than the other study OAB medications.

The tendency for decreasing composite cancer endpoint rates to be observed with increasing time since first exposure to single OAB medications, as well as the lack of an association between increasing cumulative dose of single OAB medications and increasing cancer risk, suggest that it is unlikely that the observed variations in cancer risk are the result of a carcinogenic process. Higher cancer rates during early periods of exposure than later periods could be related to protopathic or detection bias.

11.2 Limitations

The main limitation of this study is the lack of primary health care data. For this study, a planned data source for information on lifestyle factors and covariates was data from general practitioners. These data, collected in the Danish General Practice Database (DAMD), were available until recently, when Danish authorities temporarily discontinued their use over privacy/ethics concerns. Since then, these data have not been available for research, and it is not clear when or if they will be available in the future. The strategy implemented to overcome the lack of this data source for patient characteristics that may not be well recorded in hospital data (e.g., smoking, obesity) was to search for these

diagnoses in secondary hospital discharge records. Also, prescriptions for drugs to help with smoking cessation were included in the covariate definition. Although this approach enabled us to capture the most serious cases and those that explicitly required health care, it missed the mild and moderate cases.

Drug utilization and patterns of treatments were derived from dispensed prescriptions. We believe that the information is complete (in that the study drugs were not available over the counter during the study period, and free samples would not be substantial), but it can represent an overestimate of use if patients did not take the medication. In general, we do not expect this to be substantial. Further, there are no reasons to think this would affect one study drug more than others.

Use of the Danish registries is a strength of this study because these data sources have complete population coverage in the country; this is especially important for the Cancer Registry, which is critical for ascertainment of the cancer outcomes in this study. The use of census data allowed us to keep track of all patients and account for migration in or out of the population.

Another strength of this study is that we compared users of different OAB medications rather than users and nonusers (our comparisons to nonuse actually represent periods of nonuse in patients who previously used OAB medications). As mentioned in the literature review section, patients with OAB have a larger prevalence of cardiovascular morbidities than patients without such a diagnosis, so the likelihood of potential confounding of cardiovascular effects of OAB medications by differences in risk of cardiovascular outcomes among exposure groups would have been greater if nonusers of OAB medications had been included in the study.

11.3 Interpretation

In this cohort of 72,917 Danish patients with prescriptions for OAB medications in the study period January 1, 2004, through December 31, 2012, 60% of patients were females and 60% were aged 65 years or older. Of all therapy episodes, 39% were of solifenacin, 35% of tolterodine, and 12% of trospium. The observed exposure patterns are well suited to detecting acute adverse events for the most frequently prescribed OAB medications.

The risk of the targeted cardiovascular endpoints was similar among individual OAB medications and does not suggest a consistently increased risk for any specific OAB medication.

Although some of the analyses suggest a higher risk of composite cancer endpoints among patients receiving fesoterodine prescriptions, results from the single-exposure analysis do not confirm this finding. For the composite endpoint, an increased risk was found during the early exposure period, which could suggest a protopathic bias for some cancers, i.e. a prescription for an OAB medication was used to treat symptoms that were actually early symptoms of cancer, leading to earlier detection.

11.4 Generalizability

Generalizations from these findings depend on the category of the finding.[31,32] Findings that relate to drug utilization and patient characterization apply to the patient population in Denmark. The risk of events among those using OAB medications should be generalizable to all patients using these medications, apart from the effect of any as yet unidentified biological mediators.

12 Other Information

Not applicable.

13 Conclusion

In this cohort of patients with at least one prescription for an OAB medication, a majority of patients were females using one drug during follow-up. The observed exposure patterns are well suited to detecting acute adverse events for individual OAB medications. For effects potentially driven by moderate to long-term exposure or lag time for clinical manifestation, the ability will depend on the length of drug use and follow-up for each individual OAB medication.

The risk of the targeted cardiovascular endpoints was similar among individual OAB medications and does not suggest a consistently increased risk for any specific OAB medication.

Although some of the analyses suggested a higher risk of composite cancer endpoints among patients receiving fesoterodine prescriptions, results from the single-exposure analysis did not confirm this finding. For the composite endpoint, an increased risk was found during the early exposure period, which could suggest a protopathic bias for some cancers, i.e., a prescription for an OAB medication was used to treat symptoms that were actually early symptoms of cancer, leading to earlier detection.

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Appendices

Annex 1.
List of Stand-Alone Documents

None.

Annex 2. Codes to Identify Cardiovascular Endpoints

Table 2-1. Acute Myocardial Infarction: ICD-10 Codes

ICD-10 Code	Description
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified

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

NOTE: I22 Subsequent myocardial infarction is not included because denotes recurrent, extension or reinfarction occurring within 28 days.

Table 2-2. Stroke: ICD-10 Codes

ICD-10 Code	Description
I60	Subarachnoid hemorrhage
I60.0	Subarachnoid hemorrhage from carotid siphon and bifurcation
I60.1	Subarachnoid hemorrhage from middle cerebral artery
I60.2	Subarachnoid hemorrhage from anterior communicating artery
I60.3	Subarachnoid hemorrhage from posterior communicating artery
I60.4	Subarachnoid hemorrhage from basilar artery
I60.5	Subarachnoid hemorrhage from vertebral artery
I60.6	Subarachnoid hemorrhage from other intracranial arteries
I60.7	Subarachnoid hemorrhage from intracranial artery, unspecified
I60.8	Other subarachnoid hemorrhage
I60.9	Subarachnoid hemorrhage, unspecified
I61	Intracerebral hemorrhage
I61.0	Intracerebral hemorrhage in hemisphere, subcortical
I61.1	Intracerebral hemorrhage in hemisphere, cortical
I61.2	Intracerebral hemorrhage in hemisphere, unspecified
I61.3	Intracerebral hemorrhage in brain stem
I61.4	Intracerebral hemorrhage in cerebellum
I61.5	Intracerebral hemorrhage, intraventricular
I61.6	Intracerebral hemorrhage, multiple localised
I61.8	Other intracerebral hemorrhage

ICD-10 Code	Description
I61.9	Intracerebral hemorrhage, unspecified
I63	Cerebral infarction
I63.0	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I64	Stroke, not specified as hemorrhage or infarction

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

Table 2-3. Coronary Heart Disease Death: ICD-10

ICD-10 Code	Description
I20	Angina pectoris
I20.0	Unstable angina
I20.1	Angina pectoris with documented spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22	Subsequent myocardial infarction
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I23	Certain current complications of acute myocardial infarction
I23.0	Hemopericardium as current complication following acute myocardial infarction
I23.1	Atrial septal defect as current complication following acute myocardial infarction
I23.2	Ventricular septal defect as current complication following acute myocardial infarction
I23.3	Rupture of cardiac wall without hemopericardium as current complication following acute myocardial infarction
I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
I23.8	Other current complications following acute myocardial infarction
I24	Other acute ischemic heart disease
I24.0	Coronary thrombosis not resulting in myocardial infarction
I24.1	Dressler's syndrome
I24.8	Other forms of acute ischemic heart disease

Table 2-3. Coronary Heart Disease Death: ICD-10

ICD-10 Code	Description
I24.9	Acute ischemic heart disease, unspecified
I25	Chronic ischemic heart disease
I25.0	Atherosclerotic cardiovascular disease, so described
I25.1	Atherosclerotic heart disease
I25.2	Old myocardial infarction
I25.3	Aneurysm of heart
I25.4	Coronary artery aneurysm
I25.5	Ischemic cardiomyopathy
I25.6	Silent myocardial ischemia
I25.8	Other forms of chronic ischemic heart disease
I25.9	Chronic ischemic heart disease, unspecified
I42.8	Other cardiomyopathies
I42.9	Cardiomyopathy, NOS
I46	Cardiac arrest
I46.1	Sudden cardiac death, so described
I46.9	Cardiac arrest, unspecified
I47.0	Re-entry ventricular arrhythmia
I47.2	Ventricular tachycardia
I49.0	Ventricular fibrillation and flutter
I49.8	Other specified arrhythmias
I49.9	Cardiac arrhythmia, unspecified
I51.6	Cardiovascular disease, unspecified
I51.9	Heart disease, unspecified
I70.9	Atherosclerosis, NOS
R96.1	Death < 24 hours after symptoms
R98	Unattended death

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; NOS = not otherwise specified.

Table 2-4. Cerebrovascular Disease Deaths: ICD-10

ICD-10 Code	Description
I60	Subarachnoid hemorrhage
I60.0	Subarachnoid hemorrhage from carotid siphon and bifurcation
I60.1	Subarachnoid hemorrhage from middle cerebral artery
I60.2	Subarachnoid hemorrhage from anterior communicating artery
I60.3	Subarachnoid hemorrhage from posterior communicating artery
I60.4	Subarachnoid hemorrhage from basilar artery
I60.5	Subarachnoid hemorrhage from vertebral artery
I60.6	Subarachnoid hemorrhage from other intracranial arteries
I60.7	Subarachnoid hemorrhage from intracranial artery, unspecified
I60.8	Other subarachnoid hemorrhage
I60.9	Subarachnoid hemorrhage, unspecified
I61	Intracerebral hemorrhage
I61.0	Intracerebral hemorrhage in hemisphere, subcortical
I61.1	Intracerebral hemorrhage in hemisphere, cortical
I61.2	Intracerebral hemorrhage in hemisphere, unspecified
I61.3	Intracerebral hemorrhage in brain stem
I61.4	Intracerebral hemorrhage in cerebellum
I61.5	Intracerebral hemorrhage, intraventricular
I61.6	Intracerebral hemorrhage, multiple localised
I61.8	Other intracerebral hemorrhage
I61.9	Intracerebral hemorrhage, unspecified
I63	Cerebral infarction
I63.0	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I64	Stroke, not specified as hemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I65.0	Occlusion and stenosis of vertebral artery

Table 2-4. Cerebrovascular Disease Deaths: ICD-10

ICD-10 Code	Description
I65.1	Occlusion and stenosis of basilar artery
I65.2	Occlusion and stenosis of carotid artery
I65.3	Occlusion and stenosis of multiple and bilateral precerebral arteries
I65.8	Occlusion and stenosis of unspecified precerebral artery
I65.9	Occlusion and stenosis of unspecified precerebral artery
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I66.0	Occlusion and stenosis of middle cerebral artery
I66.1	Occlusion and stenosis of anterior cerebral artery
I66.2	Occlusion and stenosis of posterior cerebral artery
I66.3	Occlusion and stenosis of cerebellar arteries
I66.4	Occlusion and stenosis of multiple and bilateral cerebral arteries
I66.8	Occlusion and stenosis of other cerebral artery
I66.9	Occlusion and stenosis of unspecified cerebral artery
I67	Other cerebrovascular diseases
I67.0	Dissection of cerebral arteries, nonruptured
I67.1	Cerebral aneurysm, nonruptured
I67.2	Cerebral atherosclerosis
I67.3	Progressive vascular leukoencephalopathy
I67.4	Hypertensive encephalopathy
I67.5	Moyamoya disease
I67.6	Nonpyogenic thrombosis of intracranial venous system
I67.7	Cerebral arteritis, not elsewhere classified
I67.8	Other specified cerebrovascular diseases
I67.9	Cerebrovascular disease, unspecified
I68	Cerebrovascular disorders in diseases classified elsewhere
I68.0	Cerebral amyloid angiopathy
I68.1	Cerebral arteritis in infectious and parasitic diseases classified elsewhere
I68.2	Cerebral arteritis in other diseases classified elsewhere
I68.8	Other cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease
I69.0	Sequelae of subarachnoid hemorrhage
I69.1	Sequelae of intracerebral hemorrhage
I69.2	Sequelae of other nontraumatic intracranial hemorrhage
I69.3	Sequelae of cerebral infarction

Table 2-4. Cerebrovascular Disease Deaths: ICD-10

ICD-10 Code	Description
I69.4	Sequelae of stroke, not specified as hemorrhage or infarction
I69.8	Sequelae of other and unspecified cerebrovascular diseases
G45	Transient cerebral ischemic attacks and related syndromes
G45.0	Vertebrobasilar artery syndrome
G45.1	Carotid artery syndrome (hemispheric)
G45.2	Multiple and bilateral precerebral artery syndromes
G45.3	Amaurosis fugax
G45.4	Transient global amnesia
G45.8	Other transient cerebral ischemic attacks and related syndromes
G45.9 d	Transient cerebral ischemic attack, unspecified

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

Annex 3. Codes to Identify Cancer Outcomes

Table 3-1. ICD-10 Codes Indicating Neoplasm (Cancer Types as Defined in the Protocol)

Code	Description
C18.-	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C25.-	Malignant neoplasm of pancreas
C34.-	Malignant neoplasm of bronchus and lung
C43.-	Malignant melanoma of skin
C50.-	Malignant neoplasm of breast
C54.-	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C61	Malignant neoplasm of prostate
C64	Malignant neoplasm of kidney, except renal pelvis
C65	Malignant neoplasm of renal pelvis
C67.-	Malignant neoplasm of bladder
C82.-	Follicular lymphoma
C83.-	Non-follicular lymphoma
C84.-	Mature T/NK-cell lymphomas
C85.-	Other and unspecified types of non-Hodgkin lymphoma

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

Annex 4.
Analysis Results Tables

In the PDF, use the bookmarks pane to navigate to individual tables.

Note: As noted in the table shells that accompanied the statistical analysis plan, Tables A4, A5, A10, N2, and CV2 were not generated for this data source.

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Table A1. Characteristics of Those Exposed to Any OAB Medication (N = 72,917) at Study Cohort Entry

Variable	n (%)	Male	Female
All	n=72,917	n=29,483	n=43,434
Age at cohort entry (years)			
Mean (SD)	66 (15.1)	68 (13.7)	65 (15.8)
18-24	765 (1.0%)	211 (0.7%)	554 (1.3%)
25-34	1,692 (2.3%)	546 (1.9%)	1,146 (2.6%)
35-44	4,363 (6.0%)	1,178 (4.0%)	3,185 (7.3%)
45-54	8,202 (11.2%)	2,450 (8.3%)	5,752 (13.2%)
55-64	14,551 (20.0%)	6,092 (20.7%)	8,459 (19.5%)
65-74	19,468 (26.7%)	8,996 (30.5%)	10,472 (24.1%)
75-84	16,905 (23.2%)	7,330 (24.9%)	9,575 (22.0%)
85+	6,971 (9.6%)	2,680 (9.1%)	4,291 (9.9%)
Sex			
Male	29,483 (40.4%)	29,483 (100%)	
Female	43,434 (59.6%)		43,434 (100%)
Calendar year at cohort entry			
2004	5,122 (7.0%)	1,641 (5.6%)	3,481 (8.0%)
2005	5,755 (7.9%)	1,907 (6.5%)	3,848 (8.9%)
2006	5,766 (7.9%)	2,194 (7.4%)	3,572 (8.2%)
2007	9,969 (13.7%)	4,151 (14.1%)	5,818 (13.4%)
2008	9,018 (12.4%)	3,738 (12.7%)	5,280 (12.2%)
2009	9,575 (13.1%)	3,919 (13.3%)	5,656 (13.0%)
2010	9,596 (13.2%)	4,142 (14.0%)	5,454 (12.6%)
2011	9,391 (12.9%)	3,931 (13.3%)	5,460 (12.6%)
2012	8,725 (12.0%)	3,860 (13.1%)	4,865 (11.2%)

OAB = overactive bladder; SD = standard deviation.

Note: Study cohort entry is date of index prescription.

Table A2. Descriptive Summary of OAB Medication Exposure at Study Cohort Entry (N=72,917)

Variable	n (%)
Single exposure[a]	
Darifenacin	2361 (3.5%)
Fesoterodine	5284 (7.9%)
Oxybutynin	547 (0.8%)
Solifenacin	27607 (41.1%)
Tolterodine	23392 (34.9%)
Trospium	7862 (11.7%)
New exposure[b]	
Darifenacin	2698 (3.7%)
Fesoterodine	5749 (7.9%)
Oxybutynin	740 (1.0%)
Solifenacin	30792 (42.2%)
Tolterodine	23776 (32.6%)
Trospium	9105 (12.5%)
More than one study OAB medication at cohort entry	57 (0.1%)

OAB = overactive bladder.

Note: Anyone in the *single exposure* group will also be in the *new exposure* group for that drug.

a. Single exposure means taking this drug at cohort entry and no prior exposure to any other OAB medication; however, patient could have had exposure to this OAB medication if it was more than 12 months ago.

b. New exposure means no exposure to this drug within the prior 12 months; however, patient may have had prior exposure to other OAB medications.

Table A3. Characteristics of Exposed Patients, by OAB Medication at Study Cohort Entry

	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium	Multiple
	2,698 (100.0%)	5,749 (100.0%)	740 (100.0%)	30,792 (100.0%)	23,776 (100.0%)	9,105 (100.0%)	57 (100.0%)
Variable	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age at cohort entry (years)							
Median (interquartile range)	69 (59 - 78)	67 (56 - 76)	66 (55 - 76)	68 (57 - 77)	69 (58 - 78)	68 (56 - 77)	60 (41 - 71)
18-24	25 (0.9%)	94 (1.6%)	8 (1.1%)	323 (1.0%)	183 (0.8%)	129 (1.4%)	3 (5.3%)
25-34	51 (1.9%)	147 (2.6%)	19 (2.6%)	697 (2.3%)	502 (2.1%)	269 (3.0%)	7 (12.3%)
35-44	162 (6.0%)	387 (6.7%)	40 (5.4%)	1,830 (5.9%)	1,336 (5.6%)	601 (6.6%)	7 (12.3%)
45-54	266 (9.9%)	711 (12.4%)	108 (14.6%)	3,565 (11.6%)	2,477 (10.4%)	1,067 (11.7%)	8 (14.0%)
55-64	523 (19.4%)	1,155 (20.1%)	158 (21.4%)	6,200 (20.1%)	4,719 (19.8%)	1,786 (19.6%)	10 (17.5%)
65-74	712 (26.4%)	1,660 (28.9%)	201 (27.2%)	8,304 (27.0%)	6,194 (26.1%)	2,386 (26.2%)	11 (19.3%)
75-84	671 (24.9%)	1,143 (19.9%)	147 (19.9%)	6,984 (22.7%)	5,903 (24.8%)	2,047 (22.5%)	10 (17.5%)
85+	288 (10.7%)	452 (7.9%)	59 (8.0%)	2,889 (9.4%)	2,462 (10.4%)	820 (9.0%)	1 (1.8%)
Sex							
Male	930 (34.5%)	2,342 (40.7%)	143 (19.3%)	12,439 (40.4%)	9,964 (41.9%)	3,639 (40.0%)	26 (45.6%)
Female	1,768 (65.5%)	3,407 (59.3%)	597 (80.7%)	18,353 (59.6%)	13,812 (58.1%)	5,466 (60.0%)	31 (54.4%)
Calendar year at cohort entry							
2004	0 (0.0%)	0 (0.0%)	0 (0.0%)	310 (1.0%)	3,679 (15.5%)	1,129 (12.4%)	4 (7.0%)
2005	3 (0.1%)	0 (0.0%)	62 (8.4%)	2,067 (6.7%)	2,933 (12.3%)	686 (7.5%)	4 (7.0%)
2006	425 (15.8%)	0 (0.0%)	141 (19.1%)	1,983 (6.4%)	2,535 (10.7%)	680 (7.5%)	2 (3.5%)
2007	710 (26.3%)	0 (0.0%)	199 (26.9%)	4,140 (13.4%)	4,004 (16.8%)	911 (10.0%)	5 (8.8%)
2008	557 (20.6%)	390 (6.8%)	92 (12.4%)	4,226 (13.7%)	3,043 (12.8%)	701 (7.7%)	9 (15.8%)
2009	380 (14.1%)	1,292 (22.5%)	81 (10.9%)	4,462 (14.5%)	2,463 (10.4%)	889 (9.8%)	8 (14.0%)
2010	267 (9.9%)	1,291 (22.5%)	64 (8.6%)	4,343 (14.1%)	2,058 (8.7%)	1,567 (17.2%)	6 (10.5%)
2011	199 (7.4%)	1,454 (25.3%)	62 (8.4%)	4,580 (14.9%)	1,662 (7.0%)	1,422 (15.6%)	12 (21.1%)
2012	157 (5.8%)	1,322 (23.0%)	39 (5.3%)	4,681 (15.2%)	1,399 (5.9%)	1,120 (12.3%)	7 (12.3%)

OAB = overactive bladder; SD = standard deviation.

Note: This table does not distinguish single exposure from those who entered with prior exposure to another OAB medication.

Table A6. Comorbidities

	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium	Multiple
All	**2,698 (100.0%)**	**5,749 (100.0%)**	**740 (100.0%)**	**30,792 (100.0%)**	**23,776 (100.0%)**	**9,105 (100.0%)**	**57 (100.0%)**
Patient Characteristic	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Comorbidities:							
C1 Ischemic heart disease	152 (5.6%)	315 (5.5%)	33 (4.5%)	1,890 (6.1%)	1,464 (6.2%)	486 (5.3%)	**
C2 Congestive heart failure	133 (4.9%)	272 (4.7%)	29 (3.9%)	1,508 (4.9%)	1,344 (5.7%)	425 (4.7%)	6 (10.5%)
C3 Peripheral vascular disease	148 (5.5%)	362 (6.3%)	54 (7.3%)	1,941 (6.3%)	1,488 (6.3%)	498 (5.5%)	3 (5.3%)
C4 Cerebrovascular disease	353 (13.1%)	719 (12.5%)	121 (16.4%)	4,179 (13.6%)	3,806 (16.0%)	1,268 (13.9%)	10 (17.5%)
C5 Dementia	61 (2.3%)	105 (1.8%)	25 (3.4%)	649 (2.1%)	613 (2.6%)	214 (2.4%)	3 (5.3%)
C6 Chronic pulmonary disease	268 (9.9%)	628 (10.9%)	89 (12.0%)	3,274 (10.6%)	2,364 (9.9%)	904 (9.9%)	7 (12.3%)
C7 Connective tissue disease	147 (5.4%)	325 (5.7%)	38 (5.1%)	1,557 (5.1%)	1,096 (4.6%)	450 (4.9%)	5 (8.8%)
C8 Ulcer disease	183 (6.8%)	374 (6.5%)	43 (5.8%)	2,107 (6.8%)	1,616 (6.8%)	573 (6.3%)	4 (7.0%)
C9 Mild liver disease	39 (1.4%)	84 (1.5%)	12 (1.6%)	434 (1.4%)	360 (1.5%)	148 (1.6%)	0 (0.0%)
C10 Diabetes	207 (7.7%)	500 (8.7%)	55 (7.4%)	2,413 (7.8%)	1,881 (7.9%)	713 (7.8%)	4 (7.0%)
C11 Hemiplegia	17 (0.6%)	79 (1.4%)	18 (2.4%)	302 (1.0%)	430 (1.8%)	198 (2.2%)	14 (24.6%)
c12 Moderate to severe renal disease	51 (1.9%)	168 (2.9%)	17 (2.3%)	711 (2.3%)	551 (2.3%)	188 (2.1%)	**
C13 Diabetes with end organ damage	108 (4.0%)	248 (4.3%)	22 (3.0%)	1,233 (4.0%)	1,036 (4.4%)	354 (3.9%)	**
C14 Any solid tumor	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
C15 Leukemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
C16 Lymphoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
C17 Moderate to severe liver disease	8 (0.3%)	31 (0.5%)	4 (0.5%)	123 (0.4%)	77 (0.3%)	41 (0.5%)	0 (0.0%)
C18 Metastatic solid tumor	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
C19 AIDS	0 (0.0%)	**	**	8 (0.0%)	4 (0.0%)	0 (0.0%)	0 (0.0%)
Charlson summary score	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	1 (0 - 2)
Renal impairment	20 (0.7%)	77 (1.3%)	8 (1.1%)	374 (1.2%)	284 (1.2%)	104 (1.1%)	0 (0.0%)
Dialysis	0 (0.0%)	**	**	8 (0.0%)	6 (0.0%)	**	0 (0.0%)
Fractures	432 (16.0%)	868 (15.1%)	131 (17.7%)	4,569 (14.8%)	3,741 (15.7%)	1,367 (15.0%)	17 (29.8%)
Arthritis (rheumatoid arthritis, Bechterew, juvenile arthritis, psoriatic arthritis)	52 (1.9%)	104 (1.8%)	11 (1.5%)	504 (1.6%)	376 (1.6%)	140 (1.5%)	3 (5.3%)
Organ transplantation	4 (0.1%)	23 (0.4%)	6 (0.8%)	119 (0.4%)	79 (0.3%)	27 (0.3%)	**
Polycystic ovary syndrome	8 (0.3%)	45 (0.8%)	7 (0.9%)	154 (0.5%)	115 (0.5%)	31 (0.3%)	0 (0.0%)
Endometrial polyps or other benign growths of the uterine lining	10 (0.4%)	27 (0.5%)	12 (1.6%)	168 (0.5%)	119 (0.5%)	38 (0.4%)	0 (0.0%)
History of AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, pulmonary artery disease	608 (22.5%)	1,323 (23.0%)	190 (25.7%)	7,297 (23.7%)	6,280 (26.4%)	2,091 (23.0%)	16 (28.1%)
Diabetes without complications (diabetes with complications is included with the Charlson score)	226 (8.4%)	557 (9.7%)	57 (7.7%)	2,675 (8.7%)	2,079 (8.7%)	793 (8.7%)	4 (7.0%)
Markers of incontinence							
Unspecified incontinence	348 (12.9%)	967 (16.8%)	224 (30.3%)	3,862 (12.5%)	2,135 (9.0%)	1,217 (13.4%)	15 (26.3%)
Stress incontinence	197 (7.3%)	551 (9.6%)	137 (18.5%)	2,038 (6.6%)	967 (4.1%)	575 (6.3%)	6 (10.5%)
Other specified forms of incontinence	280 (10.4%)	802 (14.0%)	184 (24.9%)	2,640 (8.6%)	1,493 (6.3%)	927 (10.2%)	15 (26.3%)
Polyuria	24 (0.9%)	59 (1.0%)	15 (2.0%)	306 (1.0%)	203 (0.9%)	86 (0.9%)	0 (0.0%)
Other diseases of the bladder	11 (0.4%)	53 (0.9%)	13 (1.8%)	225 (0.7%)	93 (0.4%)	58 (0.6%)	7 (12.3%)
Any of the above	528 (19.6%)	1,571 (27.3%)	337 (45.5%)	6,012 (19.5%)	3,391 (14.3%)	1,879 (20.6%)	27 (47.4%)

Table A6. Comorbidities

Patient Characteristic	Darifenacin n (%)	Fesoterodine n (%)	Oxybutynin n (%)	Solifenacin n (%)	Tolterodine n (%)	Trospium n (%)	Multiple n (%)
All	**2,698 (100.0%)**	**5,749 (100.0%)**	**740 (100.0%)**	**30,792 (100.0%)**	**23,776 (100.0%)**	**9,105 (100.0%)**	**57 (100.0%)**
Prescriptions							
Hormone-replacement therapy	1,237 (45.8%)	2,286 (39.8%)	449 (60.7%)	11,931 (38.7%)	8,370 (35.2%)	3,522 (38.7%)	19 (33.3%)
Tamoxifen use	**	0 (0.0%)	0 (0.0%)	9 (0.0%)	4 (0.0%)	**	0 (0.0%)
Thyroid hormone replacement	164 (6.1%)	374 (6.5%)	67 (9.1%)	1,846 (6.0%)	1,372 (5.8%)	563 (6.2%)	4 (7.0%)
Nitrates, digoxin, antidiabetic drugs, statins	1,079 (40.0%)	2,476 (43.1%)	285 (38.5%)	12,647 (41.1%)	9,046 (38.0%)	3,459 (38.0%)	21 (36.8%)
Non-aspirin NSAIDs	2,259 (83.7%)	4,945 (86.0%)	619 (83.6%)	26,175 (85.0%)	19,537 (82.2%)	7,646 (84.0%)	46 (80.7%)
Lipid-lowering drug	814 (30.2%)	1,996 (34.7%)	203 (27.4%)	9,829 (31.9%)	6,223 (26.2%)	2,532 (27.8%)	16 (28.1%)
Low-dose aspirin	994 (36.8%)	2,053 (35.7%)	287 (38.8%)	11,280 (36.6%)	8,829 (37.1%)	3,209 (35.2%)	18 (31.6%)
Antiplatelets (including aspirin in low doses)	1,014 (37.6%)	2,092 (36.4%)	294 (39.7%)	11,498 (37.3%)	8,968 (37.7%)	3,264 (35.8%)	20 (35.1%)
Immunosuppressive agents	80 (3.0%)	196 (3.4%)	18 (2.4%)	871 (2.8%)	608 (2.6%)	243 (2.7%)	3 (5.3%)
Anti-gout drugs	111 (4.1%)	276 (4.8%)	29 (3.9%)	1,413 (4.6%)	1,066 (4.5%)	385 (4.2%)	**
Health services utilization, median (interquartile range)							
Hospitalizations	14 (8 - 24)	18 (10 - 30)	19 (11 - 30)	16 (9 - 26)	14 (8 - 24)	15 (8 - 26)	30 (16 - 50)
Sigmoidoscopies	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Socioeconomic characteristics, median (interquartile range)							
Income	146,210 (114,508-204,902)	159,449 (124,415-220,898)	148,076 (113,289-198,071)	153,106 (118,733-211,149)	144,774 (111,763-198,768)	150,030 (115,717-202,847)	180,790 (132,082-233,281)
Lifestyle factors							
Smoking	246 (9.1%)	666 (11.6%)	72 (9.7%)	3,437 (11.2%)	2,347 (9.9%)	937 (10.3%)	5 (8.8%)
Obesity	176 (6.5%)	548 (9.5%)	64 (8.6%)	2,215 (7.2%)	1,327 (5.6%)	624 (6.9%)	3 (5.3%)
Hypertension	561 (20.8%)	1,416 (24.6%)	175 (23.6%)	6,974 (22.6%)	5,012 (21.1%)	1,903 (20.9%)	10 (17.5%)
Alcohol abuse and related conditions	137 (5.1%)	363 (6.3%)	38 (5.1%)	1,822 (5.9%)	1,407 (5.9%)	561 (6.2%)	**

AMI = acute myocardial infarction; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder.

Table A7. Count and Person-years of Exposure to Each OAB Medication by Category of Exposure (Current, Recent, Ever, and Single)

			Person-years per Exposed Individual				
Study Antimuscarinic	**Patients**	**Person-years**	**Mean**	**SD**	**Median**	**P25**	**P75**
Current exposure							
Darifenacin	4,660	5,244.01	1.13	1.38	0.47	0.27	1.30
Fesoterodine	10,650	8,172.93	0.77	0.86	0.36	0.22	0.94
Oxybutynin	2,614	1,855.71	0.71	0.98	0.33	0.28	0.61
Solifenacin	38,754	46,029.51	1.19	1.51	0.51	0.25	1.43
Tolterodine	27,609	41,303.30	1.50	1.85	0.57	0.26	2.03
Trospium	12,969	12,956.66	1.00	1.49	0.35	0.21	1.04
Recent exposure							
Darifenacin	4,337	931.94	0.21	0.15	0.16	0.16	0.19
Fesoterodine	9,137	1,688.49	0.18	0.11	0.16	0.16	0.16
Oxybutynin	2,470	470.85	0.19	0.11	0.16	0.16	0.16
Solifenacin	34,122	7,839.13	0.23	0.18	0.16	0.16	0.27
Tolterodine	25,296	7,014.05	0.28	0.23	0.16	0.16	0.32
Trospium	11,694	2,740.60	0.23	0.21	0.16	0.16	0.22
Ever exposure							
Darifenacin	4,660	17,765.63	3.81	1.87	4.10	2.28	5.34
Fesoterodine	10,650	21,513.80	2.02	1.23	1.91	0.99	3.06
Oxybutynin	2,614	10,414.43	3.98	2.10	4.23	2.17	5.77
Solifenacin	38,754	125,605.01	3.24	2.15	3.01	1.35	4.89
Tolterodine	27,609	122,997.47	4.45	2.47	4.52	2.43	6.38
Trospium	12,969	45,347.68	3.50	2.51	2.80	1.46	5.44
Single exposure							
Darifenacin	3,887	4,249.39	1.09	1.35	0.45	0.27	1.25
Fesoterodine	9,458	7,105.52	0.75	0.85	0.36	0.22	0.91
Oxybutynin	1,990	1,385.76	0.70	0.95	0.33	0.28	0.61
Solifenacin	34,735	38,476.16	1.11	1.41	0.48	0.25	1.30
Tolterodine	25,913	38,121.88	1.47	1.84	0.54	0.26	1.96
Trospium	11,151	10,214.13	0.92	1.37	0.31	0.21	0.93
More than one study medication	18,227	60,262.55	3.31	2.20	2.97	1.44	5.01

OAB = overactive bladder; P25 = 25th percentile; P75 = 75th percentile; SD = standard deviation.

Table A8. Characterization of Index Therapy Episode, by OAB Medication

	Episodes Consisting of Current Exposure to a Single OAB Medication					
	Darifenacin (n=2,698)	**Fesoterodine (n=5,749)**	**Oxybutynin (n=740)**	**Solifenacin (n=30,792)**	**Tolterodine (n=23,776)**	**Trospium (n=9,105)**
Variable	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Duration of therapy episode						
Completed episodes[a]						
Mean (SD) months	7.0 (7.5)	4.9 (4.2)	6.1 (6.3)	6.4 (7.0)	7.3 (9.6)	5.6 (7.7)
<1 month	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1-3 months	1,169 (43.3%)	3,076 (53.5%)	378 (51.1%)	14,548 (47.2%)	11,417 (48.0%)	5,501 (60.4%)
4-6 months	656 (24.3%)	1,047 (18.2%)	196 (26.5%)	6,224 (20.2%)	5,147 (21.6%)	1,315 (14.4%)
7-9 months	196 (7.3%)	337 (5.9%)	39 (5.3%)	1,773 (5.8%)	1,431 (6.0%)	381 (4.2%)
>9 months	486 (18.0%)	494 (8.6%)	90 (12.2%)	4,639 (15.1%)	3,892 (16.4%)	1,090 (12.0%)
Ongoing episodes[b]						
Mean (SD) months	15.6 (18.3)	8.5 (11.0)	14.5 (17.5)	11.7 (16.9)	22.3 (26.2)	13.4 (20.7)
<1 month	6 (0.2%)	107 (1.9%)	0 (0.0%)	309 (1.0%)	91 (0.4%)	105 (1.2%)
1-3 months	59 (2.2%)	334 (5.8%)	8 (1.1%)	1,348 (4.4%)	494 (2.1%)	285 (3.1%)
4-6 months	28 (1.0%)	85 (1.5%)	10 (1.4%)	500 (1.6%)	215 (0.9%)	107 (1.2%)
7-9 months	10 (0.4%)	48 (0.8%)	3 (0.4%)	226 (0.7%)	105 (0.4%)	33 (0.4%)
>9 months	88 (3.3%)	221 (3.8%)	16 (2.2%)	1,225 (4.0%)	984 (4.1%)	288 (3.2%)
Number of prescriptions during episode[c]						
1	4,013 (42.8%)	9,883 (49.0%)	1,827 (50.5%)	39,861 (45.7%)	41,826 (53.6%)	13,197 (50.3%)
2	1,951 (20.8%)	4,092 (20.3%)	655 (18.1%)	17,671 (20.2%)	15,259 (19.6%)	3,916 (14.9%)
3	1,041 (11.1%)	1,832 (9.1%)	330 (9.1%)	9,328 (10.7%)	6,239 (8.0%)	2,325 (8.9%)
4	626 (6.7%)	1,100 (5.5%)	199 (5.5%)	5,458 (6.3%)	3,076 (3.9%)	1,399 (5.3%)
5 or more	1,752 (18.7%)	3,265 (16.2%)	605 (16.7%)	14,994 (17.2%)	11,570 (14.8%)	5,390 (20.6%)
Duration of episode; days; mean (SD)[c]	207.2 (217.8)	150.2 (151.3)	191.0 (214.4)	195.0 (225.0)	196.0 (274.4)	182.8 (255.5)

OAB = overactive bladder; SD = standard deviation.

Note: Each study participant has only one initial (index) therapy episode. Therapy episodes are created by concatenating consecutive drug episodes into a single therapy episode as long as the gap between consecutive prescriptions does not exceed the limit estimated by the waiting time duration analysis. A switch or add on of another OAB medication also defines the end of a therapy episode.

a. Refers to episodes that terminate before the end of the study.

b. Refers to episodes that terminate at end of follow-up, i.e., end of study period, emigration, or patient death.

c. All episodes are included.

Table A9. Characteristics of Index Therapy Episodes, by OAB Medication

Variable	Darifenacin n (%)	Fesoterodine n (%)	Oxybutynin n (%)	Solifenacin n (%)	Tolterodine n (%)	Trospium n (%)
All episodes	9383	20172	3616	87312	77970	26227
Episodes ending with a switch	484 (5.2%)	990 (4.9%)	386 (10.7%)	2503 (2.9%)	2328 (3.0%)	1906 (7.3%)
Switched to the following drug						
Darifenacin	NA	68 (6.9%)	42 (10.9%)	212 (8.5%)	168 (7.2%)	149 (7.8%)
Fesoterodine	79 (16.3%)	NA	54 (14.0%)	637 (25.4%)	363 (15.6%)	341 (17.9%)
Oxybutynin	46 (9.5%)	104 (10.5%)	NA	223 (8.9%)	116 (5.0%)	116 (6.1%)
Solifenacin	177 (36.6%)	426 (43.0%)	142 (36.8%)	NA	1229 (52.8%)	766 (40.2%)
Tolterodine	100 (20.7%)	167 (16.9%)	94 (24.4%)	867 (34.6%)	NA	534 (28.0%)
Trospium	82 (16.9%)	225 (22.7%)	54 (14.0%)	564 (22.5%)	452 (19.4%)	NA
Episodes ending with an add-on	542 (5.8%)	566 (2.8%)	469 (13.0%)	2423 (2.8%)	2280 (2.9%)	792 (3.0%)
Added drug						
Darifenacin	NA	46 (8.1%)	61 (13.0%)	220 (9.1%)	146 (6.4%)	66 (8.3%)
Fesoterodine	74 (13.7%)	NA	58 (12.4%)	563 (23.2%)	262 (11.5%)	128 (16.2%)
Oxybutynin	52 (9.6%)	53 (9.4%)	NA	235 (9.7%)	128 (5.6%)	50 (6.3%)
Solifenacin	180 (33.2%)	232 (41.0%)	171 (36.5%)	NA	1211 (53.1%)	293 (37.0%)
Tolterodine	139 (25.6%)	124 (21.9%)	106 (22.6%)	878 (36.2%)	NA	255 (32.2%)
Trospium	97 (17.9%)	111 (19.6%)	73 (15.6%)	527 (21.7%)	533 (23.4%)	NA

NA = not applicable; OAB = overactive bladder.

Note: Each study participant has only one initial (index) therapy episode. Therapy episodes are created by concatenating consecutive drug episodes into a single therapy episode as long as the gap between consecutive prescriptions does not exceed the limit estimated by the waiting time duration analysis. A switch or add on of another OAB medication also defines the end of a therapy episode. For all therapy episodes, each subject can contribute to more than one therapy episode.

Table N1. Baseline Characteristics of Subjects by Type of Neoplasm Event At Cohort Entry

			Type of Neoplasm Event									
	Patients Without Cancer Endpoint	Composite Event	Colon and Rectum	Pancreas	Lung and Bronchus	Female Breast	Corpus Uteri	Prostate	Urinary Bladder	Kidney	Melanoma of the Skin	Non-Hodgkin Lymphoma
	(n = 69442)	(n = 3475)	(n = 434)	(n = 139)	(n = 534)	(n = 658)	(n = 108)	(n = 881)	(n = 369)	(n =89)	(n = 179)	(n =81)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex, N (%)												
Male	27651 (39.8%)	1832 (52.7%)	200 (46.1%)	63 (45.3%)	263 (49.3%)	0 (0%)	0 (0%)	881 (100.0%)	257 (69.6%)	45 (50.6%)	83 (46.4%)	37 (45.7%)
Female	41791 (60.2%)	1643 (47.3%)	234 (53.9%)	76 (54.7%)	271 (50.7%)	658 (100.0%)	108 (100.0%)	0 (0%)	112 (30.4%)	44 (49.4%)	96 (53.6%)	44 (54.3%)
Age, N (%)												
18-24	765 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
25-34	1,689 (2.4%)	3 (0.1%)	1 (0.2%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
35-44	4,331 (6.2%)	32 (0.9%)	0 (0%)	0 (0%)	2 (0.4%)	21 (3.2%)	0 (0%)	2 (0.2%)	2 (0.5%)	1 (1.1%)	2 (1.1%)	2 (2.5%)
45-54	8,048 (11.6%)	154 (4.4%)	11 (2.5%)	3 (2.2%)	23 (4.3%)	57 (8.7%)	8 (7.4%)	18 (2.0%)	14 (3.8%)	4 (4.5%)	15 (8.4%)	1 (1.2%)
55-64	13,893 (20.0%)	658 (18.9%)	51 (11.8%)	22 (15.8%)	102 (19.1%)	169 (25.7%)	12 (11.1%)	166 (18.8%)	66 (17.9%)	18 (20.2%)	29 (16.2%)	23 (28.4%)
65-75	18,254 (26.3%)	1,214 (34.9%)	136 (31.3%)	51 (36.7%)	199 (37.3%)	205 (31.2%)	40 (37.0%)	360 (40.9%)	108 (29.3%)	34 (38.2%)	60 (33.5%)	20 (24.7%)
75-84	15,817 (22.8%)	1,088 (31.3%)	181 (41.7%)	45 (32.4%)	174 (32.6%)	164 (24.9%)	39 (36.1%)	256 (29.1%)	125 (33.9%)	22 (24.7%)	52 (29.1%)	28 (34.6%)
85+	6,645 (9.6%)	326 (9.4%)	54 (12.4%)	18 (12.9%)	34 (6.4%)	41 (6.2%)	8 (7.4%)	79 (9.0%)	54 (14.6%)	10 (11.2%)	21 (11.7%)	7 (8.6%)

Table N3a. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint for Ever Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	3475	72,917	259,072	13.4	13.0 - 13.9	5.4	5.3 - 5.6
Darifenacin	236	4,660	17,329	13.6	11.9 - 15.5	5.8	5.1 - 6.6
Fesoterodine	316	10,650	21,182	14.9	13.3 - 16.7	6.0	5.4 - 6.7
Oxybutynin	114	2,614	10,201	11.2	9.2 - 13.4	6.0	5.0 - 7.2
Solifenacin	1680	38,754	122,765	13.7	13.0 - 14.4	5.6	5.4 - 5.9
Tolterodine	1552	27,609	119,418	13.0	12.4 - 13.7	5.2	5.0 - 5.5
Trospium	599	12,969	44,114	13.6	12.5 - 14.7	5.8	5.3 - 6.2
Female ever treated with							
Any OAB drug	1643	43,434	163,236	10.1	9.6 - 10.6	4.6	4.4 - 4.9
Darifenacin	141	3,257	12,532	11.3	9.5 - 13.3	4.8	4.0 - 5.7
Fesoterodine	160	6,631	13,686	11.7	9.9 - 13.6	5.3	4.5 - 6.2
Oxybutynin	77	2,060	8,195	9.4	7.4 - 11.7	4.8	3.8 - 6.0
Solifenacin	827	23,387	78,224	10.6	9.9 - 11.3	4.8	4.5 - 5.2
Tolterodine	730	16,173	74,612	9.8	9.1 - 10.5	4.6	4.3 - 4.9
Trospium	296	8,092	28,573	10.4	9.2 - 11.6	4.8	4.3 - 5.4
Male ever treated with							
Any OAB drug	1832	29,483	95,835	19.1	18.3 - 20.0	6.2	6.0 - 6.5
Darifenacin	95	1,403	4,797	19.8	16.0 - 24.2	6.8	5.5 - 8.3
Fesoterodine	156	4,019	7,496	20.8	17.7 - 24.3	6.8	5.7 - 7.9
Oxybutynin	37	554	2,006	18.4	13.0 - 25.4	7.2	5.1 - 10.0
Solifenacin	853	15,367	44,542	19.2	17.9 - 20.5	6.4	6.0 - 6.9
Tolterodine	822	11,436	44,806	18.3	17.1 - 19.6	5.9	5.5 - 6.3
Trospium	303	4,877	15,541	19.5	17.4 - 21.8	6.7	6.0 - 7.5

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3b. Person-time, Frequency, and Incidence Rates of Bladder Cancer for Ever Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	369	72,917	259,072	1.4	1.3 - 1.6	0.6	0.6 - 0.7
Darifenacin	31	4,660	17,329	1.8	1.2 - 2.5	0.8	0.5 - 1.1
Fesoterodine	47	10,650	21,182	2.2	1.6 - 3.0	0.9	0.7 - 1.2
Oxybutynin	16	2,614	10,201	1.6	0.9 - 2.5	1.4	0.8 - 2.3
Solifenacin	209	38,754	122,765	1.7	1.5 - 1.9	0.8	0.7 - 1.0
Tolterodine	164	27,609	119,418	1.4	1.2 - 1.6	0.6	0.5 - 0.7
Trospium	58	12,969	44,114	1.3	1.0 - 1.7	0.6	0.4 - 0.7
Female ever treated with							
Any OAB drug	112	43,434	163,236	0.7	0.6 - 0.8	0.3	0.2 - 0.3
Darifenacin	15	3,257	12,532	1.2	0.7 - 2.0	0.5	0.3 - 0.9
Fesoterodine	15	6,631	13,686	1.1	0.6 - 1.8	0.5	0.3 - 0.8
Oxybutynin	6	2,060	8,195	0.7	0.3 - 1.6	0.3	0.1 - 0.6
Solifenacin	61	23,387	78,224	0.8	0.6 - 1.0	0.3	0.2 - 0.4
Tolterodine	49	16,173	74,612	0.7	0.5 - 0.9	0.3	0.2 - 0.3
Trospium	22	8,092	28,573	0.8	0.5 - 1.2	0.3	0.2 - 0.5
Male ever treated with							
Any OAB drug	257	29,483	95,835	2.7	2.4 - 3.0	1.0	0.9 - 1.1
Darifenacin	16	1,403	4,797	3.3	1.9 - 5.4	1.0	0.6 - 1.7
Fesoterodine	32	4,019	7,496	4.3	2.9 - 6.0	1.3	0.9 - 1.9
Oxybutynin	10	554	2,006	5.0	2.4 - 9.2	2.6	1.2 - 4.7
Solifenacin	148	15,367	44,542	3.3	2.8 - 3.9	1.4	1.2 - 1.6
Tolterodine	115	11,436	44,806	2.6	2.1 - 3.1	0.9	0.7 - 1.1
Trospium	36	4,877	15,541	2.3	1.6 - 3.2	0.8	0.6 - 1.1

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3c. Person-time, Frequency, and Incidence Rates of Breast Cancer for Ever Exposed Category, Females by OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Female ever treated with							
Any OAB drug	658	43,434	163,236	4.0	3.7 - 4.4	2.1	1.9 - 2.2
Darifenacin	67	3,257	12,532	5.3	4.1 - 6.8	2.3	1.8 - 3.0
Fesoterodine	91	6,631	13,686	6.6	5.4 - 8.2	3.2	2.6 - 3.9
Oxybutynin	41	2,060	8,195	5.0	3.6 - 6.8	2.8	2.0 - 3.8
Solifenacin	375	23,387	78,224	4.8	4.3 - 5.3	2.3	2.1 - 2.6
Tolterodine	309	16,173	74,612	4.1	3.7 - 4.6	2.2	1.9 - 2.4
Trospium	138	8,092	28,573	4.8	4.1 - 5.7	2.5	2.1 - 2.9

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3d. Person-time, Frequency, and Incidence Rates of Colon/Rectum Cancer for Ever Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	434	72,917	259,072	1.7	1.5 - 1.8	0.6	0.6 - 0.7
Darifenacin	35	4,660	17,329	2.0	1.4 - 2.8	0.6	0.4 - 0.9
Fesoterodine	63	10,650	21,182	3.0	2.3 - 3.8	1.2	0.9 - 1.5
Oxybutynin	18	2,614	10,201	1.8	1.0 - 2.8	0.7	0.4 - 1.1
Solifenacin	220	38,754	122,765	1.8	1.6 - 2.0	0.7	0.6 - 0.8
Tolterodine	230	27,609	119,418	1.9	1.7 - 2.2	0.7	0.6 - 0.8
Trospium	88	12,969	44,114	2.0	1.6 - 2.5	0.8	0.6 - 0.9
Female ever treated with							
Any OAB drug	234	43,434	163,236	1.4	1.3 - 1.6	0.6	0.5 - 0.6
Darifenacin	24	3,257	12,532	1.9	1.2 - 2.8	0.7	0.4 - 1.0
Fesoterodine	37	6,631	13,686	2.7	1.9 - 3.7	1.0	0.7 - 1.4
Oxybutynin	12	2,060	8,195	1.5	0.8 - 2.6	0.6	0.3 - 1.1
Solifenacin	119	23,387	78,224	1.5	1.3 - 1.8	0.6	0.5 - 0.8
Tolterodine	117	16,173	74,612	1.6	1.3 - 1.9	0.6	0.5 - 0.7
Trospium	52	8,092	28,573	1.8	1.4 - 2.4	0.7	0.5 - 0.9
Male ever treated with							
Any OAB drug	200	29,483	95,835	2.1	1.8 - 2.4	0.7	0.6 - 0.8
Darifenacin	11	1,403	4,797	2.3	1.1 - 4.1	0.5	0.3 - 1.0
Fesoterodine	26	4,019	7,496	3.5	2.3 - 5.1	1.4	0.9 - 2.0
Oxybutynin	6	554	2,006	3.0	1.1 - 6.5	0.8	0.3 - 1.7
Solifenacin	101	15,367	44,542	2.3	1.8 - 2.8	0.7	0.6 - 0.9
Tolterodine	113	11,436	44,806	2.5	2.1 - 3.0	0.8	0.6 - 0.9
Trospium	36	4,877	15,541	2.3	1.6 - 3.2	0.8	0.6 - 1.2

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3e. Person-time, Frequency, and Incidence Rates of Kidney Cancer for Ever Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	89	72,917	259,072	0.3	0.3 - 0.4	0.1	0.1 - 0.2
Darifenacin	6	4,660	17,329	0.3	0.1 - 0.8	0.1	0.0 - 0.3
Fesoterodine	10	10,650	21,182	0.5	0.2 - 0.9	0.2	0.1 - 0.4
Oxybutynin	4	2,614	10,201	0.4	0.1 - 1.0	0.2	0.1 - 0.5
Solifenacin	51	38,754	122,765	0.4	0.3 - 0.5	0.2	0.1 - 0.2
Tolterodine	41	27,609	119,418	0.3	0.2 - 0.5	0.1	0.1 - 0.2
Trospium	15	12,969	44,114	0.3	0.2 - 0.6	0.1	0.1 - 0.2
Female ever treated with							
Any OAB drug	44	43,434	163,236	0.3	0.2 - 0.4	0.1	0.1 - 0.2
Darifenacin	5	3,257	12,532	0.4	0.1 - 0.9	0.2	0.1 - 0.5
Fesoterodine	5	6,631	13,686	0.4	0.1 - 0.9	0.2	0.1 - 0.5
Oxybutynin	2	2,060	8,195	0.2	0.0 - 0.9	0.1	0.0 - 0.5
Solifenacin	25	23,387	78,224	0.3	0.2 - 0.5	0.2	0.1 - 0.3
Tolterodine	22	16,173	74,612	0.3	0.2 - 0.4	0.1	0.1 - 0.2
Trospium	6	8,092	28,573	0.2	0.1 - 0.5	0.1	0.0 - 0.2
Male ever treated with							
Any OAB drug	45	29,483	95,835	0.5	0.3 - 0.6	0.1	0.1 - 0.2
Darifenacin	1	1,403	4,797	0.2	0.0 - 1.2	0.0	0.0 - 0.2
Fesoterodine	5	4,019	7,496	0.7	0.2 - 1.6	0.2	0.1 - 0.4
Oxybutynin	2	554	2,006	1.0	0.1 - 3.6	0.3	0.0 - 1.1
Solifenacin	26	15,367	44,542	0.6	0.4 - 0.9	0.2	0.1 - 0.3
Tolterodine	19	11,436	44,806	0.4	0.3 - 0.7	0.1	0.1 - 0.2
Trospium	9	4,877	15,541	0.6	0.3 - 1.1	0.1	0.1 - 0.3

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3f. Person-time, Frequency, and Incidence Rates of Lung Cancer for Ever Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	534	72,917	259,072	2.1	1.9 - 2.2	0.8	0.7 - 0.9
Darifenacin	38	4,660	17,329	2.2	1.6 - 3.0	1.1	0.7 - 1.4
Fesoterodine	68	10,650	21,182	3.2	2.5 - 4.1	1.2	0.9 - 1.5
Oxybutynin	24	2,614	10,201	2.4	1.5 - 3.5	1.0	0.7 - 1.6
Solifenacin	268	38,754	122,765	2.2	1.9 - 2.5	0.8	0.7 - 0.9
Tolterodine	224	27,609	119,418	1.9	1.6 - 2.1	0.7	0.6 - 0.8
Trospium	92	12,969	44,114	2.1	1.7 - 2.6	0.8	0.6 - 0.9
Female ever treated with							
Any OAB drug	271	43,434	163,236	1.7	1.5 - 1.9	0.7	0.6 - 0.8
Darifenacin	20	3,257	12,532	1.6	1.0 - 2.5	0.6	0.4 - 1.0
Fesoterodine	35	6,631	13,686	2.6	1.8 - 3.6	1.1	0.8 - 1.6
Oxybutynin	16	2,060	8,195	2.0	1.1 - 3.2	1.1	0.6 - 1.7
Solifenacin	132	23,387	78,224	1.7	1.4 - 2.0	0.7	0.6 - 0.9
Tolterodine	127	16,173	74,612	1.7	1.4 - 2.0	0.8	0.6 - 0.9
Trospium	47	8,092	28,573	1.6	1.2 - 2.2	0.7	0.5 - 1.0
Male ever treated with							
Any OAB drug	263	29,483	95,835	2.7	2.4 - 3.1	0.9	0.8 - 1.0
Darifenacin	18	1,403	4,797	3.8	2.2 - 5.9	1.5	0.9 - 2.3
Fesoterodine	33	4,019	7,496	4.4	3.0 - 6.2	1.3	0.9 - 1.8
Oxybutynin	8	554	2,006	4.0	1.7 - 7.9	1.0	0.5 - 2.1
Solifenacin	136	15,367	44,542	3.1	2.6 - 3.6	0.9	0.8 - 1.1
Tolterodine	97	11,436	44,806	2.2	1.8 - 2.6	0.7	0.6 - 0.9
Trospium	45	4,877	15,541	2.9	2.1 - 3.9	0.8	0.6 - 1.0

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3g. Person-time, Frequency, and Incidence Rates of Melanoma for Ever Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	179	72,917	259,072	0.7	0.6 - 0.8	0.3	0.2 - 0.3
Darifenacin	13	4,660	17,329	0.8	0.4 - 1.3	0.3	0.1 - 0.5
Fesoterodine	22	10,650	21,182	1.0	0.7 - 1.6	0.5	0.3 - 0.7
Oxybutynin	8	2,614	10,201	0.8	0.3 - 1.5	0.5	0.2 - 1.0
Solifenacin	88	38,754	122,765	0.7	0.6 - 0.9	0.3	0.2 - 0.4
Tolterodine	89	27,609	119,418	0.7	0.6 - 0.9	0.3	0.3 - 0.4
Trospium	39	12,969	44,114	0.9	0.6 - 1.2	0.4	0.3 - 0.6
Female ever treated with							
Any OAB drug	96	43,434	163,236	0.6	0.5 - 0.7	0.3	0.2 - 0.4
Darifenacin	10	3,257	12,532	0.8	0.4 - 1.5	0.4	0.2 - 0.8
Fesoterodine	14	6,631	13,686	1.0	0.6 - 1.7	0.5	0.3 - 0.9
Oxybutynin	6	2,060	8,195	0.7	0.3 - 1.6	0.3	0.1 - 0.7
Solifenacin	53	23,387	78,224	0.7	0.5 - 0.9	0.3	0.2 - 0.4
Tolterodine	43	16,173	74,612	0.6	0.4 - 0.8	0.3	0.2 - 0.4
Trospium	23	8,092	28,573	0.8	0.5 - 1.2	0.4	0.2 - 0.6
Male ever treated with							
Any OAB drug	83	29,483	95,835	0.9	0.7 - 1.1	0.3	0.2 - 0.4
Darifenacin	3	1,403	4,797	0.6	0.1 - 1.8	0.1	0.0 - 0.4
Fesoterodine	8	4,019	7,496	1.1	0.5 - 2.1	0.4	0.2 - 0.7
Oxybutynin	2	554	2,006	1.0	0.1 - 3.6	0.7	0.1 - 2.5
Solifenacin	35	15,367	44,542	0.8	0.5 - 1.1	0.3	0.2 - 0.4
Tolterodine	46	11,436	44,806	1.0	0.8 - 1.4	0.4	0.3 - 0.5
Trospium	16	4,877	15,541	1.0	0.6 - 1.7	0.5	0.3 - 0.8

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3h. Person-time, Frequency, and Incidence Rates of Non-Hodgkin Lymphoma for Ever Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	81	72,917	259,072	0.3	0.2 - 0.4	0.1	0.1 - 0.2
Darifenacin	6	4,660	17,329	0.3	0.1 - 0.8	0.1	0.0 - 0.2
Fesoterodine	13	10,650	21,182	0.6	0.3 - 1.0	0.2	0.1 - 0.4
Oxybutynin	3	2,614	10,201	0.3	0.1 - 0.9	0.6	0.1 - 1.7
Solifenacin	47	38,754	122,765	0.4	0.3 - 0.5	0.2	0.1 - 0.2
Tolterodine	31	27,609	119,418	0.3	0.2 - 0.4	0.1	0.1 - 0.2
Trospium	18	12,969	44,114	0.4	0.2 - 0.6	0.2	0.1 - 0.3
Female ever treated with							
Any OAB drug	44	43,434	163,236	0.3	0.2 - 0.4	0.1	0.1 - 0.2
Darifenacin	5	3,257	12,532	0.4	0.1 - 0.9	0.1	0.0 - 0.3
Fesoterodine	7	6,631	13,686	0.5	0.2 - 1.1	0.2	0.1 - 0.5
Oxybutynin	2	2,060	8,195	0.2	0.0 - 0.9	0.1	0.0 - 0.4
Solifenacin	28	23,387	78,224	0.4	0.2 - 0.5	0.2	0.1 - 0.2
Tolterodine	12	16,173	74,612	0.2	0.1 - 0.3	0.1	0.0 - 0.1
Trospium	10	8,092	28,573	0.3	0.2 - 0.6	0.1	0.1 - 0.3
Male ever treated with							
Any OAB drug	37	29,483	95,835	0.4	0.3 - 0.5	0.1	0.1 - 0.2
Darifenacin	1	1,403	4,797	0.2	0.0 - 1.2	0.1	0.0 - 0.4
Fesoterodine	6	4,019	7,496	0.8	0.3 - 1.7	0.2	0.1 - 0.5
Oxybutynin	1	554	2,006	0.5	0.0 - 2.8	1.1	0.0 - 6.0
Solifenacin	19	15,367	44,542	0.4	0.3 - 0.7	0.2	0.1 - 0.3
Tolterodine	19	11,436	44,806	0.4	0.3 - 0.7	0.2	0.1 - 0.2
Trospium	8	4,877	15,541	0.5	0.2 - 1.0	0.3	0.1 - 0.5

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3i. Person-time, Frequency, and Incidence Rates of Cancer of the Corpus Uteri for Ever Exposed Category, Females by OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Female ever treated with							
Any OAB drug	108	43,434	163,236	0.7	0.5 - 0.8	0.3	0.2 - 0.4
Darifenacin	9	3,257	12,532	0.7	0.3 - 1.4	0.3	0.1 - 0.6
Fesoterodine	9	6,631	13,686	0.7	0.3 - 1.2	0.3	0.1 - 0.5
Oxybutynin	7	2,060	8,195	0.9	0.3 - 1.8	0.4	0.1 - 0.7
Solifenacin	67	23,387	78,224	0.9	0.7 - 1.1	0.4	0.3 - 0.5
Tolterodine	49	16,173	74,612	0.7	0.5 - 0.9	0.3	0.2 - 0.4
Trospium	18	8,092	28,573	0.6	0.4 - 1.0	0.2	0.1 - 0.3

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3j. Person-time, Frequency, and Incidence Rates of Prostate Cancer for Ever Exposed Category, Males by OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Male ever treated with							
Any OAB drug	881	29,483	95,835	9.2	8.6 - 9.8	2.9	2.7 - 3.1
Darifenacin	57	1,403	4,797	11.9	9.0 - 15.4	4.4	3.3 - 5.7
Fesoterodine	132	4,019	7,496	17.6	14.7 - 20.9	6.3	5.2 - 7.4
Oxybutynin	22	554	2,006	11.0	6.9 - 16.6	3.4	2.1 - 5.1
Solifenacin	478	15,367	44,542	10.7	9.8 - 11.7	3.4	3.1 - 3.7
Tolterodine	437	11,436	44,806	9.8	8.9 - 10.7	3.1	2.8 - 3.4
Trospium	173	4,877	15,541	11.1	9.5 - 12.9	3.9	3.3 - 4.5

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N3k. Person-time, Frequency, and Incidence Rates of Cancer of the Pancreas for Ever Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	139	72,917	259,072	0.5	0.5 - 0.6	0.2	0.2 - 0.2
Darifenacin	5	4,660	17,329	0.3	0.1 - 0.7	0.1	0.0 - 0.2
Fesoterodine	10	10,650	21,182	0.5	0.2 - 0.9	0.2	0.1 - 0.3
Oxybutynin	5	2,614	10,201	0.5	0.2 - 1.1	0.1	0.0 - 0.3
Solifenacin	76	38,754	122,765	0.6	0.5 - 0.8	0.2	0.2 - 0.3
Tolterodine	54	27,609	119,418	0.5	0.3 - 0.6	0.2	0.1 - 0.2
Trospium	34	12,969	44,114	0.8	0.5 - 1.1	0.3	0.2 - 0.5
Female ever treated with							
Any OAB drug	76	43,434	163,236	0.5	0.4 - 0.6	0.2	0.1 - 0.2
Darifenacin	3	3,257	12,532	0.2	0.0 - 0.7	0.1	0.0 - 0.2
Fesoterodine	3	6,631	13,686	0.2	0.0 - 0.6	0.1	0.0 - 0.3
Oxybutynin	5	2,060	8,195	0.6	0.2 - 1.4	0.3	0.1 - 0.6
Solifenacin	43	23,387	78,224	0.5	0.4 - 0.7	0.2	0.2 - 0.3
Tolterodine	31	16,173	74,612	0.4	0.3 - 0.6	0.2	0.1 - 0.2
Trospium	16	8,092	28,573	0.6	0.3 - 0.9	0.3	0.1 - 0.4
Male ever treated with							
Any OAB drug	63	29,483	95,835	0.7	0.5 - 0.8	0.2	0.2 - 0.3
Darifenacin	2	1,403	4,797	0.4	0.1 - 1.5	0.1	0.0 - 0.4
Fesoterodine	7	4,019	7,496	0.9	0.4 - 1.9	0.3	0.1 - 0.6
Oxybutynin	0	554	2,006	0.0	0.0 - 1.8	0.0	0.0 - 1.8
Solifenacin	33	15,367	44,542	0.7	0.5 - 1.0	0.2	0.2 - 0.3
Tolterodine	23	11,436	44,806	0.5	0.3 - 0.8	0.2	0.1 - 0.2
Trospium	18	4,877	15,541	1.2	0.7 - 1.8	0.4	0.2 - 0.7

CI = confidence interval; OAB = overactive bladder.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4(2)a. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint for Ever Exposure to Darifenacin

Specific OAB Medication	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Cumulative dose							
0-199 DDD	138	4,557	10,510	13.1	11.0 - 15.5	5.8	4.8 - 6.8
200-499 DDD	38	1,858	2,640	14.4	10.2 - 19.8	6.1	4.3 - 8.4
500-999 DDD	29	1,264	1,877	15.4	10.3 - 22.2	5.1	3.4 - 7.4
>1000 DDD	31	846	2,302	13.5	9.2 - 19.1	6.5	4.4 - 9.2
Cumulative duration of exposure							
0-6 months	115	3,001	8,743	13.2	10.9 - 15.8	6.0	4.9 - 7.2
6-12 months	50	1,418	3,270	15.3	11.3 - 20.2	5.4	4.0 - 7.1
>12 months	71	1,434	5,316	13.4	10.4 - 16.8	5.6	4.4 - 7.1
Time since latest exposure							
0-6 months	45	4,206	2,233	20.1	14.7 - 27.0	10.0	7.3 - 13.4
6-12 months	26	3,470	1,722	15.1	9.9 - 22.1	5.0	3.3 - 7.4
>12 months	87	3,229	8,320	10.5	8.4 - 12.9	4.3	3.4 - 5.3
Time since first exposure							
0-6 months	44	4,468	2,122	20.7	15.1 - 27.8	10.0	7.3 - 13.5
6-12 months	34	4,284	2,042	16.6	11.5 - 23.3	6.9	4.8 - 9.7
1-2 years	44	4,093	3,765	11.7	8.5 - 15.7	4.3	3.2 - 5.8
2-3 years	39	3,605	3,287	11.9	8.4 - 16.2	4.0	2.8 - 5.4
>3 years	75	3,096	6,113	12.3	9.7 - 15.4	5.8	4.6 - 7.3

CI = confidence interval; DDD = defined daily dose; OAB = overactive bladder.

Note: Accumulation of person-time stopped at the occurrence of an event or censoring.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4(2)b. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint for Ever Exposure to Fesoterodine

Specific OAB Medication	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Cumulative dose							
0-199 DDD	214	10,542	13,639	15.7	13.7 - 17.9	6.4	5.6 - 7.3
200-499 DDD	53	4,101	3,593	14.8	11.1 - 19.3	6.2	4.7 - 8.1
500-999 DDD	34	2,476	2,290	14.9	10.3 - 20.8	4.9	3.4 - 6.9
>1000 DDD	15	1,274	1,661	9.0	5.1 - 14.9	3.9	2.2 - 6.5
Cumulative duration of exposure							
0-6 months	188	7,847	12,152	15.5	13.3 - 17.8	6.4	5.6 - 7.4
6-12 months	59	3,208	3,973	14.9	11.3 - 19.2	5.7	4.4 - 7.4
>12 months	69	2,575	5,057	13.6	10.6 - 17.3	5.1	4.0 - 6.4
Time since latest exposure							
0-6 months	60	8,960	4,007	15.0	11.4 - 19.3	5.5	4.2 - 7.1
6-12 months	34	6,169	2,786	12.2	8.5 - 17.1	4.5	3.1 - 6.3
>12 months	78	4,919	6,375	12.2	9.7 - 15.3	5.3	4.2 - 6.6
Time since first exposure							
0-6 months	93	10,427	4,743	19.6	15.8 - 24.0	8.5	6.8 - 10.4
6-12 months	69	9,180	4,173	16.5	12.9 - 20.9	6.0	4.7 - 7.7
1-2 years	78	7,923	6,394	12.2	9.6 - 15.2	4.3	3.4 - 5.4
2-3 years	55	5,171	3,981	13.8	10.4 - 18.0	5.3	4.0 - 6.9
>3 years	21	2,906	1,891	11.1	6.9 - 17.0	6.4	3.9 - 9.7

CI = confidence interval; DDD = defined daily dose; OAB = overactive bladder.

Note: Accumulation of person-time stopped at the occurrence of an event or censoring.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4(2)c. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint for Ever Exposure to Oxybutynin

Specific OAB Medication	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Cumulative dose							
0-199 DDD	102	2,602	8,415	12.1	9.9 - 14.7	6.8	5.6 - 8.3
200-499 DDD	7	488	1,049	6.7	2.7 - 13.8	2.7	1.1 - 5.6
500-999 DDD	4	249	530	7.5	2.1 - 19.3	2.5	0.7 - 6.4
>1000 DDD	1	101	207	4.8	0.1 - 26.9	1.6	0.0 - 9.0
Cumulative duration of exposure							
0-6 months	78	1,956	6,856	11.4	9.0 - 14.2	6.5	5.1 - 8.1
6-12 months	24	582	1,637	14.7	9.4 - 21.8	6.7	4.3 - 10.0
>12 months	12	425	1,708	7.0	3.6 - 12.3	2.4	1.3 - 4.3
Time since latest exposure							
0-6 months	17	2,395	1,242	13.7	8.0 - 21.9	10.1	5.9 - 16.2
6-12 months	8	2,159	1,053	7.6	3.3 - 15.0	8.8	3.8 - 17.3
>12 months	64	2,039	6,102	10.5	8.1 - 13.4	4.8	3.7 - 6.1
Time since first exposure							
0-6 months	28	2,528	1,195	23.4	15.6 - 33.9	11.5	7.7 - 16.7
6-12 months	13	2,434	1,148	11.3	6.0 - 19.4	10.1	5.4 - 17.3
1-2 years	16	2,290	2,095	7.6	4.4 - 12.4	5.2	3.0 - 8.5
2-3 years	23	2,008	1,799	12.8	8.1 - 19.2	5.0	3.2 - 7.5
>3 years	34	1,694	3,964	8.6	5.9 - 12.0	4.3	3.0 - 6.1

CI = confidence interval; DDD = defined daily dose; OAB = overactive bladder.

Note: Accumulation of person-time stopped at the occurrence of an event or censoring.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4(2)d. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint for Ever Exposure to Solifenacin

Specific OAB Medication	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Cumulative dose							
0-199 DDD	1043	38,109	68,564	15.2	14.3 - 16.2	6.0	5.7 - 6.4
200-499 DDD	251	16,997	21,194	11.8	10.4 - 13.4	5.2	4.6 - 5.9
500-999 DDD	173	11,160	14,197	12.2	10.4 - 14.1	5.2	4.5 - 6.0
>1000 DDD	213	7,238	18,810	11.3	9.9 - 13.0	4.6	4.0 - 5.3
Cumulative duration of exposure							
0-6 months	859	26,017	54,920	15.6	14.6 - 16.7	6.2	5.8 - 6.6
6-12 months	330	13,475	24,311	13.6	12.1 - 15.1	5.7	5.1 - 6.3
>12 months	491	12,712	43,534	11.3	10.3 - 12.3	4.7	4.3 - 5.1
Time since latest exposure							
0-6 months	265	33,344	17,959	14.8	13.0 - 16.6	6.1	5.4 - 6.9
6-12 months	162	24,798	12,336	13.1	11.2 - 15.3	5.6	4.8 - 6.5
>12 months	536	21,405	47,772	11.2	10.3 - 12.2	4.6	4.2 - 5.0
Time since first exposure							
0-6 months	418	37,492	17,468	23.9	21.7 - 26.3	9.2	8.3 - 10.1
6-12 months	208	34,286	15,994	13.0	11.3 - 14.9	5.5	4.8 - 6.3
1-2 years	366	31,107	27,347	13.4	12.0 - 14.8	5.2	4.7 - 5.8
2-3 years	249	24,906	21,723	11.5	10.1 - 13.0	4.8	4.2 - 5.4
>3 years	439	19,568	40,233	10.9	9.9 - 12.0	4.7	4.2 - 5.1

CI = confidence interval; DDD = defined daily dose; OAB = overactive bladder.

Note: Accumulation of person-time stopped at the occurrence of an event or censoring.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4(2)e. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint for Ever Exposure to Tolterodine

Specific OAB Medication	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Cumulative dose							
0-199 DDD	1071	27,546	77,945	13.7	12.9 - 14.6	5.5	5.1 - 5.8
200-499 DDD	258	11,110	22,248	11.6	10.2 - 13.1	4.8	4.2 - 5.4
500-999 DDD	210	7,820	16,247	12.9	11.2 - 14.8	4.9	4.3 - 5.6
>1000 DDD	227	6,176	21,025	10.8	9.4 - 12.3	4.7	4.1 - 5.3
Cumulative duration of exposure							
0-6 months	689	17,430	49,790	13.8	12.8 - 14.9	5.5	5.1 - 5.9
6-12 months	379	10,440	26,786	14.1	12.8 - 15.6	5.4	4.9 - 6.0
>12 months	698	13,335	60,888	11.5	10.6 - 12.3	4.8	4.4 - 5.1
Time since latest exposure							
0-6 months	220	24,526	15,422	14.3	12.4 - 16.3	5.0	4.4 - 5.8
6-12 months	121	19,716	10,611	11.4	9.5 - 13.6	5.2	4.3 - 6.3
>12 months	635	18,281	53,538	11.9	11.0 - 12.8	4.9	4.5 - 5.3
Time since first exposure							
0-6 months	259	22,155	10,537	24.6	21.7 - 27.8	9.1	8.1 - 10.3
6-12 months	126	21,093	10,047	12.5	10.4 - 14.9	4.7	3.9 - 5.6
1-2 years	193	20,473	18,722	10.3	8.9 - 11.9	3.5	3.0 - 4.1
2-3 years	204	18,910	16,983	12.0	10.4 - 13.8	5.0	4.3 - 5.7
>3 years	984	23,835	81,175	12.1	11.4 - 12.9	5.1	4.8 - 5.4

CI = confidence interval; DDD = defined daily dose; OAB = overactive bladder.

Note: Accumulation of person-time stopped at the occurrence of an event or censoring.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4(2)f. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint for Ever Exposure to Trospium

Specific OAB Medication	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Cumulative dose							
0-199 DDD	447	13,115	33,391	13.4	12.2 - 14.7	5.7	5.2 - 6.2
200-499 DDD	114	4,048	7,632	14.9	12.3 - 17.9	5.8	4.8 - 7.0
500-999 DDD	54	2,230	4,690	11.5	8.7 - 15.0	5.4	4.0 - 7.0
>1000 DDD	32	1,048	2,708	11.8	8.1 - 16.7	4.5	3.1 - 6.4
Cumulative duration of exposure							
0-6 months	363	10,017	26,358	13.8	12.4 - 15.3	5.8	5.2 - 6.5
6-12 months	95	3,301	6,952	13.7	11.1 - 16.7	6.0	4.9 - 7.4
>12 months	189	3,742	15,110	12.5	10.8 - 14.4	5.1	4.4 - 5.9
Time since latest exposure							
0-6 months	103	11,346	6,406	16.1	13.1 - 19.5	6.6	5.4 - 8.0
6-12 months	55	9,136	4,592	12.0	9.0 - 15.6	4.8	3.6 - 6.3
>12 months	254	8,106	20,598	12.3	10.9 - 13.9	5.2	4.6 - 5.9
Time since first exposure							
0-6 months	120	11,994	5,560	21.6	17.9 - 25.8	9.0	7.4 - 10.7
6-12 months	63	11,016	5,143	12.2	9.4 - 15.7	5.0	3.8 - 6.3
1-2 years	124	10,353	8,942	13.9	11.5 - 16.5	5.8	4.8 - 6.9
2-3 years	98	8,432	7,006	14.0	11.4 - 17.0	5.4	4.3 - 6.5
>3 years	242	7,071	21,769	11.1	9.8 - 12.6	4.9	4.3 - 5.6

CI = confidence interval; DDD = defined daily dose; OAB = overactive bladder.
Note: Accumulation of person-time stopped at the occurrence of an event or censoring.
a. The reference for standardization was the Danish population on January 1, 2008.

Table N4a. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint for Single Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	2483	51,956	158,716	15.6	15.0 - 16.3	6.2	6.0 - 6.4
Darifenacin	96	1,753	6,033	15.9	12.9 - 19.4	6.7	5.4 - 8.1
Fesoterodine	137	4,476	8,414	16.3	13.7 - 19.2	6.6	5.6 - 7.9
Oxybutynin	12	317	1,081	11.1	5.7 - 19.4	4.8	2.5 - 8.5
Solifenacin	989	23,368	64,650	15.3	14.4 - 16.3	6.2	5.8 - 6.6
Tolterodine	982	16,349	62,827	15.6	14.7 - 16.6	6.0	5.6 - 6.4
Trospium	267	5,693	15,711	17.0	15.0 - 19.2	7.0	6.2 - 7.9
Female ever treated with							
Any OAB drug	1073	29,589	94,935	11.3	10.6 - 12.0	5.3	4.9 - 5.6
Darifenacin	46	1,078	3,861	11.9	8.7 - 15.9	5.1	3.7 - 6.8
Fesoterodine	56	2,555	5,030	11.1	8.4 - 14.5	5.2	4.0 - 6.8
Oxybutynin	6	245	846	7.1	2.6 - 15.4	2.7	1.0 - 6.0
Solifenacin	436	13,346	38,583	11.3	10.3 - 12.4	5.3	4.8 - 5.8
Tolterodine	414	9,103	37,328	11.1	10.0 - 12.2	5.2	4.7 - 5.7
Trospium	115	3,262	9,288	12.4	10.2 - 14.9	6.0	4.9 - 7.2
Male ever treated with							
Any OAB drug	1410	22,367	63,781	22.1	21.0 - 23.3	7.2	6.8 - 7.5
Darifenacin	50	675	2,173	23.0	17.1 - 30.3	8.3	6.1 - 10.9
Fesoterodine	81	1,921	3,384	23.9	19.0 - 29.8	8.1	6.4 - 10.0
Oxybutynin	6	72	235	25.5	9.4 - 55.6	7.0	2.6 - 15.2
Solifenacin	553	10,022	26,067	21.2	19.5 - 23.1	7.1	6.5 - 7.7
Tolterodine	568	7,246	25,498	22.3	20.5 - 24.2	6.8	6.3 - 7.4
Trospium	152	2,431	6,423	23.7	20.1 - 27.7	8.1	6.8 - 9.5

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4b. Person-time, Frequency, and Incidence Rates of Bladder Cancer for Single Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	282	51,956	158,716	1.8	1.6 - 2.0	0.7	0.7 - 0.8
Darifenacin	13	1,753	6,033	2.2	1.1 - 3.7	0.8	0.4 - 1.3
Fesoterodine	19	4,476	8,414	2.3	1.4 - 3.5	1.0	0.6 - 1.6
Oxybutynin	0	317	1,081	0.0	0.0 - 3.4	0.0	0.0 - 3.4
Solifenacin	116	23,368	64,650	1.8	1.5 - 2.2	0.9	0.7 - 1.1
Tolterodine	102	16,349	62,827	1.6	1.3 - 2.0	0.6	0.5 - 0.7
Trospium	32	5,693	15,711	2.0	1.4 - 2.9	0.7	0.5 - 1.0
Female ever treated with							
Any OAB drug	76	29,589	94,935	0.8	0.6 - 1.0	0.3	0.2 - 0.4
Darifenacin	6	1,078	3,861	1.6	0.6 - 3.4	0.6	0.2 - 1.3
Fesoterodine	9	2,555	5,030	1.8	0.8 - 3.4	0.8	0.4 - 1.5
Oxybutynin	0	245	846	0.0	0.0 - 4.4	0.0	0.0 - 4.4
Solifenacin	27	13,346	38,583	0.7	0.5 - 1.0	0.3	0.2 - 0.4
Tolterodine	25	9,103	37,328	0.7	0.4 - 1.0	0.2	0.2 - 0.4
Trospium	9	3,262	9,288	1.0	0.4 - 1.8	0.4	0.2 - 0.8
Male ever treated with							
Any OAB drug	206	22,367	63,781	3.2	2.8 - 3.7	1.2	1.0 - 1.4
Darifenacin	7	675	2,173	3.2	1.3 - 6.6	0.9	0.4 - 1.9
Fesoterodine	10	1,921	3,384	3.0	1.4 - 5.4	1.2	0.6 - 2.2
Oxybutynin	0	72	235	0.0	0.0 - 15.7	0.0	0.0 - 15.7
Solifenacin	89	10,022	26,067	3.4	2.7 - 4.2	1.5	1.2 - 1.8
Tolterodine	77	7,246	25,498	3.0	2.4 - 3.8	1.0	0.8 - 1.2
Trospium	23	2,431	6,423	3.6	2.3 - 5.4	1.1	0.7 - 1.6

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4c. Person-time, Frequency, and Incidence Rates of Breast Cancer for Single Exposed Category, Females by OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Female ever treated with							
Any OAB drug	428	29,589	94,935	4.5	4.1 - 5.0	2.3	2.1 - 2.6
Darifenacin	16	1,078	3,861	4.1	2.4 - 6.7	2.0	1.1 - 3.2
Fesoterodine	22	2,555	5,030	4.4	2.7 - 6.6	2.4	1.5 - 3.6
Oxybutynin	3	245	846	3.5	0.7 - 10.4	1.3	0.3 - 3.8
Solifenacin	179	13,346	38,583	4.6	4.0 - 5.4	2.3	2.0 - 2.7
Tolterodine	168	9,103	37,328	4.5	3.8 - 5.2	2.4	2.0 - 2.8
Trospium	40	3,262	9,288	4.3	3.1 - 5.9	2.5	1.8 - 3.4

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4d. Person-time, Frequency, and Incidence Rates of Colon/Rectum Cancer for Single Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	285	51,956	158,716	1.8	1.6 - 2.0	0.7	0.6 - 0.7
Darifenacin	10	1,753	6,033	1.7	0.8 - 3.0	0.5	0.2 - 0.9
Fesoterodine	16	4,476	8,414	1.9	1.1 - 3.1	0.8	0.5 - 1.3
Oxybutynin	2	317	1,081	1.9	0.2 - 6.7	1.1	0.1 - 3.9
Solifenacin	97	23,368	64,650	1.5	1.2 - 1.8	0.6	0.5 - 0.7
Tolterodine	126	16,349	62,827	2.0	1.7 - 2.4	0.7	0.6 - 0.8
Trospium	34	5,693	15,711	2.2	1.5 - 3.0	0.8	0.5 - 1.1
Female ever treated with							
Any OAB drug	148	29,589	94,935	1.6	1.3 - 1.8	0.6	0.5 - 0.7
Darifenacin	6	1,078	3,861	1.6	0.6 - 3.4	0.6	0.2 - 1.3
Fesoterodine	8	2,555	5,030	1.6	0.7 - 3.1	0.6	0.3 - 1.2
Oxybutynin	1	245	846	1.2	0.0 - 6.6	0.5	0.0 - 2.9
Solifenacin	53	13,346	38,583	1.4	1.0 - 1.8	0.6	0.5 - 0.8
Tolterodine	59	9,103	37,328	1.6	1.2 - 2.0	0.5	0.4 - 0.7
Trospium	21	3,262	9,288	2.3	1.4 - 3.5	0.7	0.5 - 1.1
Male ever treated with							
Any OAB drug	137	22,367	63,781	2.1	1.8 - 2.5	0.7	0.6 - 0.9
Darifenacin	4	675	2,173	1.8	0.5 - 4.7	0.4	0.1 - 1.0
Fesoterodine	8	1,921	3,384	2.4	1.0 - 4.7	1.0	0.4 - 2.0
Oxybutynin	1	72	235	4.3	0.1 - 23.7	1.7	0.0 - 9.2
Solifenacin	44	10,022	26,067	1.7	1.2 - 2.3	0.6	0.4 - 0.7
Tolterodine	67	7,246	25,498	2.6	2.0 - 3.3	0.8	0.6 - 1.1
Trospium	13	2,431	6,423	2.0	1.1 - 3.5	0.8	0.4 - 1.4

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4e. Person-time, Frequency, and Incidence Rates of Kidney Cancer for Single Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	64	51,956	158,716	0.4	0.3 - 0.5	0.2	0.1 - 0.2
Darifenacin	2	1,753	6,033	0.3	0.0 - 1.2	0.1	0.0 - 0.3
Fesoterodine	3	4,476	8,414	0.4	0.1 - 1.0	0.1	0.0 - 0.4
Oxybutynin	1	317	1,081	0.9	0.0 - 5.2	0.3	0.0 - 1.7
Solifenacin	27	23,368	64,650	0.4	0.3 - 0.6	0.2	0.1 - 0.3
Tolterodine	25	16,349	62,827	0.4	0.3 - 0.6	0.2	0.1 - 0.2
Trospium	6	5,693	15,711	0.4	0.1 - 0.8	0.2	0.1 - 0.3
Female ever treated with							
Any OAB drug	31	29,589	94,935	0.3	0.2 - 0.5	0.2	0.1 - 0.2
Darifenacin	2	1,078	3,861	0.5	0.1 - 1.9	0.2	0.0 - 0.5
Fesoterodine	1	2,555	5,030	0.2	0.0 - 1.1	0.1	0.0 - 0.4
Oxybutynin	0	245	846	0.0	0.0 - 4.4	0.0	0.0 - 4.4
Solifenacin	11	13,346	38,583	0.3	0.1 - 0.5	0.2	0.1 - 0.3
Tolterodine	14	9,103	37,328	0.4	0.2 - 0.6	0.2	0.1 - 0.3
Trospium	3	3,262	9,288	0.3	0.1 - 0.9	0.2	0.0 - 0.5
Male ever treated with							
Any OAB drug	33	22,367	63,781	0.5	0.4 - 0.7	0.2	0.1 - 0.2
Darifenacin	0	675	2,173	0.0	0.0 - 1.7	0.0	0.0 - 1.7
Fesoterodine	2	1,921	3,384	0.6	0.1 - 2.1	0.2	0.0 - 0.6
Oxybutynin	1	72	235	4.3	0.1 - 23.7	0.6	0.0 - 3.4
Solifenacin	16	10,022	26,067	0.6	0.4 - 1.0	0.2	0.1 - 0.3
Tolterodine	11	7,246	25,498	0.4	0.2 - 0.8	0.1	0.1 - 0.2
Trospium	3	2,431	6,423	0.5	0.1 - 1.4	0.1	0.0 - 0.4

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4f. Person-time, Frequency, and Incidence Rates of Lung Cancer for Single Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	385	51,956	158,716	2.4	2.2 - 2.7	0.9	0.8 - 1.0
Darifenacin	20	1,753	6,033	3.3	2.0 - 5.1	1.7	1.0 - 2.6
Fesoterodine	27	4,476	8,414	3.2	2.1 - 4.7	1.0	0.7 - 1.5
Oxybutynin	2	317	1,081	1.9	0.2 - 6.7	1.1	0.1 - 3.9
Solifenacin	155	23,368	64,650	2.4	2.0 - 2.8	0.9	0.8 - 1.0
Tolterodine	142	16,349	62,827	2.3	1.9 - 2.7	0.9	0.8 - 1.1
Trospium	39	5,693	15,711	2.5	1.8 - 3.4	0.9	0.7 - 1.3
Female ever treated with							
Any OAB drug	182	29,589	94,935	1.9	1.6 - 2.2	0.9	0.7 - 1.0
Darifenacin	8	1,078	3,861	2.1	0.9 - 4.1	0.7	0.3 - 1.4
Fesoterodine	9	2,555	5,030	1.8	0.8 - 3.4	0.7	0.3 - 1.3
Oxybutynin	1	245	846	1.2	0.0 - 6.6	0.5	0.0 - 2.8
Solifenacin	70	13,346	38,583	1.8	1.4 - 2.3	0.8	0.6 - 1.0
Tolterodine	74	9,103	37,328	2.0	1.6 - 2.5	1.0	0.7 - 1.2
Trospium	20	3,262	9,288	2.2	1.3 - 3.3	1.1	0.7 - 1.7
Male ever treated with							
Any OAB drug	203	22,367	63,781	3.2	2.8 - 3.7	1.0	0.9 - 1.2
Darifenacin	12	675	2,173	5.5	2.9 - 9.6	2.7	1.4 - 4.7
Fesoterodine	18	1,921	3,384	5.3	3.2 - 8.4	1.4	0.8 - 2.2
Oxybutynin	1	72	235	4.3	0.1 - 23.7	1.7	0.0 - 9.2
Solifenacin	85	10,022	26,067	3.3	2.6 - 4.0	1.0	0.8 - 1.3
Tolterodine	68	7,246	25,498	2.7	2.1 - 3.4	0.9	0.7 - 1.1
Trospium	19	2,431	6,423	3.0	1.8 - 4.6	0.7	0.4 - 1.2

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4g. Person-time, Frequency, and Incidence Rates of Melanoma for Single Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	115	51,956	158,716	0.7	0.6 - 0.9	0.3	0.2 - 0.3
Darifenacin	3	1,753	6,033	0.5	0.1 - 1.5	0.2	0.0 - 0.7
Fesoterodine	8	4,476	8,414	1.0	0.4 - 1.9	0.4	0.2 - 0.8
Oxybutynin	1	317	1,081	0.9	0.0 - 5.2	0.1	0.0 - 0.8
Solifenacin	39	23,368	64,650	0.6	0.4 - 0.8	0.2	0.2 - 0.3
Tolterodine	52	16,349	62,827	0.8	0.6 - 1.1	0.3	0.2 - 0.4
Trospium	12	5,693	15,711	0.8	0.4 - 1.3	0.3	0.1 - 0.5
Female ever treated with							
Any OAB drug	53	29,589	94,935	0.6	0.4 - 0.7	0.3	0.2 - 0.4
Darifenacin	1	1,078	3,861	0.3	0.0 - 1.4	0.3	0.0 - 1.8
Fesoterodine	3	2,555	5,030	0.6	0.1 - 1.7	0.4	0.1 - 1.2
Oxybutynin	0	245	846	0.0	0.0 - 4.4	0.0	0.0 - 4.4
Solifenacin	21	13,346	38,583	0.5	0.3 - 0.8	0.3	0.2 - 0.4
Tolterodine	23	9,103	37,328	0.6	0.4 - 0.9	0.3	0.2 - 0.5
Trospium	5	3,262	9,288	0.5	0.2 - 1.3	0.3	0.1 - 0.6
Male ever treated with							
Any OAB drug	62	22,367	63,781	1.0	0.7 - 1.2	0.3	0.2 - 0.4
Darifenacin	2	675	2,173	0.9	0.1 - 3.3	0.2	0.0 - 0.6
Fesoterodine	5	1,921	3,384	1.5	0.5 - 3.4	0.4	0.1 - 0.9
Oxybutynin	1	72	235	4.3	0.1 - 23.7	0.3	0.0 - 1.6
Solifenacin	18	10,022	26,067	0.7	0.4 - 1.1	0.2	0.1 - 0.4
Tolterodine	29	7,246	25,498	1.1	0.8 - 1.6	0.3	0.2 - 0.5
Trospium	7	2,431	6,423	1.1	0.4 - 2.2	0.3	0.1 - 0.6

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4h. Person-time, Frequency, and Incidence Rates of Non-Hodgkin Lymphoma for Single Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	53	51,956	158,716	0.3	0.3 - 0.4	0.1	0.1 - 0.2
Darifenacin	5	1,753	6,033	0.8	0.3 - 1.9	0.3	0.1 - 0.7
Fesoterodine	4	4,476	8,414	0.5	0.1 - 1.2	0.2	0.0 - 0.5
Oxybutynin	0	317	1,081	0.0	0.0 - 3.4	0.0	0.0 - 3.4
Solifenacin	22	23,368	64,650	0.3	0.2 - 0.5	0.2	0.1 - 0.2
Tolterodine	15	16,349	62,827	0.2	0.1 - 0.4	0.1	0.0 - 0.1
Trospium	7	5,693	15,711	0.4	0.2 - 0.9	0.2	0.1 - 0.3
Female ever treated with							
Any OAB drug	30	29,589	94,935	0.3	0.2 - 0.5	0.1	0.1 - 0.2
Darifenacin	4	1,078	3,861	1.0	0.3 - 2.7	0.4	0.1 - 1.1
Fesoterodine	3	2,555	5,030	0.6	0.1 - 1.7	0.3	0.1 - 0.8
Oxybutynin	0	245	846	0.0	0.0 - 4.4	0.0	0.0 - 4.4
Solifenacin	14	13,346	38,583	0.4	0.2 - 0.6	0.2	0.1 - 0.3
Tolterodine	6	9,103	37,328	0.2	0.1 - 0.3	0.1	0.0 - 0.1
Trospium	3	3,262	9,288	0.3	0.1 - 0.9	0.1	0.0 - 0.3
Male ever treated with							
Any OAB drug	23	22,367	63,781	0.4	0.2 - 0.5	0.1	0.1 - 0.2
Darifenacin	1	675	2,173	0.5	0.0 - 2.6	0.2	0.0 - 1.1
Fesoterodine	1	1,921	3,384	0.3	0.0 - 1.6	0.1	0.0 - 0.4
Oxybutynin	0	72	235	0.0	0.0 - 15.7	0.0	0.0 - 15.7
Solifenacin	8	10,022	26,067	0.3	0.1 - 0.6	0.1	0.1 - 0.3
Tolterodine	9	7,246	25,498	0.4	0.2 - 0.7	0.1	0.0 - 0.2
Trospium	4	2,431	6,423	0.6	0.2 - 1.6	0.2	0.1 - 0.5

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4i. Person-time, Frequency, and Incidence Rates of Cancer of the Corpus Uteri for Single Exposed Category, Females by OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Female ever treated with							
Any OAB drug	75	29,589	94,935	0.8	0.6 - 1.0	0.4	0.3 - 0.4
Darifenacin	2	1,078	3,861	0.5	0.1 - 1.9	0.3	0.0 - 1.0
Fesoterodine	0	2,555	5,030	0.0	0.0 - 0.7	0.0	0.0 - 0.7
Oxybutynin	0	245	846	0.0	0.0 - 4.4	0.0	0.0 - 4.4
Solifenacin	35	13,346	38,583	0.9	0.6 - 1.3	0.4	0.3 - 0.6
Tolterodine	29	9,103	37,328	0.8	0.5 - 1.1	0.4	0.3 - 0.5
Trospium	9	3,262	9,288	1.0	0.4 - 1.8	0.4	0.2 - 0.7

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4j. Person-time, Frequency, and Incidence Rates of Prostate Cancer for Single Exposed Category, Males by OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Male ever treated with							
Any OAB drug	698	22,367	63,781	10.9	10.1 - 11.8	3.5	3.2 - 3.7
Darifenacin	24	675	2,173	11.0	7.1 - 16.4	3.9	2.5 - 5.8
Fesoterodine	31	1,921	3,384	9.2	6.2 - 13.0	3.2	2.2 - 4.6
Oxybutynin	2	72	235	8.5	1.0 - 30.8	2.8	0.3 - 10.0
Solifenacin	273	10,022	26,067	10.5	9.3 - 11.8	3.3	2.9 - 3.7
Tolterodine	291	7,246	25,498	11.4	10.1 - 12.8	3.4	3.1 - 3.9
Trospium	77	2,431	6,423	12.0	9.5 - 15.0	4.5	3.5 - 5.6

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

Table N4k. Person-time, Frequency, and Incidence Rates of Cancer of the Pancreas for Single Exposed Category, by Sex and OAB Medication

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
Overall ever treated with							
Any OAB drug	95	51,956	158,716	0.6	0.5 - 0.7	0.2	0.2 - 0.2
Darifenacin	1	1,753	6,033	0.2	0.0 - 0.9	0.0	0.0 - 0.2
Fesoterodine	6	4,476	8,414	0.7	0.3 - 1.6	0.3	0.1 - 0.6
Oxybutynin	1	317	1,081	0.9	0.0 - 5.2	0.2	0.0 - 1.1
Solifenacin	45	23,368	64,650	0.7	0.5 - 0.9	0.2	0.2 - 0.3
Tolterodine	31	16,349	62,827	0.5	0.3 - 0.7	0.2	0.1 - 0.2
Trospium	11	5,693	15,711	0.7	0.3 - 1.3	0.3	0.2 - 0.6
Female ever treated with							
Any OAB drug	50	29,589	94,935	0.5	0.4 - 0.7	0.2	0.2 - 0.3
Darifenacin	1	1,078	3,861	0.3	0.0 - 1.4	0.1	0.0 - 0.5
Fesoterodine	1	2,555	5,030	0.2	0.0 - 1.1	0.1	0.0 - 0.4
Oxybutynin	1	245	846	1.2	0.0 - 6.6	0.4	0.0 - 2.2
Solifenacin	26	13,346	38,583	0.7	0.4 - 1.0	0.3	0.2 - 0.4
Tolterodine	16	9,103	37,328	0.4	0.2 - 0.7	0.2	0.1 - 0.3
Trospium	5	3,262	9,288	0.5	0.2 - 1.3	0.3	0.1 - 0.6
Male ever treated with							
Any OAB drug	45	22,367	63,781	0.7	0.5 - 0.9	0.2	0.1 - 0.3
Darifenacin	0	675	2,173	0.0	0.0 - 1.7	0.0	0.0 - 1.7
Fesoterodine	5	1,921	3,384	1.5	0.5 - 3.4	0.5	0.2 - 1.1
Oxybutynin	0	72	235	0.0	0.0 - 15.7	0.0	0.0 - 15.7
Solifenacin	19	10,022	26,067	0.7	0.4 - 1.1	0.2	0.1 - 0.3
Tolterodine	15	7,246	25,498	0.6	0.3 - 1.0	0.1	0.1 - 0.2
Trospium	6	2,431	6,423	0.9	0.3 - 2.0	0.4	0.1 - 0.8

CI = confidence interval; OAB = overactive bladder.

Note: Single use was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer endpoint, whichever came first.

a. The reference for standardization was the Danish population on January 1, 2008.

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

	Patients Without a Cardiovas-cular Endpoint Event		Type of Cardiovascular Event													
			Acute Myocardial Infarction		Stroke		Cardiovas-cular Mortality		Coronary Heart Death		Cerebrovas-cular Death		Composite Endpoint		All-Cause Death	
	(n = 60543)		(n = 1698)		(n = 637)		(n = 3488)		(n =2055)		(n = 1433)		(n = 5074)		(n = 11044)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sex, N (%)																
Male	23,167	(38.3%)	918	(54.1%)	280	(44.0%)	1,874	(53.7%)	1,146	(55.8%)	728	(50.8%)	2,689	(53.0%)	5,630	(51.0%)
Female	37,376	(61.7%)	780	(45.9%)	357	(56.0%)	1,614	(46.3%)	909	(44.2%)	705	(49.2%)	2,385	(47.0%)	5,414	(49.0%)
Age																
18-24	760	(1.3%)	0	(0.0%)	1	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.0%)	4	(0.0%)
25-34	1,672	(2.8%)	2	(0.1%)	3	(0.5%)	3	(0.1%)	3	(0.1%)	0	(0.0%)	7	(0.1%)	16	(0.1%)
35-44	4,287	(7.1%)	10	(0.6%)	14	(2.2%)	19	(0.5%)	9	(0.4%)	10	(0.7%)	37	(0.7%)	58	(0.5%)
45-54	7,874	(13.0%)	65	(3.8%)	38	(6.0%)	49	(1.4%)	31	(1.5%)	18	(1.3%)	138	(2.7%)	243	(2.2%)
55-64	13,448	(22.2%)	240	(14.1%)	92	(14.4%)	217	(6.2%)	132	(6.4%)	85	(5.9%)	492	(9.7%)	843	(7.6%)
65-74	16,816	(27.8%)	453	(26.7%)	183	(28.7%)	698	(20.0%)	381	(18.5%)	317	(22.1%)	1,171	(23.1%)	2,231	(20.2%)
75-84	12,021	(19.9%)	642	(37.8%)	223	(35.0%)	1,505	(43.1%)	870	(42.3%)	635	(44.3%)	2,025	(39.9%)	4,479	(40.6%)
85+	3,665	(6.1%)	286	(16.8%)	83	(13.0%)	997	(28.6%)	629	(30.6%)	368	(25.7%)	1,203	(23.7%)	3,170	(28.7%)

Table CV3a. Person-time, Frequency, and Incidence Rates for Acute Myocardial Infarction, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	742	72,917	111,647.05	6.65	[6.2-7.1]	2.66	[2.5-2.9]
Darifenacin	30	4,643	5,203.89	5.76	[3.9-8.2]	2.24	[1.5-3.2]
Fesoterodine	43	10,591	8,105.14	5.31	[3.8-7.1]	1.76	[1.3-2.4]
Oxybutynin	6	2,604	1,840.85	3.26	[1.2-7.1]	1.45	[0.5-3.2]
Solifenacin	296	38,667	45,587.21	6.49	[5.8-7.3]	2.88	[2.6-3.2]
Tolterodine	293	27,583	40,863.21	7.17	[6.4-8]	2.71	[2.4-3]
Trospium	91	12,932	12,810.98	7.10	[5.7-8.7]	2.69	[2.2-3.3]
AGE OVER 65							
Any OAB drug	607	41,396	63,551.81	9.55	[8.8-10.3]	1.83	[1.7-2]
Darifenacin	23	2,667	2,993.91	7.68	[4.9-11.5]	1.77	[1.1-2.7]
Fesoterodine	36	5,462	4,227.86	8.51	[6-11.8]	1.45	[1-2]
Oxybutynin	6	1,314	961.25	6.24	[2.3-13.6]	1.98	[0.7-4.3]
Solifenacin	234	21,675	25,722.17	9.10	[8-10.3]	1.71	[1.5-1.9]
Tolterodine	247	16,240	23,969.66	10.30	[9.1-11.7]	2.04	[1.8-2.3]
Trospium	74	6,989	7,105.88	10.41	[8.2-13.1]	1.97	[1.5-2.5]
HIGH CV RISK							
Any OAB drug	522	32,456	47,721.28	10.94	[10-11.9]	4.52	[4.1-4.9]
Darifenacin	16	1,867	2,091.42	7.65	[4.4-12.4]	2.34	[1.3-3.8]
Fesoterodine	38	4,546	3,530.92	10.76	[7.6-14.8]	3.51	[2.5-4.8]
Oxybutynin	4	1,003	735.58	5.44	[1.5-13.9]	1.38	[0.4-3.5]
Solifenacin	206	17,029	19,563.57	10.53	[9.1-12.1]	5.89	[5.1-6.8]
Tolterodine	204	12,071	17,664.13	11.55	[10-13.2]	3.74	[3.2-4.3]
Trospium	67	5,360	5,293.99	12.66	[9.8-16.1]	4.04	[3.1-5.1]
FEMALES							
Any OAB drug	370	43,434	74,258.19	4.98	[4.5-5.5]	0.95	[0.9-1]
Darifenacin	18	3,246	3,801.21	4.74	[2.8-7.5]	0.92	[0.5-1.5]
Fesoterodine	25	6,602	5,388.89	4.64	[3-6.8]	0.99	[0.6-1.5]
Oxybutynin	2	2,058	1,452.63	1.38	[0.2-5]	0.23	[0-.8]
Solifenacin	157	23,352	30,585.58	5.13	[4.4-6]	1.04	[0.9-1.2]
Tolterodine	129	16,161	26,426.36	4.88	[4.1-5.8]	0.83	[0.7-1]
Trospium	45	8,075	8,495.16	5.30	[3.9-7.1]	1.02	[0.7-1.4]
FEMALES OVER 65 YEARS							
Any OAB drug	313	23,272	40,286.04	7.77	[6.9-8.7]	0.79	[0.7-.9]
Darifenacin	14	1,816	2,116.72	6.61	[3.6-11.1]	0.92	[0.5-1.5]
Fesoterodine	20	3,132	2,594.95	7.71	[4.7-11.9]	0.66	[0.4-1]
Oxybutynin	2	964	723.48	2.76	[0.3-10]	0.23	[0-.8]
Solifenacin	130	12,215	16,255.25	8.00	[6.7-9.5]	0.86	[0.7-1]
Tolterodine	114	9,133	15,033.15	7.58	[6.3-9.1]	0.69	[0.6-.8]
Trospium	38	4,126	4,486.87	8.47	[6-11.6]	0.97	[0.7-1.3]

Table CV3a. Person-time, Frequency, and Incidence Rates for Acute Myocardial Infarction, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	248	17,401	28,202.83	8.79	[7.7-10]	1.79	[1.6-2]
Darifenacin	9	1,205	1,420.30	6.34	[2.9-12]	0.97	[0.4-1.8]
Fesoterodine	23	2,547	2,108.86	10.91	[6.9-16.4]	2.41	[1.5-3.6]
Oxybutynin	1	733	534.65	1.87	[0-10.4]	0.23	[0-1.3]
Solifenacin	107	9,183	11,614.21	9.21	[7.6-11.1]	2.22	[1.8-2.7]
Tolterodine	81	6,280	10,096.43	8.02	[6.4-10]	1.33	[1.1-1.6]
Trospium	31	3,014	3,127.46	9.91	[6.7-14.1]	1.84	[1.2-2.6]
MALES							
Any OAB drug	372	29,483	37,388.86	9.95	[9-11]	1.72	[1.5-1.9]
Darifenacin	12	1,397	1,402.68	8.56	[4.4-14.9]	1.33	[0.7-2.3]
Fesoterodine	18	3,989	2,716.24	6.63	[3.9-10.5]	0.77	[0.5-1.2]
Oxybutynin	4	546	388.22	10.30	[2.8-26.4]	1.22	[0.3-3.1]
Solifenacin	139	15,315	15,001.63	9.27	[7.8-10.9]	1.84	[1.6-2.2]
Tolterodine	164	11,422	14,436.86	11.36	[9.7-13.2]	1.88	[1.6-2.2]
Trospium	46	4,857	4,315.82	10.66	[7.8-14.2]	1.68	[1.2-2.2]
MALES OVER 65 YEARS							
Any OAB drug	294	18,124	23,265.77	12.64	[11.2-14.2]	1.05	[0.9-1.2]
Darifenacin	9	851	877.19	10.26	[4.7-19.5]	0.86	[0.4-1.6]
Fesoterodine	16	2,330	1,632.91	9.80	[5.6-15.9]	0.79	[0.5-1.3]
Oxybutynin	4	350	237.78	16.82	[4.6-43.1]	1.75	[0.5-4.5]
Solifenacin	104	9,460	9,466.93	10.99	[9-13.3]	0.85	[0.7-1]
Tolterodine	133	7,107	8,936.51	14.88	[12.5-17.6]	1.35	[1.1-1.6]
Trospium	36	2,863	2,619.01	13.75	[9.6-19]	1.00	[0.7-1.4]
MALES WITH HIGH CV RISK							
Any OAB drug	274	15,055	19,518.46	14.04	[12.4-15.8]	2.74	[2.4-3.1]
Darifenacin	7	662	671.13	10.43	[4.2-21.5]	1.37	[0.6-2.8]
Fesoterodine	15	1,999	1,422.06	10.55	[5.9-17.4]	1.10	[0.6-1.8]
Oxybutynin	3	270	200.93	14.93	[3.1-43.6]	1.15	[0.2-3.4]
Solifenacin	99	7,846	7,949.36	12.45	[10.1-15.2]	3.67	[3-4.5]
Tolterodine	123	5,791	7,567.70	16.25	[13.5-19.4]	2.41	[2-2.9]
Trospium	36	2,346	2,166.53	16.62	[11.6-23]	2.20	[1.5-3]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV3b. Person-time, Frequency, and Incidence Rates for Stroke, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	310	72,917	112,359.24	2.76	[2.5-3.1]	1.34	[1.2-1.5]
Darifenacin	15	4,657	5,230.35	2.87	[1.6-4.7]	1.19	[0.7-2]
Fesoterodine	20	10,635	8,143.24	2.46	[1.5-3.8]	0.94	[0.6-1.4]
Oxybutynin	3	2,611	1,850.24	1.62	[0.3-4.7]	0.69	[0.1-2]
Solifenacin	126	38,737	45,866.67	2.75	[2.3-3.3]	1.35	[1.1-1.6]
Tolterodine	116	27,600	41,155.79	2.82	[2.3-3.4]	1.52	[1.3-1.8]
Trospium	36	12,955	12,890.31	2.79	[2-3.9]	1.15	[0.8-1.6]
AGE OVER 65							
Any OAB drug	221	41,396	64,164.68	3.44	[3-3.9]	0.71	[0.6-0.8]
Darifenacin	11	2,675	3,020.84	3.64	[1.8-6.5]	0.60	[0.3-1.1]
Fesoterodine	14	5,491	4,260.57	3.29	[1.8-5.5]	0.68	[0.4-1.1]
Oxybutynin	3	1,319	969.47	3.09	[0.6-9]	1.22	[0.3-3.6]
Solifenacin	90	21,729	25,939.60	3.47	[2.8-4.3]	0.68	[0.5-0.8]
Tolterodine	82	16,250	24,243.13	3.38	[2.7-4.2]	0.78	[0.6-1]
Trospium	25	7,007	7,174.30	3.48	[2.3-5.1]	0.69	[0.4-1]
HIGH CV RISK							
Any OAB drug	224	32,456	48,088.43	4.66	[4.1-5.3]	2.68	[2.3-3.1]
Darifenacin	11	1,871	2,096.94	5.25	[2.6-9.4]	2.29	[1.1-4.1]
Fesoterodine	15	4,567	3,544.63	4.23	[2.4-7]	1.76	[1-2.9]
Oxybutynin	2	1,005	741.06	2.70	[0.3-9.7]	1.06	[0.1-3.8]
Solifenacin	90	17,074	19,728.69	4.56	[3.7-5.6]	2.74	[2.2-3.4]
Tolterodine	88	12,082	17,808.32	4.94	[4-6.1]	3.20	[2.6-3.9]
Trospium	24	5,370	5,328.14	4.50	[2.9-6.7]	2.00	[1.3-3]
FEMALES							
Any OAB drug	167	43,434	74,560.17	2.24	[1.9-2.6]	0.53	[0.4-0.6]
Darifenacin	11	3,255	3,819.65	2.88	[1.4-5.2]	0.54	[0.3-1]
Fesoterodine	9	6,623	5,409.27	1.66	[0.8-3.2]	0.38	[0.2-0.7]
Oxybutynin	2	2,058	1,457.43	1.37	[0.2-5]	0.20	[0-0.7]
Solifenacin	63	23,374	30,717.68	2.05	[1.6-2.6]	0.55	[0.4-0.7]
Tolterodine	62	16,167	26,537.23	2.34	[1.8-3]	0.51	[0.4-0.7]
Trospium	21	8,081	8,520.09	2.46	[1.5-3.8]	0.56	[0.3-0.9]
FEMALES OVER 65 YEARS							
Any OAB drug	126	23,272	40,580.20	3.10	[2.6-3.7]	0.33	[0.3-0.4]
Darifenacin	9	1,821	2,133.79	4.22	[1.9-8]	0.48	[0.2-0.9]
Fesoterodine	7	3,146	2,610.99	2.68	[1.1-5.5]	0.22	[0.1-0.5]
Oxybutynin	2	965	728.55	2.75	[0.3-9.9]	0.20	[0-0.7]
Solifenacin	48	12,236	16,354.39	2.93	[2.2-3.9]	0.31	[0.2-0.4]
Tolterodine	48	9,140	15,163.70	3.17	[2.3-4.2]	0.37	[0.3-0.5]
Trospium	13	4,132	4,519.51	2.88	[1.5-4.9]	0.28	[0.1-0.5]

Table CV3b. Person-time, Frequency, and Incidence Rates for Stroke, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	115	17,401	28,349.86	4.06	[3.3-4.9]	1.42	[1.2-1.7]
Darifenacin	7	1,209	1,421.43	4.92	[2-10.1]	0.67	[0.3-1.4]
Fesoterodine	7	2,557	2,117.37	3.31	[1.3-6.8]	0.98	[0.4-2]
Oxybutynin	1	731	537.25	1.86	[0-10.4]	0.19	[0-1]
Solifenacin	42	9,197	11,690.67	3.59	[2.6-4.9]	1.72	[1.2-2.3]
Tolterodine	45	6,284	10,144.99	4.44	[3.2-5.9]	1.31	[1-1.7]
Trospium	14	3,018	3,140.30	4.46	[2.4-7.5]	1.20	[0.7-2]
MALES							
Any OAB drug	143	29,483	37,799.07	3.78	[3.2-4.5]	0.81	[0.7-1]
Darifenacin	4	1,402	1,410.70	2.84	[0.8-7.3]	0.65	[0.2-1.7]
Fesoterodine	11	4,012	2,733.97	4.02	[2-7.2]	0.56	[0.3-1]
Oxybutynin	1	553	392.81	2.55	[0.1-14.2]	0.49	[0-2.7]
Solifenacin	63	15,363	15,149.00	4.16	[3.2-5.3]	0.80	[0.6-1]
Tolterodine	54	11,433	14,618.56	3.69	[2.8-4.8]	1.01	[0.8-1.3]
Trospium	15	4,874	4,370.22	3.43	[1.9-5.7]	0.59	[0.3-1]
MALES OVER 65 YEARS							
Any OAB drug	95	18,124	23,584.49	4.03	[3.3-4.9]	0.38	[0.3-0.5]
Darifenacin	2	854	887.05	2.25	[0.3-8.1]	0.11	[0-0.4]
Fesoterodine	7	2,345	1,649.58	4.24	[1.7-8.7]	0.46	[0.2-0.9]
Oxybutynin	1	354	240.92	4.15	[0.1-23.1]	1.02	[0-5.7]
Solifenacin	42	9,493	9,585.22	4.38	[3.2-5.9]	0.37	[0.3-0.5]
Tolterodine	34	7,110	9,079.43	3.74	[2.6-5.2]	0.42	[0.3-0.6]
Trospium	12	2,875	2,654.79	4.52	[2.3-7.9]	0.41	[0.2-0.7]
MALES WITH HIGH CV RISK							
Any OAB drug	109	15,055	19,738.57	5.52	[4.5-6.7]	1.26	[1-1.5]
Darifenacin	4	662	675.51	5.92	[1.6-15.2]	1.62	[0.4-4.1]
Fesoterodine	8	2,010	1,427.26	5.61	[2.4-11]	0.78	[0.3-1.5]
Oxybutynin	1	274	203.80	4.91	[0.1-27.3]	0.88	[0-4.9]
Solifenacin	48	7,877	8,038.02	5.97	[4.4-7.9]	1.02	[0.8-1.4]
Tolterodine	43	5,798	7,663.33	5.61	[4.1-7.6]	1.89	[1.4-2.5]
Trospium	10	2,352	2,187.84	4.57	[2.2-8.4]	0.79	[0.4-1.5]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV3c. Person-time, Frequency, and Incidence Rates for All-Cause Mortality, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	4799	72,917	112,768	42.56	[41.4-43.8]	15.19	[14.8-15.6]
Darifenacin	183	4,660	5,244	34.90	[30-40.3]	11.67	[10-13.5]
Fesoterodine	257	10,650	8,173	31.45	[27.7-35.5]	11.15	[9.8-12.6]
Oxybutynin	69	2,614	1,856	37.18	[28.9-47.1]	34.51	[26.9-43.7]
Solifenacin	1889	38,754	46,030	41.04	[39.2-42.9]	14.58	[13.9-15.2]
Tolterodine	1954	27,609	41,303	47.31	[45.2-49.5]	17.41	[16.6-18.2]
Trospium	538	12,969	12,957	41.52	[38.1-45.2]	15.57	[14.3-16.9]
AGE OVER 65							
Any OAB drug	4263	41,396	64,412	66.18	[64.2-68.2]	11.37	[11-11.7]
Darifenacin	163	2,676	3,024	53.90	[45.9-62.8]	9.25	[7.9-10.8]
Fesoterodine	227	5,500	4,276	53.08	[46.4-60.5]	9.93	[8.7-11.3]
Oxybutynin	55	1,320	972	56.59	[42.6-73.7]	13.22	[10-17.2]
Solifenacin	1685	21,741	26,045	64.69	[61.6-67.9]	11.27	[10.7-11.8]
Tolterodine	1740	16,257	24,319	71.55	[68.2-75]	13.13	[12.5-13.8]
Trospium	466	7,018	7,225	64.50	[58.8-70.6]	11.53	[10.5-12.6]
HIGH CV RISK							
Any OAB drug	3254	32,456	48,395	67.24	[64.9-69.6]	26.81	[25.9-27.7]
Darifenacin	106	1,874	2,111	50.22	[41.1-60.7]	14.40	[11.8-17.4]
Fesoterodine	182	4,578	3,571	50.97	[43.8-58.9]	15.24	[13.1-17.6]
Oxybutynin	50	1,008	745	67.10	[49.8-88.5]	626.81	[465.2-826.4]
Solifenacin	1324	17,085	19,837	66.74	[63.2-70.4]	18.95	[17.9-20]
Tolterodine	1308	12,088	17,928	72.96	[69.1-77]	51.16	[48.4-54]
Trospium	349	5,379	5,379	64.88	[58.3-72.1]	17.08	[15.3-19]
FEMALES							
Any OAB drug	2293	43,434	74,816	30.65	[29.4-31.9]	5.61	[5.4-5.8]
Darifenacin	104	3,257	3,827	27.17	[22.2-32.9]	4.79	[3.9-5.8]
Fesoterodine	128	6,631	5,421	23.61	[19.7-28.1]	5.02	[4.2-6]
Oxybutynin	35	2,060	1,459	23.98	[16.7-33.4]	5.08	[3.5-7.1]
Solifenacin	921	23,387	30,809	29.89	[28-31.9]	5.79	[5.4-6.2]
Tolterodine	929	16,173	26,635	34.88	[32.7-37.2]	5.95	[5.6-6.3]
Trospium	218	8,092	8,572	25.43	[22.2-29]	4.82	[4.2-5.5]
FEMALES OVER 65 YEARS							
Any OAB drug	2022	23,272	40,746	49.62	[47.5-51.8]	4.79	[4.6-5]
Darifenacin	95	1,822	2,137	44.45	[36-54.3]	4.29	[3.5-5.2]
Fesoterodine	112	3,150	2,616	42.81	[35.3-51.5]	4.76	[3.9-5.7]
Oxybutynin	27	966	730	36.97	[24.4-53.8]	3.50	[2.3-5.1]
Solifenacin	810	12,245	16,419	49.33	[46-52.9]	5.01	[4.7-5.4]
Tolterodine	823	9,144	15,219	54.08	[50.4-57.9]	4.83	[4.5-5.2]
Trospium	186	4,141	4,560	40.79	[35.1-47.1]	4.06	[3.5-4.7]

Table CV3c. Person-time, Frequency, and Incidence Rates for All-Cause Mortality, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	1435	17,401	28,529	50.30	[47.7-53]	8.80	[8.4-9.3]
Darifenacin	50	1,211	1,429	34.99	[26-46.1]	4.37	[3.2-5.8]
Fesoterodine	89	2,562	2,128	41.82	[33.6-51.5]	7.43	[6-9.1]
Oxybutynin	24	733	538	44.63	[28.6-66.4]	7.72	[4.9-11.5]
Solifenacin	589	9,207	11,745	50.15	[46.2-54.4]	9.11	[8.4-9.9]
Tolterodine	580	6,289	10,220	56.75	[52.2-61.6]	10.11	[9.3-11]
Trospium	131	3,024	3,177	41.23	[34.5-48.9]	7.30	[6.1-8.7]
MALES							
Any OAB drug	2506	29,483	37,953	66.03	[63.5-68.7]	9.58	[9.2-10]
Darifenacin	79	1,403	1,417	55.76	[44.1-69.5]	6.88	[5.5-8.6]
Fesoterodine	129	4,019	2,752	46.88	[39.1-55.7]	6.13	[5.1-7.3]
Oxybutynin	34	554	396	85.79	[59.4-119.9]	29.43	[20.4-41.1]
Solifenacin	968	15,367	15,221	63.60	[59.7-67.7]	8.79	[8.2-9.4]
Tolterodine	1025	11,436	14,669	69.88	[65.7-74.3]	11.46	[10.8-12.2]
Trospium	320	4,877	4,385	72.98	[65.2-81.4]	10.76	[9.6-12]
MALES OVER 65 YEARS							
Any OAB drug	2241	18,124	23,665	94.69	[90.8-98.7]	6.59	[6.3-6.9]
Darifenacin	68	854	887	76.66	[59.5-97.2]	4.96	[3.9-6.3]
Fesoterodine	115	2,350	1,660	69.27	[57.2-83.1]	5.17	[4.3-6.2]
Oxybutynin	28	354	242	115.90	[77-167.5]	9.73	[6.5-14.1]
Solifenacin	875	9,496	9,627	90.89	[85-97.1]	6.25	[5.8-6.7]
Tolterodine	917	7,113	9,100	100.77	[94.4-107.5]	8.30	[7.8-8.9]
Trospium	280	2,877	2,665	105.07	[93.1-118.1]	7.47	[6.6-8.4]
MALES WITH HIGH CV RISK							
Any OAB drug	1819	15,055	19,865	91.57	[87.4-95.9]	18.01	[17.2-18.9]
Darifenacin	56	663	682	82.15	[62.1-106.7]	10.03	[7.6-13]
Fesoterodine	93	2,016	1,442	64.48	[52-79]	7.81	[6.3-9.6]
Oxybutynin	26	275	207	125.41	[81.9-183.8]	619.08	[404.4-907.1]
Solifenacin	735	7,878	8,092	90.83	[84.4-97.6]	9.84	[9.1-10.6]
Tolterodine	728	5,799	7,708	94.45	[87.7-101.6]	41.06	[38.1-44.1]
Trospium	218	2,355	2,202	99.01	[86.3-113.1]	9.78	[8.5-11.2]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV3d. Person-time, Frequency, and Incidence Rates for Cardiovascular Mortality, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	1656	72,917	112,768.36	14.68	[14-15.4]	4.76	[4.5-5]
Darifenacin	60	4,660	5,244.01	11.44	[8.7-14.7]	3.92	[3-5]
Fesoterodine	88	10,650	8,172.93	10.77	[8.6-13.3]	3.83	[3.1-4.7]
Oxybutynin	26	2,614	1,855.71	14.01	[9.2-20.5]	6.88	[4.5-10.1]
Solifenacin	664	38,754	46,029.51	14.43	[13.3-15.6]	4.86	[4.5-5.2]
Tolterodine	659	27,609	41,303.30	15.96	[14.8-17.2]	6.22	[5.8-6.7]
Trospium	182	12,969	12,956.66	14.05	[12.1-16.2]	4.55	[3.9-5.3]
AGE OVER 65							
Any OAB drug	1497	41,396	64,411.86	23.24	[22.1-24.4]	4.10	[3.9-4.3]
Darifenacin	54	2,676	3,024.13	17.86	[13.4-23.3]	2.99	[2.2-3.9]
Fesoterodine	78	5,500	4,276.25	18.24	[14.4-22.8]	3.21	[2.5-4]
Oxybutynin	21	1,320	971.82	21.61	[13.4-33]	5.46	[3.4-8.4]
Solifenacin	603	21,741	26,045.34	23.15	[21.3-25.1]	4.18	[3.9-4.5]
Tolterodine	603	16,257	24,319.14	24.80	[22.9-26.9]	5.59	[5.2-6.1]
Trospium	160	7,018	7,225.19	22.14	[18.8-25.9]	4.03	[3.4-4.7]
HIGH CV RISK							
Any OAB drug	1310	32,456	48,394.60	27.07	[25.6-28.6]	7.51	[7.1-7.9]
Darifenacin	43	1,874	2,110.60	20.37	[14.7-27.4]	5.51	[4-7.4]
Fesoterodine	72	4,578	3,570.59	20.16	[15.8-25.4]	6.21	[4.9-7.8]
Oxybutynin	24	1,008	745.12	32.21	[20.6-47.9]	13.66	[8.8-20.3]
Solifenacin	534	17,085	19,836.89	26.92	[24.7-29.3]	8.00	[7.3-8.7]
Tolterodine	517	12,088	17,927.69	28.84	[26.4-31.4]	8.75	[8-9.5]
Trospium	140	5,379	5,378.87	26.03	[21.9-30.7]	6.53	[5.5-7.7]
FEMALES							
Any OAB drug	759	43,434	74,815.80	10.14	[9.4-10.9]	1.84	[1.7-2]
Darifenacin	36	3,257	3,827.11	9.41	[6.6-13]	2.00	[1.4-2.8]
Fesoterodine	43	6,631	5,421.05	7.93	[5.7-10.7]	1.61	[1.2-2.2]
Oxybutynin	12	2,060	1,459.39	8.22	[4.2-14.4]	1.46	[0.8-2.6]
Solifenacin	315	23,387	30,808.55	10.22	[9.1-11.4]	2.02	[1.8-2.3]
Tolterodine	295	16,173	26,634.66	11.08	[9.8-12.4]	1.76	[1.6-2]
Trospium	64	8,092	8,571.79	7.47	[5.8-9.5]	1.38	[1.1-1.8]
FEMALES OVER 65 YEARS							
Any OAB drug	680	23,272	40,746.38	16.69	[15.5-18]	1.62	[1.5-1.7]
Darifenacin	32	1,822	2,137.07	14.97	[10.2-21.1]	1.39	[0.9-2]
Fesoterodine	39	3,150	2,616.04	14.91	[10.6-20.4]	1.53	[1.1-2.1]
Oxybutynin	10	966	730.24	13.69	[6.6-25.2]	1.08	[0.5-2]
Solifenacin	281	12,245	16,418.81	17.11	[15.2-19.2]	1.80	[1.6-2]
Tolterodine	271	9,144	15,219.17	17.81	[15.7-20.1]	1.62	[1.4-1.8]
Trospium	53	4,141	4,560.22	11.62	[8.7-15.2]	1.11	[0.8-1.5]

Table CV3d. Person-time, Frequency, and Incidence Rates for Cardiovascular Mortality, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	558	17,401	28,529.45	19.56	[18-21.3]	3.62	[3.3-3.9]
Darifenacin	22	1,211	1,428.89	15.40	[9.6-23.3]	2.01	[1.3-3]
Fesoterodine	35	2,562	2,128.20	16.45	[11.5-22.9]	2.93	[2-4.1]
Oxybutynin	10	733	537.81	18.59	[8.9-34.2]	2.71	[1.3-5]
Solifenacin	240	9,207	11,745.09	20.43	[17.9-23.2]	4.24	[3.7-4.8]
Tolterodine	212	6,289	10,219.82	20.74	[18-23.7]	3.52	[3.1-4]
Trospium	44	3,024	3,177.04	13.85	[10.1-18.6]	2.38	[1.7-3.2]
MALES							
Any OAB drug	897	29,483	37,952.56	23.63	[22.1-25.2]	2.93	[2.7-3.1]
Darifenacin	24	1,403	1,416.89	16.94	[10.9-25.2]	1.92	[1.2-2.9]
Fesoterodine	45	4,019	2,751.88	16.35	[11.9-21.9]	2.21	[1.6-3]
Oxybutynin	14	554	396.32	35.32	[19.3-59.3]	5.42	[3-9.1]
Solifenacin	349	15,367	15,220.96	22.93	[20.6-25.5]	2.84	[2.5-3.2]
Tolterodine	364	11,436	14,668.64	24.81	[22.3-27.5]	4.46	[4-4.9]
Trospium	118	4,877	4,384.88	26.91	[22.3-32.2]	3.17	[2.6-3.8]
MALES OVER 65 YEARS							
Any OAB drug	817	18,124	23,665.48	34.52	[32.2-37]	2.47	[2.3-2.6]
Darifenacin	22	854	887.05	24.80	[15.5-37.5]	1.61	[1-2.4]
Fesoterodine	39	2,350	1,660.21	23.49	[16.7-32.1]	1.67	[1.2-2.3]
Oxybutynin	11	354	241.58	45.53	[22.7-81.5]	4.39	[2.2-7.8]
Solifenacin	322	9,496	9,626.53	33.45	[29.9-37.3]	2.38	[2.1-2.7]
Tolterodine	332	7,113	9,099.97	36.48	[32.7-40.6]	3.97	[3.6-4.4]
Trospium	107	2,877	2,664.98	40.15	[32.9-48.5]	2.91	[2.4-3.5]
MALES WITH HIGH CV RISK							
Any OAB drug	752	15,055	19,865.15	37.86	[35.2-40.7]	3.89	[3.6-4.2]
Darifenacin	21	663	681.71	30.81	[19.1-47.1]	3.50	[2.2-5.4]
Fesoterodine	37	2,016	1,442.38	25.65	[18.1-35.4]	3.28	[2.3-4.5]
Oxybutynin	14	275	207.31	67.53	[36.9-113.3]	10.95	[6-18.4]
Solifenacin	294	7,878	8,091.80	36.33	[32.3-40.7]	3.76	[3.3-4.2]
Tolterodine	305	5,799	7,707.87	39.57	[35.3-44.3]	5.23	[4.7-5.9]
Trospium	96	2,355	2,201.83	43.60	[35.3-53.2]	4.15	[3.4-5.1]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV3e. Person-time, Frequency, and Incidence Rates for Major Adverse Cardiac Events, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	2382	72,917	111,249.03	21.41	[20.6-22.3]	7.81	[7.5-8.1]
Darifenacin	91	4,640	5,191.18	17.53	[14.1-21.5]	6.63	[5.3-8.1]
Fesoterodine	136	10,576	8,075.45	16.84	[14.1-19.9]	6.07	[5.1-7.2]
Oxybutynin	32	2,602	1,838.22	17.41	[11.9-24.6]	8.57	[5.9-12.1]
Solifenacin	949	38,651	45,430.22	20.89	[19.6-22.3]	8.14	[7.6-8.7]
Tolterodine	945	27,574	40,717.14	23.21	[21.8-24.7]	9.36	[8.8-10]
Trospium	273	12,918	12,744.64	21.42	[19-24.1]	7.62	[6.7-8.6]
AGE OVER 65							
Any OAB drug	2040	41,396	63,312.35	32.22	[30.8-33.7]	5.99	[5.7-6.3]
Darifenacin	76	2,666	2,991.57	25.40	[20-31.8]	4.85	[3.8-6.1]
Fesoterodine	114	5,453	4,212.18	27.06	[22.3-32.5]	4.91	[4-5.9]
Oxybutynin	27	1,313	958.90	28.16	[18.6-41]	8.17	[5.4-11.9]
Solifenacin	809	21,664	25,621.76	31.57	[29.4-33.8]	5.84	[5.4-6.3]
Tolterodine	824	16,233	23,895.08	34.48	[32.2-36.9]	7.81	[7.3-8.4]
Trospium	227	6,978	7,054.99	32.18	[28.1-36.6]	6.09	[5.3-6.9]
HIGH CV RISK							
Any OAB drug	1800	32,456	47,422.83	37.96	[36.2-39.8]	13.22	[12.6-13.8]
Darifenacin	61	1,864	2,078.72	29.35	[22.4-37.7]	9.44	[7.2-12.1]
Fesoterodine	113	4,535	3,504.96	32.24	[26.6-38.8]	10.96	[9-13.2]
Oxybutynin	27	1,001	734.36	36.77	[24.2-53.5]	15.48	[10.2-22.5]
Solifenacin	724	17,019	19,457.86	37.21	[34.5-40]	14.50	[13.5-15.6]
Tolterodine	710	12,065	17,546.21	40.46	[37.5-43.6]	14.57	[13.5-15.7]
Trospium	202	5,351	5,243.26	38.53	[33.4-44.2]	11.42	[9.9-13.1]
FEMALES							
Any OAB drug	1130	43,434	74,006.57	15.27	[14.4-16.2]	2.92	[2.8-3.1]
Darifenacin	56	3,244	3,794.69	14.76	[11.1-19.2]	3.05	[2.3-4]
Fesoterodine	70	6,594	5,377.12	13.02	[10.1-16.4]	2.75	[2.1-3.5]
Oxybutynin	15	2,056	1,450.67	10.34	[5.8-17.1]	1.81	[1-3]
Solifenacin	456	23,339	30,497.77	14.95	[13.6-16.4]	3.08	[2.8-3.4]
Tolterodine	432	16,155	26,328.92	16.41	[14.9-18]	2.82	[2.6-3.1]
Trospium	114	8,064	8,443.47	13.50	[11.1-16.2]	2.63	[2.2-3.2]
FEMALES OVER 65 YEARS							
Any OAB drug	975	23,272	40,123.87	24.30	[22.8-25.9]	2.43	[2.3-2.6]
Darifenacin	47	1,815	2,114.38	22.23	[16.3-29.6]	2.49	[1.8-3.3]
Fesoterodine	60	3,128	2,589.90	23.17	[17.7-29.8]	2.22	[1.7-2.9]
Oxybutynin	13	963	721.79	18.01	[9.6-30.8]	1.42	[0.8-2.4]
Solifenacin	390	12,206	16,193.89	24.08	[21.8-26.6]	2.55	[2.3-2.8]
Tolterodine	386	9,129	14,977.67	25.77	[23.3-28.5]	2.46	[2.2-2.7]
Trospium	91	4,117	4,446.16	20.47	[16.5-25.1]	2.11	[1.7-2.6]

Table CV3e. Person-time, Frequency, and Incidence Rates for Major Adverse Cardiac Events, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	794	17,401	28,024.35	28.33	[26.4-30.4]	5.85	[5.4-6.3]
Darifenacin	33	1,203	1,413.78	23.34	[16.1-32.8]	3.33	[2.3-4.7]
Fesoterodine	60	2,542	2,098.03	28.60	[21.8-36.8]	6.05	[4.6-7.8]
Oxybutynin	11	731	534.10	20.60	[10.3-36.9]	2.96	[1.5-5.3]
Solifenacin	327	9,173	11,559.96	28.29	[25.3-31.5]	6.52	[5.8-7.3]
Tolterodine	297	6,275	10,021.60	29.64	[26.4-33.2]	5.67	[5-6.4]
Trospium	76	3,008	3,090.71	24.59	[19.4-30.8]	4.69	[3.7-5.9]
MALES							
Any OAB drug	1252	29,483	37,242.45	33.62	[31.8-35.5]	4.89	[4.6-5.2]
Darifenacin	35	1,396	1,396.49	25.06	[17.5-34.9]	3.57	[2.5-5]
Fesoterodine	66	3,982	2,698.33	24.46	[18.9-31.1]	3.32	[2.6-4.2]
Oxybutynin	17	546	387.56	43.86	[25.6-70.2]	6.76	[3.9-10.8]
Solifenacin	493	15,312	14,932.45	33.02	[30.2-36.1]	5.06	[4.6-5.5]
Tolterodine	513	11,419	14,388.22	35.65	[32.6-38.9]	6.54	[6-7.1]
Trospium	159	4,854	4,301.16	36.97	[31.4-43.2]	4.99	[4.2-5.8]
MALES OVER 65 YEARS							
Any OAB drug	1065	18,124	23,188.48	45.93	[43.2-48.8]	3.57	[3.4-3.8]
Darifenacin	29	851	877.19	33.06	[22.1-47.5]	2.36	[1.6-3.4]
Fesoterodine	54	2,325	1,622.28	33.29	[25-43.4]	2.69	[2-3.5]
Oxybutynin	14	350	237.11	59.04	[32.3-99.1]	6.74	[3.7-11.3]
Solifenacin	419	9,458	9,427.87	44.44	[40.3-48.9]	3.29	[3-3.6]
Tolterodine	438	7,104	8,917.41	49.12	[44.6-53.9]	5.34	[4.9-5.9]
Trospium	136	2,861	2,608.83	52.13	[43.7-61.7]	3.98	[3.3-4.7]
MALES WITH HIGH CV RISK							
Any OAB drug	1006	15,055	19,398.49	51.86	[48.7-55.2]	7.37	[6.9-7.8]
Darifenacin	28	661	664.94	42.11	[28-60.9]	6.11	[4.1-8.8]
Fesoterodine	53	1,993	1,406.93	37.67	[28.2-49.3]	4.91	[3.7-6.4]
Oxybutynin	16	270	200.27	79.89	[45.7-129.7]	12.53	[7.2-20.3]
Solifenacin	397	7,846	7,897.89	50.27	[45.4-55.5]	7.98	[7.2-8.8]
Tolterodine	413	5,790	7,524.61	54.89	[49.7-60.4]	8.90	[8.1-9.8]
Trospium	126	2,343	2,152.55	58.54	[48.8-69.7]	6.73	[5.6-8]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV3f. Person-time, Frequency, and Incidence Rates for Coronary Heart Disease Death, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	959	72,917	112,768.36	8.50	[8-9.1]	2.72	[2.5-2.9]
Darifenacin	29	4,660	5,244.01	5.53	[3.7-7.9]	2.34	[1.6-3.4]
Fesoterodine	58	10,650	8,172.93	7.10	[5.4-9.2]	2.31	[1.8-3]
Oxybutynin	13	2,614	1,855.71	7.01	[3.7-12]	2.96	[1.6-5.1]
Solifenacin	388	38,754	46,029.51	8.43	[7.6-9.3]	2.83	[2.6-3.1]
Tolterodine	379	27,609	41,303.30	9.18	[8.3-10.1]	4.10	[3.7-4.5]
Trospium	106	12,969	12,956.66	8.18	[6.7-9.9]	2.51	[2.1-3]
AGE OVER 65							
Any OAB drug	866	41,396	64,411.86	13.44	[12.6-14.4]	2.25	[2.1-2.4]
Darifenacin	24	2,676	3,024.13	7.94	[5.1-11.8]	1.41	[0.9-2.1]
Fesoterodine	53	5,500	4,276.25	12.39	[9.3-16.2]	1.96	[1.5-2.6]
Oxybutynin	11	1,320	971.82	11.32	[5.7-20.3]	2.33	[1.2-4.2]
Solifenacin	351	21,741	26,045.34	13.48	[12.1-15]	2.32	[2.1-2.6]
Tolterodine	348	16,257	24,319.14	14.31	[12.8-15.9]	3.75	[3.4-4.2]
Trospium	93	7,018	7,225.19	12.87	[10.4-15.8]	2.04	[1.6-2.5]
HIGH CV RISK							
Any OAB drug	757	32,456	48,394.60	15.64	[14.5-16.8]	3.95	[3.7-4.2]
Darifenacin	21	1,874	2,110.60	9.95	[6.2-15.2]	3.48	[2.2-5.3]
Fesoterodine	51	4,578	3,570.59	14.28	[10.6-18.8]	3.76	[2.8-4.9]
Oxybutynin	11	1,008	745.12	14.76	[7.4-26.4]	4.84	[2.4-8.7]
Solifenacin	320	17,085	19,836.89	16.13	[14.4-18]	4.52	[4-5]
Tolterodine	287	12,088	17,927.69	16.01	[14.2-18]	4.85	[4.3-5.4]
Trospium	79	5,379	5,378.87	14.69	[11.6-18.3]	3.24	[2.6-4]
FEMALES							
Any OAB drug	429	43,434	74,815.80	5.73	[5.2-6.3]	1.03	[0.9-1.1]
Darifenacin	17	3,257	3,827.11	4.44	[2.6-7.1]	1.13	[0.7-1.8]
Fesoterodine	33	6,631	5,421.05	6.09	[4.2-8.5]	1.22	[0.8-1.7]
Oxybutynin	5	2,060	1,459.39	3.43	[1.1-8]	0.60	[0.2-1.4]
Solifenacin	186	23,387	30,808.55	6.04	[5.2-7]	1.17	[1-1.3]
Tolterodine	160	16,173	26,634.66	6.01	[5.1-7]	0.93	[0.8-1.1]
Trospium	34	8,092	8,571.79	3.97	[2.7-5.5]	0.72	[0.5-1]
FEMALES OVER 65 YEARS							
Any OAB drug	385	23,272	40,746.38	9.45	[8.5-10.4]	0.90	[0.8-1]
Darifenacin	14	1,822	2,137.07	6.55	[3.6-11]	0.51	[0.3-.9]
Fesoterodine	31	3,150	2,616.04	11.85	[8.1-16.8]	1.19	[0.8-1.7]
Oxybutynin	4	966	730.24	5.48	[1.5-14]	0.45	[0.1-1.1]
Solifenacin	165	12,245	16,418.81	10.05	[8.6-11.7]	0.97	[0.8-1.1]
Tolterodine	149	9,144	15,219.17	9.79	[8.3-11.5]	0.95	[0.8-1.1]
Trospium	28	4,141	4,560.22	6.14	[4.1-8.9]	0.54	[0.4-.8]

Table CV3f. Person-time, Frequency, and Incidence Rates for Coronary Heart Disease Death, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	310	17,401	28,529.45	10.87	[9.7-12.1]	1.87	[1.7-2.1]
Darifenacin	11	1,211	1,428.89	7.70	[3.8-13.8]	1.09	[0.5-2]
Fesoterodine	29	2,562	2,128.20	13.63	[9.1-19.6]	2.45	[1.6-3.5]
Oxybutynin	3	733	537.81	5.58	[1.2-16.3]	0.65	[0.1-1.9]
Solifenacin	147	9,207	11,745.09	12.52	[10.6-14.7]	2.61	[2.2-3.1]
Tolterodine	104	6,289	10,219.82	10.18	[8.3-12.3]	1.28	[1-1.6]
Trospium	21	3,024	3,177.04	6.61	[4.1-10.1]	1.05	[0.6-1.6]
MALES							
Any OAB drug	530	29,483	37,952.56	13.96	[12.8-15.2]	1.69	[1.5-1.8]
Darifenacin	12	1,403	1,416.89	8.47	[4.4-14.8]	1.21	[0.6-2.1]
Fesoterodine	25	4,019	2,751.88	9.08	[5.9-13.4]	1.09	[0.7-1.6]
Oxybutynin	8	554	396.32	20.19	[8.7-39.8]	2.36	[1-4.6]
Solifenacin	202	15,367	15,220.96	13.27	[11.5-15.2]	1.66	[1.4-1.9]
Tolterodine	219	11,436	14,668.64	14.93	[13-17]	3.17	[2.8-3.6]
Trospium	72	4,877	4,384.88	16.42	[12.8-20.7]	1.78	[1.4-2.2]
MALES OVER 65 YEARS							
Any OAB drug	481	18,124	23,665.48	20.32	[18.5-22.2]	1.35	[1.2-1.5]
Darifenacin	10	854	887.05	11.27	[5.4-20.7]	0.90	[0.4-1.6]
Fesoterodine	22	2,350	1,660.21	13.25	[8.3-20.1]	0.77	[0.5-1.2]
Oxybutynin	7	354	241.58	28.98	[11.6-59.7]	1.88	[0.8-3.9]
Solifenacin	186	9,496	9,626.53	19.32	[16.6-22.3]	1.35	[1.2-1.6]
Tolterodine	199	7,113	9,099.97	21.87	[18.9-25.1]	2.80	[2.4-3.2]
Trospium	65	2,877	2,664.98	24.39	[18.8-31.1]	1.50	[1.2-1.9]
MALES WITH HIGH CV RISK							
Any OAB drug	447	15,055	19,865.15	22.50	[20.5-24.7]	2.08	[1.9-2.3]
Darifenacin	10	663	681.71	14.67	[7-27]	2.39	[1.1-4.4]
Fesoterodine	22	2,016	1,442.38	15.25	[9.6-23.1]	1.30	[0.8-2]
Oxybutynin	8	275	207.31	38.59	[16.7-76]	4.20	[1.8-8.3]
Solifenacin	173	7,878	8,091.80	21.38	[18.3-24.8]	1.91	[1.6-2.2]
Tolterodine	183	5,799	7,707.87	23.74	[20.4-27.4]	3.57	[3.1-4.1]
Trospium	58	2,355	2,201.83	26.34	[20-34.1]	2.19	[1.7-2.8]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV3g. Person-time, Frequency, and Incidence Rates for Cerebrovascular Death, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	697	72,917	112,768.36	6.18	[5.7-6.7]	2.05	[1.9-2.2]
Darifenacin	31	4,660	5,244.01	5.91	[4-8.4]	1.58	[1.1-2.2]
Fesoterodine	30	10,650	8,172.93	3.67	[2.5-5.2]	1.52	[1-2.2]
Oxybutynin	13	2,614	1,855.71	7.01	[3.7-12]	3.92	[2.1-6.7]
Solifenacin	276	38,754	46,029.51	6.00	[5.3-6.7]	2.03	[1.8-2.3]
Tolterodine	280	27,609	41,303.30	6.78	[6-7.6]	2.12	[1.9-2.4]
Trospium	76	12,969	12,956.66	5.87	[4.6-7.3]	2.05	[1.6-2.6]
AGE OVER 65							
Any OAB drug	631	41,396	64,411.86	9.80	[9-10.6]	1.85	[1.7-2]
Darifenacin	30	2,676	3,024.13	9.92	[6.7-14.2]	1.58	[1.1-2.3]
Fesoterodine	25	5,500	4,276.25	5.85	[3.8-8.6]	1.25	[0.8-1.8]
Oxybutynin	10	1,320	971.82	10.29	[4.9-18.9]	3.13	[1.5-5.8]
Solifenacin	252	21,741	26,045.34	9.68	[8.5-10.9]	1.86	[1.6-2.1]
Tolterodine	255	16,257	24,319.14	10.49	[9.2-11.9]	1.84	[1.6-2.1]
Trospium	67	7,018	7,225.19	9.27	[7.2-11.8]	1.99	[1.5-2.5]
HIGH CV RISK							
Any OAB drug	553	32,456	48,394.60	11.43	[10.5-12.4]	3.56	[3.3-3.9]
Darifenacin	22	1,874	2,110.60	10.42	[6.5-15.8]	2.03	[1.3-3.1]
Fesoterodine	21	4,578	3,570.59	5.88	[3.6-9]	2.46	[1.5-3.8]
Oxybutynin	13	1,008	745.12	17.45	[9.3-29.8]	8.81	[4.7-15.1]
Solifenacin	214	17,085	19,836.89	10.79	[9.4-12.3]	3.48	[3-4]
Tolterodine	230	12,088	17,927.69	12.83	[11.2-14.6]	3.90	[3.4-4.4]
Trospium	61	5,379	5,378.87	11.34	[8.7-14.6]	3.28	[2.5-4.2]
FEMALES							
Any OAB drug	330	43,434	74,815.80	4.41	[3.9-4.9]	0.81	[0.7-.9]
Darifenacin	19	3,257	3,827.11	4.96	[3-7.8]	0.87	[0.5-1.4]
Fesoterodine	10	6,631	5,421.05	1.84	[0.9-3.4]	0.39	[0.2-.7]
Oxybutynin	7	2,060	1,459.39	4.80	[1.9-9.9]	0.86	[0.3-1.8]
Solifenacin	129	23,387	30,808.55	4.19	[3.5-5]	0.85	[0.7-1]
Tolterodine	135	16,173	26,634.66	5.07	[4.2-6]	0.83	[0.7-1]
Trospium	30	8,092	8,571.79	3.50	[2.4-5]	0.66	[0.4-.9]
FEMALES OVER 65 YEARS							
Any OAB drug	295	23,272	40,746.38	7.24	[6.4-8.1]	0.73	[0.6-.8]
Darifenacin	18	1,822	2,137.07	8.42	[5-13.3]	0.87	[0.5-1.4]
Fesoterodine	8	3,150	2,616.04	3.06	[1.3-6]	0.34	[0.1-.7]
Oxybutynin	6	966	730.24	8.22	[3-17.9]	0.63	[0.2-1.4]
Solifenacin	116	12,245	16,418.81	7.07	[5.8-8.5]	0.82	[0.7-1]
Tolterodine	122	9,144	15,219.17	8.02	[6.7-9.6]	0.67	[0.6-.8]
Trospium	25	4,141	4,560.22	5.48	[3.5-8.1]	0.57	[0.4-.8]

Table CV3g. Person-time, Frequency, and Incidence Rates for Cerebrovascular Death, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	248	17,401	28,529.45	8.69	[7.6-9.8]	1.75	[1.5-2]
Darifenacin	11	1,211	1,428.89	7.70	[3.8-13.8]	0.92	[0.5-1.6]
Fesoterodine	6	2,562	2,128.20	2.82	[1-6.1]	0.47	[0.2-1]
Oxybutynin	7	733	537.81	13.02	[5.2-26.8]	2.06	[0.8-4.3]
Solifenacin	93	9,207	11,745.09	7.92	[6.4-9.7]	1.63	[1.3-2]
Tolterodine	108	6,289	10,219.82	10.57	[8.7-12.8]	2.24	[1.8-2.7]
Trospium	23	3,024	3,177.04	7.24	[4.6-10.9]	1.33	[0.8-2]
MALES							
Any OAB drug	367	29,483	37,952.56	9.67	[8.7-10.7]	1.24	[1.1-1.4]
Darifenacin	12	1,403	1,416.89	8.47	[4.4-14.8]	0.71	[0.4-1.2]
Fesoterodine	20	4,019	2,751.88	7.27	[4.4-11.2]	1.13	[0.7-1.7]
Oxybutynin	6	554	396.32	15.14	[5.6-33]	3.06	[1.1-6.7]
Solifenacin	147	15,367	15,220.96	9.66	[8.2-11.4]	1.18	[1-1.4]
Tolterodine	145	11,436	14,668.64	9.89	[8.3-11.6]	1.29	[1.1-1.5]
Trospium	46	4,877	4,384.88	10.49	[7.7-14]	1.38	[1-1.8]
MALES OVER 65 YEARS							
Any OAB drug	336	18,124	23,665.48	14.20	[12.7-15.8]	1.12	[1-1.2]
Darifenacin	12	854	887.05	13.53	[7-23.6]	0.71	[0.4-1.2]
Fesoterodine	17	2,350	1,660.21	10.24	[6-16.4]	0.90	[0.5-1.4]
Oxybutynin	4	354	241.58	16.56	[4.5-42.4]	2.50	[0.7-6.4]
Solifenacin	136	9,496	9,626.53	14.13	[11.9-16.7]	1.04	[0.9-1.2]
Tolterodine	133	7,113	9,099.97	14.62	[12.2-17.3]	1.17	[1-1.4]
Trospium	42	2,877	2,664.98	15.76	[11.4-21.3]	1.42	[1-1.9]
MALES WITH HIGH CV RISK							
Any OAB drug	305	15,055	19,865.15	15.35	[13.7-17.2]	1.81	[1.6-2]
Darifenacin	11	663	681.71	16.14	[8.1-28.9]	1.11	[0.6-2]
Fesoterodine	15	2,016	1,442.38	10.40	[5.8-17.2]	1.98	[1.1-3.3]
Oxybutynin	6	275	207.31	28.94	[10.6-63]	6.75	[2.5-14.7]
Solifenacin	121	7,878	8,091.80	14.95	[12.4-17.9]	1.85	[1.5-2.2]
Tolterodine	122	5,799	7,707.87	15.83	[13.1-18.9]	1.66	[1.4-2]
Trospium	38	2,355	2,201.83	17.26	[12.2-23.7]	1.96	[1.4-2.7]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV4a. Person-time, Frequency, and Incidence Rates for Acute Myocardial Infarction, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	150	64,666	17,935.98	8.36	[7.1-9.8]	3.07	[2.6-3.6]
Darifenacin	6	3,764	766.04	7.83	[2.9-17]	3.10	[1.1-6.7]
Fesoterodine	15	8,266	1,438.28	10.43	[5.8-17.2]	3.43	[1.9-5.7]
Oxybutynin	3	1,875	327.82	9.15	[1.9-26.7]	2.14	[0.4-6.2]
Solifenacin	52	32,244	7,099.15	7.32	[5.5-9.6]	2.54	[1.9-3.3]
Tolterodine	60	23,550	6,261.50	9.58	[7.3-12.3]	3.68	[2.8-4.7]
Trospium	19	10,327	2,274.92	8.35	[5-13]	3.32	[2-5.2]
AGE OVER 65							
Any OAB drug	126	35,860	9,690.52	13.00	[10.8-15.5]	2.57	[2.1-3.1]
Darifenacin	5	2,136	425.07	11.76	[3.8-27.5]	3.52	[1.1-8.2]
Fesoterodine	14	4,187	722.58	19.37	[10.6-32.5]	4.44	[2.4-7.4]
Oxybutynin	3	949	165.66	18.11	[3.7-52.9]	3.24	[0.7-9.5]
Solifenacin	45	17,688	3,828.42	11.75	[8.6-15.7]	2.02	[1.5-2.7]
Tolterodine	49	13,553	3,456.77	14.18	[10.5-18.7]	2.77	[2-3.7]
Trospium	13	5,487	1,206.86	10.77	[5.7-18.4]	2.18	[1.2-3.7]
HIGH CV RISK							
Any OAB drug	101	27,703	7,094.19	14.24	[11.6-17.3]	4.18	[3.4-5.1]
Darifenacin	4	1,493	295.04	13.56	[3.7-34.7]	4.17	[1.1-10.7]
Fesoterodine	9	3,489	602.41	14.94	[6.8-28.4]	3.23	[1.5-6.1]
Oxybutynin	3	729	123.74	24.24	[5-70.9]	4.68	[1-13.7]
Solifenacin	37	13,660	2,847.44	12.99	[9.1-17.9]	4.34	[3.1-6]
Tolterodine	40	9,912	2,468.71	16.20	[11.6-22.1]	4.54	[3.2-6.2]
Trospium	11	4,158	850.24	12.94	[6.5-23.1]	3.58	[1.8-6.4]
FEMALES							
Any OAB drug	61	38,901	11,315.73	5.39	[4.1-6.9]	1.05	[0.8-1.3]
Darifenacin	2	2,613	544.99	3.67	[0.4-13.3]	0.50	[0.1-1.8]
Fesoterodine	5	5,117	900.03	5.56	[1.8-13]	1.03	[0.3-2.4]
Oxybutynin	3	1,486	262.03	11.45	[2.4-33.5]	2.14	[0.4-6.2]
Solifenacin	19	19,513	4,447.09	4.27	[2.6-6.7]	0.86	[0.5-1.3]
Tolterodine	25	13,876	3,863.54	6.47	[4.2-9.6]	1.14	[0.7-1.7]
Trospium	8	6,408	1,446.11	5.53	[2.4-10.9]	1.43	[0.6-2.8]
FEMALES OVER 65 YEARS							
Any OAB drug	53	20,439	5,843.42	9.07	[6.8-11.9]	0.87	[0.7-1.1]
Darifenacin	2	1,450	292.70	6.83	[0.8-24.7]	0.50	[0.1-1.8]
Fesoterodine	4	2,371	417.61	9.58	[2.6-24.5]	0.78	[0.2-2]
Oxybutynin	3	702	124.38	24.12	[5-70.5]	3.24	[0.7-9.5]
Solifenacin	17	10,039	2,263.23	7.51	[4.4-12]	0.62	[0.4-1]
Tolterodine	22	7,727	2,071.61	10.62	[6.7-16.1]	1.07	[0.7-1.6]
Trospium	6	3,258	745.94	8.04	[3-17.5]	0.94	[0.3-2]

Table CV4a. Person-time, Frequency, and Incidence Rates for Acute Myocardial Infarction, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	42	15,071	4,010.02	10.47	[7.5-14.2]	1.86	[1.3-2.5]
Darifenacin	1	969	195.37	5.12	[0.1-28.5]	0.54	[0-3]
Fesoterodine	3	1,942	337.25	8.90	[1.8-26]	1.05	[0.2-3.1]
Oxybutynin	3	551	94.63	31.70	[6.5-92.7]	4.68	[1-13.7]
Solifenacin	15	7,430	1,593.76	9.41	[5.3-15.5]	2.30	[1.3-3.8]
Tolterodine	17	5,228	1,349.26	12.60	[7.3-20.2]	1.89	[1.1-3]
Trospium	4	2,344	493.85	8.10	[2.2-20.7]	0.84	[0.2-2.2]
MALES							
Any OAB drug	89	25,765	6,620.25	13.44	[10.8-16.5]	2.02	[1.6-2.5]
Darifenacin	4	1,151	221.05	18.10	[4.9-46.3]	2.60	[0.7-6.6]
Fesoterodine	10	3,149	538.25	18.58	[8.9-34.2]	2.40	[1.2-4.4]
Oxybutynin	0	389	65.79	0.00	[0-56.1]	0.00	[.-.]
Solifenacin	33	12,731	2,652.06	12.44	[8.6-17.5]	1.69	[1.2-2.4]
Tolterodine	35	9,674	2,397.95	14.60	[10.2-20.3]	2.54	[1.8-3.5]
Trospium	11	3,919	828.81	13.27	[6.6-23.7]	1.89	[0.9-3.4]
MALES OVER 65 YEARS							
Any OAB drug	73	15,421	3,847.10	18.98	[14.9-23.9]	1.70	[1.3-2.1]
Darifenacin	3	686	132.37	22.66	[4.7-66.2]	3.02	[0.6-8.8]
Fesoterodine	10	1,816	304.97	32.79	[15.7-60.3]	3.66	[1.8-6.7]
Oxybutynin	0	247	41.28	0.00	[0-89.4]	0.00	[.-.]
Solifenacin	28	7,649	1,565.19	17.89	[11.9-25.9]	1.40	[0.9-2]
Tolterodine	27	5,826	1,385.17	19.49	[12.8-28.4]	1.70	[1.1-2.5]
Trospium	7	2,229	460.92	15.19	[6.1-31.3]	1.24	[0.5-2.6]
MALES WITH HIGH CV RISK							
Any OAB drug	59	12,632	3,084.17	19.13	[14.6-24.7]	2.31	[1.8-3]
Darifenacin	3	524	99.67	30.10	[6.2-88]	3.64	[0.7-10.6]
Fesoterodine	6	1,547	265.15	22.63	[8.3-49.3]	2.18	[0.8-4.8]
Oxybutynin	0	178	29.12	0.00	[0-126.7]	0.00	[.-.]
Solifenacin	22	6,230	1,253.68	17.55	[11-26.6]	2.04	[1.3-3.1]
Tolterodine	23	4,684	1,119.45	20.55	[13-30.8]	2.65	[1.7-4]
Trospium	7	1,814	356.39	19.64	[7.9-40.5]	2.74	[1.1-5.6]

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV4b. Person-time, Frequency, and Incidence Rates for Stroke, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	53	64,785	18,049.32	2.94	[2.2-3.8]	5.55	[4.2-7.3]
Darifenacin	2	3,786	770.29	2.60	[0.3-9.4]	1.20	[0.1-4.3]
Fesoterodine	7	8,303	1,448.02	4.83	[1.9-10]	1.97	[0.8-4.1]
Oxybutynin	0	1,882	329.19	0.00	[0-11.2]	0.00	[.-.]
Solifenacin	21	32,352	7,138.11	2.94	[1.8-4.5]	1.09	[0.7-1.7]
Tolterodine	14	23,606	6,305.45	2.22	[1.2-3.7]	14.13	[7.7-23.7]
Trospium	9	10,367	2,292.84	3.93	[1.8-7.5]	2.46	[1.1-4.7]
AGE OVER 65							
Any OAB drug	34	35,964	9,784.19	3.47	[2.4-4.9]	0.75	[0.5-1.1]
Darifenacin	1	2,155	428.92	2.33	[0.1-13]	0.45	[0-2.5]
Fesoterodine	5	4,217	729.90	6.85	[2.2-16]	0.92	[0.3-2.1]
Oxybutynin	0	953	166.55	0.00	[0-22.1]	0.00	[.-.]
Solifenacin	15	17,772	3,859.56	3.89	[2.2-6.4]	1.02	[0.6-1.7]
Tolterodine	7	13,599	3,493.33	2.00	[0.8-4.1]	0.38	[0.2-0.8]
Trospium	6	5,520	1,222.41	4.91	[1.8-10.7]	0.99	[0.4-2.2]
HIGH CV RISK							
Any OAB drug	34	27,796	7,163.55	4.75	[3.3-6.6]	2.21	[1.5-3.1]
Darifenacin	2	1,503	296.12	6.75	[0.8-24.4]	4.68	[0.6-16.9]
Fesoterodine	5	3,510	607.68	8.23	[2.7-19.2]	6.38	[2.1-14.9]
Oxybutynin	0	731	124.87	0.00	[0-29.5]	0.00	[.-.]
Solifenacin	13	13,731	2,873.64	4.52	[2.4-7.7]	1.34	[0.7-2.3]
Tolterodine	10	9,953	2,496.16	4.01	[1.9-7.4]	2.32	[1.1-4.3]
Trospium	4	4,186	860.30	4.65	[1.3-11.9]	0.85	[0.2-2.2]
FEMALES							
Any OAB drug	29	38,950	11,366.37	2.55	[1.7-3.7]	0.80	[0.5-1.1]
Darifenacin	1	2,626	547.23	1.83	[0-10.2]	0.75	[0-4.2]
Fesoterodine	4	5,135	904.07	4.42	[1.2-11.3]	1.41	[0.4-3.6]
Oxybutynin	0	1,485	262.16	0.00	[0-14.1]	0.00	[.-.]
Solifenacin	9	19,557	4,466.08	2.02	[0.9-3.8]	0.47	[0.2-0.9]
Tolterodine	8	13,894	3,881.80	2.06	[0.9-4.1]	0.72	[0.3-1.4]
Trospium	7	6,424	1,454.68	4.81	[1.9-9.9]	1.68	[0.7-3.5]
FEMALES OVER 65 YEARS							
Any OAB drug	16	20,485	5,889.60	2.72	[1.6-4.4]	0.28	[0.2-0.5]
Darifenacin	0	1,462	295.00	0.00	[0-12.5]	0.00	[.-.]
Fesoterodine	2	2,385	420.21	4.76	[0.6-17.2]	0.36	[0-1.3]
Oxybutynin	0	701	124.51	0.00	[0-29.6]	0.00	[.-.]
Solifenacin	5	10,079	2,279.42	2.19	[0.7-5.1]	0.26	[0.1-0.6]
Tolterodine	4	7,745	2,088.30	1.92	[0.5-4.9]	0.27	[0.1-0.7]
Trospium	5	3,273	755.11	6.62	[2.2-15.5]	0.49	[0.2-1.1]

Table CV4b. Person-time, Frequency, and Incidence Rates for Stroke, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	20	15,109	4,042.46	4.95	[3-7.6]	1.65	[1-2.5]
Darifenacin	1	975	195.36	5.12	[0.1-28.5]	3.92	[0.1-21.9]
Fesoterodine	4	1,952	339.74	11.77	[3.2-30.1]	6.12	[1.7-15.7]
Oxybutynin	0	549	95.15	0.00	[0-38.8]	0.00	[.-.]
Solifenacin	5	7,462	1,607.09	3.11	[1-7.3]	0.47	[0.2-1.1]
Tolterodine	6	5,239	1,361.27	4.41	[1.6-9.6]	1.85	[0.7-4]
Trospium	4	2,355	499.09	8.01	[2.2-20.5]	0.85	[0.2-2.2]
MALES							
Any OAB drug	24	25,835	6,682.95	3.59	[2.3-5.3]	4.75	[3-7.1]
Darifenacin	1	1,160	223.05	4.48	[0.1-25]	0.45	[0-2.5]
Fesoterodine	3	3,168	543.94	5.52	[1.1-16.1]	0.56	[0.1-1.6]
Oxybutynin	0	397	67.03	0.00	[0-55]	0.00	[.-.]
Solifenacin	12	12,795	2,672.03	4.49	[2.3-7.8]	0.62	[0.3-1.1]
Tolterodine	6	9,712	2,423.66	2.48	[0.9-5.4]	13.42	[4.9-29.2]
Trospium	2	3,943	838.16	2.39	[0.3-8.6]	0.78	[0.1-2.8]
MALES OVER 65 YEARS							
Any OAB drug	18	15,479	3,894.59	4.62	[2.7-7.3]	0.47	[0.3-0.7]
Darifenacin	1	693	133.92	7.47	[0.2-41.6]	0.45	[0-2.5]
Fesoterodine	3	1,832	309.69	9.69	[2-28.3]	0.56	[0.1-1.6]
Oxybutynin	0	252	42.04	0.00	[0-87.7]	0.00	[.-.]
Solifenacin	10	7,693	1,580.14	6.33	[3-11.6]	0.76	[0.4-1.4]
Tolterodine	3	5,854	1,405.04	2.14	[0.4-6.2]	0.11	[0-0.3]
Trospium	1	2,247	467.30	2.14	[0.1-11.9]	0.50	[0-2.8]
MALES WITH HIGH CV RISK							
Any OAB drug	14	12,687	3,121.09	4.49	[2.5-7.5]	0.57	[0.3-1]
Darifenacin	1	528	100.76	9.92	[0.3-55.3]	0.75	[0-4.2]
Fesoterodine	1	1,558	267.94	3.73	[0.1-20.8]	0.26	[0-1.5]
Oxybutynin	0	182	29.72	0.00	[0-124.1]	0.00	[.-.]
Solifenacin	8	6,269	1,266.55	6.32	[2.7-12.4]	0.86	[0.4-1.7]
Tolterodine	4	4,714	1,134.89	3.52	[1-9]	0.47	[0.1-1.2]
Trospium	0	1,831	361.21	0.00	[0-10.2]	0.00	[.-.]

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV4c. Person-time, Frequency, and Incidence Rates for All-Cause Mortality, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	892	64,878	18,101.67	49.28	[46.1-52.6]	17.23	[16.1-18.4]
Darifenacin	40	3,791	772.51	51.78	[37-70.5]	15.50	[11.1-21.1]
Fesoterodine	64	8,320	1,451.78	44.08	[33.9-56.3]	14.76	[11.4-18.8]
Oxybutynin	12	1,885	330.13	36.35	[18.8-63.5]	16.35	[8.4-28.6]
Solifenacin	349	32,402	7,156.94	48.76	[43.8-54.2]	17.32	[15.6-19.2]
Tolterodine	324	23,656	6,325.65	51.22	[45.8-57.1]	18.81	[16.8-21]
Trospium	114	10,390	2,299.41	49.58	[40.9-59.6]	15.95	[13.2-19.2]
AGE OVER 65							
Any OAB drug	783	36,027	9,817.22	79.76	[74.3-85.5]	13.45	[12.5-14.4]
Darifenacin	36	2,157	429.67	83.79	[58.7-116]	16.39	[11.5-22.7]
Fesoterodine	58	4,228	732.63	79.17	[60.1-102.3]	14.16	[10.8-18.3]
Oxybutynin	10	955	167.29	59.78	[28.7-109.9]	18.68	[9-34.3]
Solifenacin	303	17,805	3,872.50	78.24	[69.7-87.6]	12.68	[11.3-14.2]
Tolterodine	284	13,634	3,505.09	81.02	[71.9-91]	13.97	[12.4-15.7]
Trospium	101	5,538	1,226.64	82.34	[67.1-100]	13.69	[11.2-16.6]
HIGH CV RISK							
Any OAB drug	585	27,861	7,199.30	81.26	[74.8-88.1]	23.36	[21.5-25.3]
Darifenacin	28	1,508	298.35	93.85	[62.4-135.6]	22.71	[15.1-32.8]
Fesoterodine	40	3,523	610.40	65.53	[46.8-89.2]	16.34	[11.7-22.2]
Oxybutynin	8	734	125.26	63.87	[27.6-125.8]	27.46	[11.9-54.1]
Solifenacin	226	13,764	2,885.95	78.31	[68.4-89.2]	24.65	[21.5-28.1]
Tolterodine	219	9,990	2,510.23	87.24	[76.1-99.6]	25.14	[21.9-28.7]
Trospium	70	4,199	864.46	80.98	[63.1-102.3]	17.83	[13.9-22.5]
FEMALES							
Any OAB drug	430	38,997	11,395.27	37.73	[34.3-41.5]	7.14	[6.5-7.9]
Darifenacin	24	2,630	549.10	43.71	[28-65]	7.64	[4.9-11.4]
Fesoterodine	29	5,142	905.46	32.03	[21.4-46]	6.94	[4.7-10]
Oxybutynin	6	1,487	262.90	22.82	[8.4-49.7]	4.02	[1.5-8.7]
Solifenacin	171	19,584	4,475.24	38.21	[32.7-44.4]	6.94	[5.9-8.1]
Tolterodine	155	13,920	3,892.84	39.82	[33.8-46.6]	7.54	[6.4-8.8]
Trospium	51	6,440	1,459.54	34.94	[26-45.9]	7.29	[5.4-9.6]
FEMALES OVER 65 YEARS							
Any OAB drug	377	20,520	5,908.10	63.81	[57.5-70.6]	6.09	[5.5-6.7]
Darifenacin	21	1,464	295.75	71.01	[44-108.5]	6.79	[4.2-10.4]
Fesoterodine	26	2,389	421.06	61.75	[40.3-90.5]	6.07	[4-8.9]
Oxybutynin	5	703	125.25	39.92	[13-93.2]	3.21	[1-7.5]
Solifenacin	149	10,097	2,285.62	65.19	[55.1-76.5]	6.08	[5.1-7.1]
Tolterodine	139	7,766	2,095.46	66.33	[55.8-78.3]	6.51	[5.5-7.7]
Trospium	42	3,285	758.02	55.41	[39.9-74.9]	5.74	[4.1-7.8]

Table CV4c. Person-time, Frequency, and Incidence Rates for All-Cause Mortality, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	265	15,141	4,059.90	65.27	[57.6-73.6]	9.00	[7.9-10.1]
Darifenacin	18	979	197.23	91.27	[54.1-144.2]	14.21	[8.4-22.5]
Fesoterodine	16	1,958	340.86	46.94	[26.8-76.2]	8.33	[4.8-13.5]
Oxybutynin	3	551	95.34	31.47	[6.5-92]	4.65	[1-13.6]
Solifenacin	106	7,479	1,611.92	65.76	[53.8-79.5]	9.18	[7.5-11.1]
Tolterodine	96	5,259	1,367.72	70.19	[56.9-85.7]	8.88	[7.2-10.8]
Trospium	29	2,363	502.19	57.75	[38.7-82.9]	7.90	[5.3-11.3]
MALES							
Any OAB drug	462	25,881	6,706.40	68.89	[62.8-75.5]	10.09	[9.2-11]
Darifenacin	16	1,161	223.41	71.62	[40.9-116.3]	7.86	[4.5-12.8]
Fesoterodine	35	3,178	546.33	64.06	[44.6-89.1]	7.81	[5.4-10.9]
Oxybutynin	6	398	67.23	89.25	[32.8-194.3]	12.34	[4.5-26.9]
Solifenacin	178	12,818	2,681.69	66.38	[57-76.9]	10.39	[8.9-12]
Tolterodine	169	9,736	2,432.81	69.47	[59.4-80.8]	11.27	[9.6-13.1]
Trospium	63	3,950	839.87	75.01	[57.6-96]	8.66	[6.7-11.1]
MALES OVER 65 YEARS							
Any OAB drug	406	15,507	3,909.11	103.86	[94-114.5]	7.36	[6.7-8.1]
Darifenacin	15	693	133.92	112.01	[62.7-184.7]	9.60	[5.4-15.8]
Fesoterodine	32	1,839	311.57	102.70	[70.2-145]	8.09	[5.5-11.4]
Oxybutynin	5	252	42.04	118.92	[38.6-277.5]	15.46	[5-36.1]
Solifenacin	154	7,708	1,586.87	97.05	[82.3-113.6]	6.60	[5.6-7.7]
Tolterodine	145	5,868	1,409.63	102.86	[86.8-121]	7.47	[6.3-8.8]
Trospium	59	2,253	468.62	125.90	[95.8-162.4]	7.95	[6.1-10.3]
MALES WITH HIGH CV RISK							
Any OAB drug	320	12,720	3,139.40	101.93	[91.1-113.7]	14.36	[12.8-16]
Darifenacin	10	529	101.13	98.89	[47.4-181.9]	8.50	[4.1-15.6]
Fesoterodine	24	1,565	269.54	89.04	[57-132.5]	8.00	[5.1-11.9]
Oxybutynin	5	183	29.92	167.11	[54.3-390]	22.81	[7.4-53.2]
Solifenacin	120	6,285	1,274.03	94.19	[78.1-112.6]	15.47	[12.8-18.5]
Tolterodine	123	4,731	1,142.50	107.66	[89.5-128.5]	16.26	[13.5-19.4]
Trospium	41	1,836	362.27	113.18	[81.2-153.5]	9.93	[7.1-13.5]

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV4d. Person-time, Frequency, and Incidence Rates for Cardiovascular Mortality, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	239	64,878	18,101.67	13.20	[11.6-15]	4.38	[3.8-5]
Darifenacin	15	3,791	772.51	19.42	[10.9-32]	6.11	[3.4-10.1]
Fesoterodine	18	8,320	1,451.78	12.40	[7.3-19.6]	4.06	[2.4-6.4]
Oxybutynin	4	1,885	330.13	12.12	[3.3-31]	4.05	[1.1-10.4]
Solifenacin	84	32,402	7,156.94	11.74	[9.4-14.5]	5.24	[4.2-6.5]
Tolterodine	92	23,656	6,325.65	14.54	[11.7-17.8]	3.88	[3.1-4.8]
Trospium	29	10,390	2,299.41	12.61	[8.4-18.1]	3.55	[2.4-5.1]
AGE OVER 65							
Any OAB drug	212	36,027	9,817.22	21.59	[18.8-24.7]	3.61	[3.1-4.1]
Darifenacin	15	2,157	429.67	34.91	[19.5-57.6]	8.11	[4.5-13.4]
Fesoterodine	16	4,228	732.63	21.84	[12.5-35.5]	3.43	[2-5.6]
Oxybutynin	4	955	167.29	23.91	[6.5-61.2]	4.05	[1.1-10.4]
Solifenacin	68	17,805	3,872.50	17.56	[13.6-22.3]	3.30	[2.6-4.2]
Tolterodine	86	13,634	3,505.09	24.54	[19.6-30.3]	3.82	[3.1-4.7]
Trospium	26	5,538	1,226.64	21.20	[13.8-31.1]	2.97	[1.9-4.3]
HIGH CV RISK							
Any OAB drug	179	27,861	7,199.30	24.86	[21.4-28.8]	5.78	[5-6.7]
Darifenacin	13	1,508	298.35	43.57	[23.2-74.5]	9.01	[4.8-15.4]
Fesoterodine	9	3,523	610.40	14.74	[6.7-28]	3.37	[1.5-6.4]
Oxybutynin	3	734	125.26	23.95	[4.9-70]	6.66	[1.4-19.5]
Solifenacin	62	13,764	2,885.95	21.48	[16.5-27.5]	5.85	[4.5-7.5]
Tolterodine	72	9,990	2,510.23	28.68	[22.4-36.1]	5.93	[4.6-7.5]
Trospium	22	4,199	864.46	25.45	[15.9-38.5]	5.55	[3.5-8.4]
FEMALES							
Any OAB drug	110	38,997	11,395.27	9.65	[7.9-11.6]	1.71	[1.4-2.1]
Darifenacin	8	2,630	549.10	14.57	[6.3-28.7]	2.63	[1.1-5.2]
Fesoterodine	8	5,142	905.46	8.84	[3.8-17.4]	1.66	[0.7-3.3]
Oxybutynin	2	1,487	262.90	7.61	[0.9-27.5]	1.32	[0.2-4.8]
Solifenacin	31	19,584	4,475.24	6.93	[4.7-9.8]	1.38	[0.9-2]
Tolterodine	51	13,920	3,892.84	13.10	[9.8-17.2]	2.11	[1.6-2.8]
Trospium	12	6,440	1,459.54	8.22	[4.2-14.4]	1.34	[0.7-2.3]
FEMALES OVER 65 YEARS							
Any OAB drug	97	20,520	5,908.10	16.42	[13.3-20]	1.65	[1.3-2]
Darifenacin	8	1,464	295.75	27.05	[11.7-53.3]	3.32	[1.4-6.5]
Fesoterodine	8	2,389	421.06	19.00	[8.2-37.4]	1.66	[0.7-3.3]
Oxybutynin	2	703	125.25	15.97	[1.9-57.7]	1.32	[0.2-4.8]
Solifenacin	23	10,097	2,285.62	10.06	[6.4-15.1]	1.19	[0.8-1.8]
Tolterodine	48	7,766	2,095.46	22.91	[16.9-30.4]	2.17	[1.6-2.9]
Trospium	10	3,285	758.02	13.19	[6.3-24.3]	0.99	[0.5-1.8]

Table CV4d. Person-time, Frequency, and Incidence Rates for Cardiovascular Mortality, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	79	15,141	4,059.90	19.46	[15.4-24.3]	2.70	[2.1-3.4]
Darifenacin	7	979	197.23	35.49	[14.3-73.1]	4.67	[1.9-9.6]
Fesoterodine	4	1,958	340.86	11.74	[3.2-30]	1.36	[0.4-3.5]
Oxybutynin	1	551	95.34	10.49	[0.3-58.4]	1.34	[0-7.5]
Solifenacin	25	7,479	1,611.92	15.51	[10-22.9]	2.62	[1.7-3.9]
Tolterodine	35	5,259	1,367.72	25.59	[17.8-35.6]	3.08	[2.1-4.3]
Trospium	8	2,363	502.19	15.93	[6.9-31.4]	1.97	[0.9-3.9]
MALES							
Any OAB drug	129	25,881	6,706.40	19.24	[16.1-22.9]	2.67	[2.2-3.2]
Darifenacin	7	1,161	223.41	31.33	[12.6-64.6]	3.48	[1.4-7.2]
Fesoterodine	10	3,178	546.33	18.30	[8.8-33.7]	2.40	[1.2-4.4]
Oxybutynin	2	398	67.23	29.75	[3.6-107.5]	2.74	[0.3-9.9]
Solifenacin	53	12,818	2,681.69	19.76	[14.8-25.9]	3.86	[2.9-5.1]
Tolterodine	41	9,736	2,432.81	16.85	[12.1-22.9]	1.77	[1.3-2.4]
Trospium	17	3,950	839.87	20.24	[11.8-32.4]	2.21	[1.3-3.5]
MALES OVER 65 YEARS							
Any OAB drug	115	15,507	3,909.11	29.42	[24.3-35.3]	1.96	[1.6-2.4]
Darifenacin	7	693	133.92	52.27	[21-107.7]	4.79	[1.9-9.9]
Fesoterodine	8	1,839	311.57	25.68	[11.1-50.6]	1.77	[0.8-3.5]
Oxybutynin	2	252	42.04	47.57	[5.8-171.8]	2.74	[0.3-9.9]
Solifenacin	45	7,708	1,586.87	28.36	[20.7-37.9]	2.11	[1.5-2.8]
Tolterodine	38	5,868	1,409.63	26.96	[19.1-37]	1.65	[1.2-2.3]
Trospium	16	2,253	468.62	34.14	[19.5-55.4]	1.98	[1.1-3.2]
MALES WITH HIGH CV RISK							
Any OAB drug	100	12,720	3,139.40	31.85	[25.9-38.7]	3.08	[2.5-3.7]
Darifenacin	6	529	101.13	59.33	[21.8-129.1]	4.34	[1.6-9.4]
Fesoterodine	5	1,565	269.54	18.55	[6-43.3]	2.01	[0.7-4.7]
Oxybutynin	2	183	29.92	66.84	[8.1-241.5]	5.31	[0.6-19.2]
Solifenacin	37	6,285	1,274.03	29.04	[20.4-40]	3.23	[2.3-4.5]
Tolterodine	37	4,731	1,142.50	32.39	[22.8-44.6]	2.84	[2-3.9]
Trospium	14	1,836	362.27	38.65	[21.1-64.8]	3.58	[2-6]

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV4e. Person-time, Frequency, and Incidence Rates for MACE, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	370	64,574	17,885.15	20.69	[18.6-22.9]	11.84	[10.7-13.1]
Darifenacin	17	3,759	763.93	22.25	[13-35.6]	7.68	[4.5-12.3]
Fesoterodine	37	8,249	1,434.51	25.79	[18.2-35.6]	9.02	[6.4-12.4]
Oxybutynin	7	1,873	327.08	21.40	[8.6-44.1]	6.28	[2.5-12.9]
Solifenacin	129	32,196	7,081.16	18.22	[15.2-21.6]	7.65	[6.4-9.1]
Tolterodine	134	23,500	6,241.67	21.47	[18-25.4]	20.32	[17-24.1]
Trospium	53	10,304	2,268.36	23.36	[17.5-30.6]	8.95	[6.7-11.7]
AGE OVER 65							
Any OAB drug	311	35,798	9,658.77	32.20	[28.7-36]	5.91	[5.3-6.6]
Darifenacin	15	2,134	424.44	35.34	[19.8-58.3]	8.03	[4.5-13.2]
Fesoterodine	32	4,176	719.86	44.45	[30.4-62.8]	8.32	[5.7-11.8]
Oxybutynin	7	947	164.92	42.44	[17.1-87.5]	7.39	[3-15.2]
Solifenacin	107	17,657	3,816.32	28.04	[23-33.9]	5.42	[4.4-6.6]
Tolterodine	113	13,518	3,445.33	32.80	[27-39.4]	5.65	[4.7-6.8]
Trospium	42	5,469	1,202.63	34.92	[25.2-47.2]	5.91	[4.3-8]
HIGH CV RISK							
Any OAB drug	260	27,638	7,059.78	36.83	[32.5-41.6]	10.53	[9.3-11.9]
Darifenacin	14	1,488	292.94	47.79	[26.1-80.2]	14.38	[7.9-24.1]
Fesoterodine	20	3,476	599.69	33.35	[20.4-51.5]	12.23	[7.5-18.9]
Oxybutynin	6	727	123.55	48.56	[17.8-105.7]	11.55	[4.2-25.1]
Solifenacin	94	13,628	2,835.78	33.15	[26.8-40.6]	9.87	[8-12.1]
Tolterodine	95	9,875	2,455.02	38.70	[31.3-47.3]	10.71	[8.7-13.1]
Trospium	35	4,145	846.08	41.37	[28.8-57.5]	9.68	[6.7-13.5]
FEMALES							
Any OAB drug	166	38,855	11,287.30	14.71	[12.6-17.1]	2.99	[2.6-3.5]
Darifenacin	8	2,609	543.25	14.73	[6.4-29]	2.91	[1.3-5.7]
Fesoterodine	15	5,110	898.65	16.69	[9.3-27.5]	3.75	[2.1-6.2]
Oxybutynin	5	1,484	261.29	19.14	[6.2-44.7]	3.48	[1.1-8.1]
Solifenacin	48	19,487	4,438.28	10.82	[8-14.3]	2.14	[1.6-2.8]
Tolterodine	69	13,850	3,852.50	17.91	[13.9-22.7]	3.32	[2.6-4.2]
Trospium	23	6,392	1,441.26	15.96	[10.1-23.9]	4.01	[2.5-6]
FEMALES OVER 65 YEARS							
Any OAB drug	139	20,405	5,825.39	23.86	[20.1-28.2]	2.33	[2-2.8]
Darifenacin	7	1,448	292.06	23.97	[9.6-49.4]	2.85	[1.1-5.9]
Fesoterodine	12	2,367	416.77	28.79	[14.9-50.3]	2.44	[1.3-4.3]
Oxybutynin	5	700	123.64	40.44	[13.1-94.4]	4.58	[1.5-10.7]
Solifenacin	39	10,022	2,257.37	17.28	[12.3-23.6]	1.77	[1.3-2.4]
Tolterodine	60	7,706	2,064.44	29.06	[22.2-37.4]	2.76	[2.1-3.6]
Trospium	18	3,246	743.02	24.23	[14.4-38.3]	2.14	[1.3-3.4]

Table CV4e. Person-time, Frequency, and Incidence Rates for MACE, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	117	15,039	3,992.86	29.30	[24.2-35.1]	5.35	[4.4-6.4]
Darifenacin	6	965	193.62	30.99	[11.4-67.4]	7.08	[2.6-15.4]
Fesoterodine	9	1,936	336.14	26.77	[12.2-50.8]	8.04	[3.7-15.3]
Oxybutynin	4	549	94.44	42.36	[11.5-108.4]	6.05	[1.6-15.5]
Solifenacin	37	7,413	1,589.10	23.28	[16.4-32.1]	4.34	[3.1-6]
Tolterodine	48	5,208	1,342.81	35.75	[26.4-47.4]	6.03	[4.4-8]
Trospium	14	2,336	490.75	28.53	[15.6-47.9]	3.30	[1.8-5.5]
MALES							
Any OAB drug	204	25,719	6,597.85	30.92	[26.8-35.5]	8.85	[7.7-10.2]
Darifenacin	9	1,150	220.69	40.78	[18.6-77.4]	4.77	[2.2-9.1]
Fesoterodine	22	3,139	535.87	41.05	[25.7-62.2]	5.27	[3.3-8]
Oxybutynin	2	389	65.79	30.40	[3.7-109.8]	2.80	[0.3-10.1]
Solifenacin	81	12,709	2,642.88	30.65	[24.3-38.1]	5.51	[4.4-6.8]
Tolterodine	65	9,650	2,389.18	27.21	[21-34.7]	17.00	[13.1-21.7]
Trospium	30	3,912	827.10	36.27	[24.5-51.8]	4.94	[3.3-7.1]
MALES OVER 65 YEARS							
Any OAB drug	172	15,393	3,833.38	44.87	[38.4-52.1]	3.58	[3.1-4.2]
Darifenacin	8	686	132.37	60.44	[26.1-119.1]	5.19	[2.2-10.2]
Fesoterodine	20	1,809	303.09	65.99	[40.3-101.9]	5.88	[3.6-9.1]
Oxybutynin	2	247	41.28	48.45	[5.9-175]	2.80	[0.3-10.1]
Solifenacin	68	7,635	1,558.94	43.62	[33.9-55.3]	3.65	[2.8-4.6]
Tolterodine	53	5,812	1,380.89	38.38	[28.7-50.2]	2.89	[2.2-3.8]
Trospium	24	2,223	459.60	52.22	[33.5-77.7]	3.77	[2.4-5.6]
MALES WITH HIGH CV RISK							
Any OAB drug	143	12,599	3,066.92	46.63	[39.3-54.9]	5.18	[4.4-6.1]
Darifenacin	8	523	99.31	80.55	[34.8-158.7]	7.31	[3.2-14.4]
Fesoterodine	11	1,540	263.56	41.74	[20.8-74.7]	4.20	[2.1-7.5]
Oxybutynin	2	178	29.12	68.69	[8.3-248.1]	5.49	[0.7-19.8]
Solifenacin	57	6,215	1,246.68	45.72	[34.6-59.2]	5.53	[4.2-7.2]
Tolterodine	47	4,667	1,112.21	42.26	[31-56.2]	4.68	[3.4-6.2]
Trospium	21	1,809	355.33	59.10	[36.6-90.3]	6.38	[3.9-9.8]

CI = confidence interval; CV = cardiovascular; MACE = major adverse cardiac event; OAB = overactive bladder.

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV4f. Person-time, Frequency, and Incidence Rates for Coronary Heart Disease Death, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	145	64,878	18,101.67	8.01	[6.8-9.4]	2.82	[2.4-3.3]
Darifenacin	10	3,791	772.51	12.94	[6.2-23.8]	4.26	[2-7.8]
Fesoterodine	17	8,320	1,451.78	11.71	[6.8-18.7]	3.87	[2.3-6.2]
Oxybutynin	2	1,885	330.13	6.06	[0.7-21.9]	2.11	[0.3-7.6]
Solifenacin	44	32,402	7,156.94	6.15	[4.5-8.3]	3.40	[2.5-4.6]
Tolterodine	60	23,656	6,325.65	9.49	[7.2-12.2]	2.49	[1.9-3.2]
Trospium	15	10,390	2,299.41	6.52	[3.7-10.8]	1.85	[1-3.1]
AGE OVER 65							
Any OAB drug	129	36,027	9,817.22	13.14	[11-15.6]	2.10	[1.8-2.5]
Darifenacin	10	2,157	429.67	23.27	[11.2-42.8]	6.26	[3-11.5]
Fesoterodine	15	4,228	732.63	20.47	[11.5-33.8]	3.23	[1.8-5.3]
Oxybutynin	2	955	167.29	11.96	[1.4-43.2]	2.11	[0.3-7.6]
Solifenacin	34	17,805	3,872.50	8.78	[6.1-12.3]	1.44	[1-2]
Tolterodine	57	13,634	3,505.09	16.26	[12.3-21.1]	2.46	[1.9-3.2]
Trospium	14	5,538	1,226.64	11.41	[6.2-19.1]	1.63	[0.9-2.7]
HIGH CV RISK							
Any OAB drug	109	27,861	7,199.30	15.14	[12.4-18.3]	3.43	[2.8-4.1]
Darifenacin	8	1,508	298.35	26.81	[11.6-52.8]	5.72	[2.5-11.3]
Fesoterodine	8	3,523	610.40	13.11	[5.7-25.8]	3.02	[1.3-6]
Oxybutynin	2	734	125.26	15.97	[1.9-57.7]	4.00	[0.5-14.5]
Solifenacin	33	13,764	2,885.95	11.43	[7.9-16.1]	3.04	[2.1-4.3]
Tolterodine	49	9,990	2,510.23	19.52	[14.4-25.8]	3.94	[2.9-5.2]
Trospium	11	4,199	864.46	12.72	[6.4-22.8]	2.78	[1.4-5]
FEMALES							
Any OAB drug	58	38,997	11,395.27	5.09	[3.9-6.6]	0.91	[0.7-1.2]
Darifenacin	6	2,630	549.10	10.93	[4-23.8]	2.13	[0.8-4.6]
Fesoterodine	7	5,142	905.46	7.73	[3.1-15.9]	1.47	[0.6-3]
Oxybutynin	1	1,487	262.90	3.80	[0.1-21.2]	0.74	[0-4.1]
Solifenacin	13	19,584	4,475.24	2.90	[1.5-5]	0.61	[0.3-1]
Tolterodine	30	13,920	3,892.84	7.71	[5.2-11]	1.22	[0.8-1.7]
Trospium	3	6,440	1,459.54	2.06	[0.4-6]	0.30	[0.1-.9]
FEMALES OVER 65 YEARS							
Any OAB drug	53	20,520	5,908.10	8.97	[6.7-11.7]	0.91	[0.7-1.2]
Darifenacin	6	1,464	295.75	20.29	[7.4-44.2]	2.82	[1-6.1]
Fesoterodine	7	2,389	421.06	16.62	[6.7-34.3]	1.47	[0.6-3]
Oxybutynin	1	703	125.25	7.98	[0.2-44.5]	0.74	[0-4.1]
Solifenacin	9	10,097	2,285.62	3.94	[1.8-7.5]	0.44	[0.2-.8]
Tolterodine	29	7,766	2,095.46	13.84	[9.3-19.9]	1.35	[0.9-1.9]
Trospium	3	3,285	758.02	3.96	[0.8-11.6]	0.30	[0.1-.9]

Table CV4f. Person-time, Frequency, and Incidence Rates for Coronary Heart Disease Death, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	42	15,141	4,059.90	10.35	[7.5-14]	1.52	[1.1-2.1]
Darifenacin	5	979	197.23	25.35	[8.2-59.2]	3.64	[1.2-8.5]
Fesoterodine	3	1,958	340.86	8.80	[1.8-25.7]	1.01	[0.2-3]
Oxybutynin	1	551	95.34	10.49	[0.3-58.4]	1.34	[0-7.5]
Solifenacin	11	7,479	1,611.92	6.82	[3.4-12.2]	1.41	[0.7-2.5]
Tolterodine	21	5,259	1,367.72	15.35	[9.5-23.5]	1.89	[1.2-2.9]
Trospium	2	2,363	502.19	3.98	[0.5-14.4]	0.41	[0-1.5]
MALES							
Any OAB drug	87	25,881	6,706.40	12.97	[10.4-16]	1.91	[1.5-2.4]
Darifenacin	4	1,161	223.41	17.90	[4.9-45.8]	2.13	[0.6-5.4]
Fesoterodine	10	3,178	546.33	18.30	[8.8-33.7]	2.40	[1.2-4.4]
Oxybutynin	1	398	67.23	14.87	[0.4-82.9]	1.37	[0-7.6]
Solifenacin	31	12,818	2,681.69	11.56	[7.9-16.4]	2.79	[1.9-4]
Tolterodine	30	9,736	2,432.81	12.33	[8.3-17.6]	1.27	[0.9-1.8]
Trospium	12	3,950	839.87	14.29	[7.4-25]	1.56	[0.8-2.7]
MALES OVER 65 YEARS							
Any OAB drug	76	15,507	3,909.11	19.44	[15.3-24.3]	1.19	[0.9-1.5]
Darifenacin	4	693	133.92	29.87	[8.1-76.5]	3.44	[0.9-8.8]
Fesoterodine	8	1,839	311.57	25.68	[11.1-50.6]	1.77	[0.8-3.5]
Oxybutynin	1	252	42.04	23.78	[0.6-132.5]	1.37	[0-7.6]
Solifenacin	25	7,708	1,586.87	15.75	[10.2-23.3]	1.00	[0.6-1.5]
Tolterodine	28	5,868	1,409.63	19.86	[13.2-28.7]	1.11	[0.7-1.6]
Trospium	11	2,253	468.62	23.47	[11.7-42]	1.33	[0.7-2.4]
MALES WITH HIGH CV RISK							
Any OAB drug	67	12,720	3,139.40	21.34	[16.5-27.1]	1.91	[1.5-2.4]
Darifenacin	3	529	101.13	29.67	[6.1-86.7]	2.09	[0.4-6.1]
Fesoterodine	5	1,565	269.54	18.55	[6-43.3]	2.01	[0.7-4.7]
Oxybutynin	1	183	29.92	33.42	[0.8-186.2]	2.66	[0.1-14.8]
Solifenacin	22	6,285	1,274.03	17.27	[10.8-26.1]	1.63	[1-2.5]
Tolterodine	28	4,731	1,142.50	24.51	[16.3-35.4]	2.05	[1.4-3]
Trospium	9	1,836	362.27	24.84	[11.4-47.2]	2.37	[1.1-4.5]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV4g. Person-time, Frequency, and Incidence Rates for Cerebrovascular Death, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
OVERALL							
Any OAB drug	94	64,878	18,101.67	5.19	[4.2-6.4]	1.56	[1.3-1.9]
Darifenacin	5	3,791	772.51	6.47	[2.1-15.1]	1.85	[0.6-4.3]
Fesoterodine	1	8,320	1,451.78	0.69	[0-3.8]	0.20	[0-1.1]
Oxybutynin	2	1,885	330.13	6.06	[0.7-21.9]	1.94	[0.2-7]
Solifenacin	40	32,402	7,156.94	5.59	[4-7.6]	1.84	[1.3-2.5]
Tolterodine	32	23,656	6,325.65	5.06	[3.5-7.1]	1.39	[1-2]
Trospium	14	10,390	2,299.41	6.09	[3.3-10.2]	1.69	[0.9-2.8]
AGE OVER 65							
Any OAB drug	83	36,027	9,817.22	8.45	[6.7-10.5]	1.51	[1.2-1.9]
Darifenacin	5	2,157	429.67	11.64	[3.8-27.2]	1.85	[0.6-4.3]
Fesoterodine	1	4,228	732.63	1.36	[0-7.6]	0.20	[0-1.1]
Oxybutynin	2	955	167.29	11.96	[1.4-43.2]	1.94	[0.2-7]
Solifenacin	34	17,805	3,872.50	8.78	[6.1-12.3]	1.86	[1.3-2.6]
Tolterodine	29	13,634	3,505.09	8.27	[5.5-11.9]	1.35	[0.9-1.9]
Trospium	12	5,538	1,226.64	9.78	[5.1-17.1]	1.34	[0.7-2.3]
HIGH CV RISK							
Any OAB drug	70	27,861	7,199.30	9.72	[7.6-12.3]	2.34	[1.8-3]
Darifenacin	5	1,508	298.35	16.76	[5.4-39.1]	3.29	[1.1-7.7]
Fesoterodine	1	3,523	610.40	1.64	[0-9.1]	0.34	[0-1.9]
Oxybutynin	1	734	125.26	7.98	[0.2-44.5]	2.66	[0.1-14.8]
Solifenacin	29	13,764	2,885.95	10.05	[6.7-14.4]	2.81	[1.9-4]
Tolterodine	23	9,990	2,510.23	9.16	[5.8-13.7]	1.99	[1.3-3]
Trospium	11	4,199	864.46	12.72	[6.4-22.8]	2.76	[1.4-4.9]
FEMALES							
Any OAB drug	52	38,997	11,395.27	4.56	[3.4-6]	0.80	[0.6-1.1]
Darifenacin	2	2,630	549.10	3.64	[0.4-13.2]	0.50	[0.1-1.8]
Fesoterodine	1	5,142	905.46	1.10	[0-6.2]	0.20	[0-1.1]
Oxybutynin	1	1,487	262.90	3.80	[0.1-21.2]	0.57	[0-3.2]
Solifenacin	18	19,584	4,475.24	4.02	[2.4-6.4]	0.77	[0.5-1.2]
Tolterodine	21	13,920	3,892.84	5.39	[3.3-8.2]	0.89	[0.5-1.4]
Trospium	9	6,440	1,459.54	6.17	[2.8-11.7]	1.04	[0.5-2]
FEMALES OVER 65 YEARS							
Any OAB drug	44	20,520	5,908.10	7.45	[5.4-10]	0.73	[0.5-1]
Darifenacin	2	1,464	295.75	6.76	[0.8-24.4]	0.50	[0.1-1.8]
Fesoterodine	1	2,389	421.06	2.37	[0.1-13.2]	0.20	[0-1.1]
Oxybutynin	1	703	125.25	7.98	[0.2-44.5]	0.57	[0-3.2]
Solifenacin	14	10,097	2,285.62	6.13	[3.3-10.3]	0.75	[0.4-1.3]
Tolterodine	19	7,766	2,095.46	9.07	[5.5-14.2]	0.82	[0.5-1.3]
Trospium	7	3,285	758.02	9.23	[3.7-19]	0.69	[0.3-1.4]

Table CV4g. Person-time, Frequency, and Incidence Rates for Cerebrovascular Death, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)	Standardized Incidence Rate[a]	(95% CI)
FEMALES WITH HIGH CV RISK							
Any OAB drug	37	15,141	4,059.90	9.11	[6.4-12.6]	1.17	[0.8-1.6]
Darifenacin	2	979	197.23	10.14	[1.2-36.6]	1.03	[0.1-3.7]
Fesoterodine	1	1,958	340.86	2.93	[0.1-16.3]	0.34	[0-1.9]
Oxybutynin	0	551	95.34	0.00	[0-38.7]	0.00	[.-.]
Solifenacin	14	7,479	1,611.92	8.69	[4.7-14.6]	1.21	[0.7-2]
Tolterodine	14	5,259	1,367.72	10.24	[5.6-17.2]	1.20	[0.7-2]
Trospium	6	2,363	502.19	11.95	[4.4-26]	1.56	[0.6-3.4]
MALES							
Any OAB drug	42	25,881	6,706.40	6.26	[4.5-8.5]	0.76	[0.5-1]
Darifenacin	3	1,161	223.41	13.43	[2.8-39.2]	1.35	[0.3-3.9]
Fesoterodine	0	3,178	546.33	0.00	[0-6.8]	0.00	[.-.]
Oxybutynin	1	398	67.23	14.87	[0.4-82.9]	1.37	[0-7.6]
Solifenacin	22	12,818	2,681.69	8.20	[5.1-12.4]	1.08	[0.7-1.6]
Tolterodine	11	9,736	2,432.81	4.52	[2.3-8.1]	0.51	[0.3-.9]
Trospium	5	3,950	839.87	5.95	[1.9-13.9]	0.65	[0.2-1.5]
MALES OVER 65 YEARS							
Any OAB drug	39	15,507	3,909.11	9.98	[7.1-13.6]	0.78	[0.6-1.1]
Darifenacin	3	693	133.92	22.40	[4.6-65.5]	1.35	[0.3-3.9]
Fesoterodine	0	1,839	311.57	0.00	[0-11.8]	0.00	[.-.]
Oxybutynin	1	252	42.04	23.78	[0.6-132.5]	1.37	[0-7.6]
Solifenacin	20	7,708	1,586.87	12.60	[7.7-19.5]	1.11	[0.7-1.7]
Tolterodine	10	5,868	1,409.63	7.09	[3.4-13]	0.54	[0.3-1]
Trospium	5	2,253	468.62	10.67	[3.5-24.9]	0.65	[0.2-1.5]
MALES WITH HIGH CV RISK							
Any OAB drug	33	12,720	3,139.40	10.51	[7.2-14.8]	1.17	[0.8-1.6]
Darifenacin	3	529	101.13	29.67	[6.1-86.7]	2.25	[0.5-6.6]
Fesoterodine	0	1,565	269.54	0.00	[0-13.7]	0.00	[.-.]
Oxybutynin	1	183	29.92	33.42	[0.8-186.2]	2.66	[0.1-14.8]
Solifenacin	15	6,285	1,274.03	11.77	[6.6-19.4]	1.60	[0.9-2.6]
Tolterodine	9	4,731	1,142.50	7.88	[3.6-15]	0.79	[0.4-1.5]
Trospium	5	1,836	362.27	13.80	[4.5-32.2]	1.20	[0.4-2.8]

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.88	0.83 - 0.93	0.97	0.91 - 1.03
Darifenacin	0.80	0.57 - 1.12	0.83	0.59 - 1.16
Fesoterodine	0.74	0.56 - 0.97	0.65	0.49 - 0.86
Oxybutynin	0.45	0.21 - 0.97	0.54	0.25 - 1.16
Solifenacin	0.91	0.84 - 0.98	1.06	0.98 - 1.15
Trospium	0.99	0.83 - 1.18	0.99	0.83 - 1.18
AGE OVER 65				
Any OAB drug (not tolterodine)	0.88	0.82 - 0.94	0.83	0.78 - 0.89
Darifenacin	0.75	0.51 - 1.10	0.87	0.59 - 1.28
Fesoterodine	0.83	0.61 - 1.12	0.71	0.52 - 0.96
Oxybutynin	0.61	0.29 - 1.31	0.97	0.46 - 2.08
Solifenacin	0.88	0.80 - 0.96	0.84	0.76 - 0.92
Trospium	1.01	0.83 - 1.23	0.97	0.79 - 1.18
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.92	0.86 - 0.98	1.35	1.26 - 1.44
Darifenacin	0.66	0.41 - 1.05	0.63	0.40 - 1.00
Fesoterodine	0.93	0.69 - 1.24	0.94	0.70 - 1.25
Oxybutynin	0.47	0.19 - 1.19	0.37	0.15 - 0.93
Solifenacin	0.91	0.82 - 1.00	1.58	1.43 - 1.74
Trospium	1.10	0.89 - 1.35	1.08	0.88 - 1.32
FEMALES				
Any OAB drug (not tolterodine)	1.03	0.95 - 1.11	1.22	1.13 - 1.31
Darifenacin	0.97	0.63 - 1.48	1.10	0.72 - 1.68
Fesoterodine	0.95	0.66 - 1.35	1.19	0.83 - 1.69
Oxybutynin	0.28	0.09 - 0.99	0.28	0.09 - 0.99
Solifenacin	1.05	0.94 - 1.16	1.25	1.12 - 1.38
Trospium	1.09	0.85 - 1.39	1.23	0.95 - 1.57
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	1.04	0.95 - 1.13	1.21	1.11 - 1.31
Darifenacin	0.87	0.53 - 1.41	1.33	0.82 - 2.15
Fesoterodine	1.02	0.68 - 1.51	0.95	0.63 - 1.41
Oxybutynin	0.36	0.11 - 1.27	0.34	0.11 - 1.20
Solifenacin	1.05	0.93 - 1.18	1.24	1.10 - 1.39
Trospium	1.12	0.85 - 1.46	1.40	1.06 - 1.83

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	1.15	1.05 - 1.25	1.56	1.43 - 1.69
Darifenacin	0.79	0.43 - 1.43	0.73	0.40 - 1.32
Fesoterodine	1.36	0.95 - 1.93	1.82	1.27 - 2.58
Oxybutynin	0.23	0.06 - 1.25	0.17	0.04 - 0.92
Solifenacin	1.15	1.01 - 1.30	1.67	1.47 - 1.88
Trospium	1.24	0.92 - 1.65	1.39	1.03 - 1.85
MALES				
Any OAB drug (not tolterodine)	0.80	0.73 - 0.87	0.86	0.78 - 0.94
Darifenacin	0.75	0.44 - 1.28	0.70	0.41 - 1.19
Fesoterodine	0.58	0.38 - 0.89	0.41	0.27 - 0.63
Oxybutynin	0.91	0.37 - 2.29	0.65	0.27 - 1.63
Solifenacin	0.82	0.72 - 0.92	0.98	0.86 - 1.10
Trospium	0.94	0.73 - 1.21	0.89	0.69 - 1.14
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.75	0.67 - 0.83	0.64	0.58 - 0.71
Darifenacin	0.69	0.37 - 1.27	0.63	0.34 - 1.16
Fesoterodine	0.66	0.42 - 1.04	0.59	0.37 - 0.93
Oxybutynin	1.13	0.46 - 2.83	1.29	0.53 - 3.23
Solifenacin	0.74	0.64 - 0.85	0.63	0.54 - 0.72
Trospium	0.92	0.69 - 1.22	0.74	0.55 - 0.98
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.78	0.70 - 0.86	1.23	1.10 - 1.36
Darifenacin	0.64	0.32 - 1.28	0.57	0.29 - 1.14
Fesoterodine	0.65	0.41 - 1.03	0.46	0.29 - 0.73
Oxybutynin	0.92	0.34 - 2.63	0.48	0.18 - 1.37
Solifenacin	0.77	0.66 - 0.89	1.52	1.31 - 1.75
Trospium	1.02	0.76 - 1.35	0.91	0.68 - 1.20

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Stroke, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.97	0.89 - 1.05	0.80	0.73 - 0.87
Darifenacin	1.02	0.64 - 1.62	0.78	0.49 - 1.24
Fesoterodine	0.87	0.58 - 1.29	0.62	0.41 - 0.92
Oxybutynin	0.58	0.21 - 1.65	0.45	0.16 - 1.28
Solifenacin	0.97	0.86 - 1.09	0.89	0.79 - 1.00
Trospium	0.99	0.74 - 1.31	0.76	0.57 - 1.00
AGE OVER 65				
Any OAB drug (not tolterodine)	1.03	0.93 - 1.13	0.86	0.77 - 0.95
Darifenacin	1.08	0.63 - 1.84	0.76	0.44 - 1.30
Fesoterodine	0.97	0.60 - 1.55	0.86	0.53 - 1.37
Oxybutynin	0.91	0.33 - 2.57	1.55	0.57 - 4.38
Solifenacin	1.03	0.89 - 1.18	0.87	0.75 - 1.00
Trospium	1.03	0.73 - 1.43	0.88	0.62 - 1.23
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.91	0.82 - 1.01	0.74	0.66 - 0.82
Darifenacin	1.06	0.61 - 1.81	0.71	0.41 - 1.21
Fesoterodine	0.86	0.54 - 1.35	0.55	0.35 - 0.86
Oxybutynin	0.55	0.17 - 1.93	0.33	0.10 - 1.16
Solifenacin	0.92	0.79 - 1.06	0.86	0.74 - 0.99
Trospium	0.91	0.64 - 1.28	0.62	0.43 - 0.87
FEMALES				
Any OAB drug (not tolterodine)	0.94	0.83 - 1.05	1.07	0.95 - 1.19
Darifenacin	1.23	0.72 - 2.07	1.06	0.62 - 1.78
Fesoterodine	0.71	0.39 - 1.27	0.74	0.41 - 1.33
Oxybutynin	0.59	0.18 - 2.05	0.39	0.12 - 1.35
Solifenacin	0.88	0.74 - 1.04	1.09	0.91 - 1.29
Trospium	1.05	0.72 - 1.50	1.10	0.76 - 1.57
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.97	0.84 - 1.10	0.85	0.74 - 0.97
Darifenacin	1.33	0.74 - 2.35	1.32	0.73 - 2.33
Fesoterodine	0.85	0.43 - 1.63	0.60	0.31 - 1.15
Oxybutynin	0.87	0.27 - 2.98	0.54	0.17 - 1.85
Solifenacin	0.93	0.76 - 1.12	0.85	0.69 - 1.03
Trospium	0.91	0.56 - 1.44	0.77	0.48 - 1.22

Table CV5b. Crude and Standardized Incidence Rate Ratios for Stroke, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.87	0.75 - 1.00	1.15	0.99 - 1.32
Darifenacin	1.11	0.57 - 2.13	0.51	0.26 - 0.98
Fesoterodine	0.75	0.38 - 1.44	0.75	0.38 - 1.44
Oxybutynin	0.42	0.10 - 2.23	0.14	0.03 - 0.74
Solifenacin	0.81	0.65 - 0.99	1.32	1.05 - 1.62
Trospium	1.01	0.64 - 1.56	0.92	0.58 - 1.42
MALES				
Any OAB drug (not tolterodine)	1.04	0.91 - 1.17	0.67	0.59 - 0.76
Darifenacin	0.77	0.32 - 1.87	0.64	0.27 - 1.55
Fesoterodine	1.09	0.64 - 1.82	0.55	0.32 - 0.92
Oxybutynin	0.69	0.17 - 3.69	0.49	0.12 - 2.62
Solifenacin	1.13	0.95 - 1.32	0.79	0.66 - 0.93
Trospium	0.93	0.59 - 1.42	0.58	0.37 - 0.89
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	1.12	0.96 - 1.29	0.86	0.73 - 0.99
Darifenacin	0.60	0.19 - 2.02	0.27	0.09 - 0.91
Fesoterodine	1.13	0.58 - 2.12	1.09	0.56 - 2.05
Oxybutynin	1.11	0.27 - 5.80	2.44	0.60 - 12.74
Solifenacin	1.17	0.95 - 1.41	0.89	0.72 - 1.07
Trospium	1.21	0.74 - 1.91	0.99	0.61 - 1.56
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.97	0.83 - 1.12	0.46	0.39 - 0.53
Darifenacin	1.06	0.44 - 2.54	0.86	0.36 - 2.06
Fesoterodine	1.00	0.54 - 1.82	0.41	0.22 - 0.75
Oxybutynin	0.87	0.21 - 4.60	0.46	0.11 - 2.43
Solifenacin	1.06	0.87 - 1.27	0.54	0.44 - 0.65
Trospium	0.81	0.47 - 1.37	0.42	0.24 - 0.71

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5c. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.84	0.82 - 0.86	0.85	0.83 - 0.87
Darifenacin	0.74	0.64 - 0.85	0.67	0.58 - 0.77
Fesoterodine	0.66	0.59 - 0.74	0.64	0.57 - 0.72
Oxybutynin	0.79	0.63 - 1.00	1.98	1.57 - 2.49
Solifenacin	0.87	0.84 - 0.90	0.84	0.81 - 0.87
Trospium	0.88	0.82 - 0.95	0.89	0.83 - 0.96
AGE OVER 65				
Any OAB drug (not tolterodine)	0.88	0.86 - 0.90	0.85	0.83 - 0.87
Darifenacin	0.75	0.65 - 0.87	0.70	0.60 - 0.81
Fesoterodine	0.74	0.65 - 0.84	0.76	0.67 - 0.86
Oxybutynin	0.79	0.61 - 1.02	1.01	0.78 - 1.31
Solifenacin	0.90	0.87 - 0.93	0.86	0.83 - 0.89
Trospium	0.90	0.83 - 0.98	0.88	0.81 - 0.95
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.88	0.86 - 0.90	0.44	0.43 - 0.45
Darifenacin	0.69	0.57 - 0.83	0.28	0.23 - 0.34
Fesoterodine	0.70	0.61 - 0.80	0.30	0.26 - 0.34
Oxybutynin	0.92	0.70 - 1.21	12.25	9.35 - 16.05
Solifenacin	0.91	0.88 - 0.94	0.37	0.36 - 0.38
Trospium	0.89	0.81 - 0.98	0.33	0.30 - 0.36
FEMALES				
Any OAB drug (not tolterodine)	0.81	0.78 - 0.84	0.92	0.89 - 0.95
Darifenacin	0.78	0.65 - 0.93	0.81	0.67 - 0.97
Fesoterodine	0.68	0.58 - 0.80	0.84	0.71 - 0.99
Oxybutynin	0.69	0.50 - 0.95	0.85	0.62 - 1.17
Solifenacin	0.86	0.82 - 0.90	0.97	0.93 - 1.01
Trospium	0.73	0.65 - 0.82	0.81	0.72 - 0.91
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.87	0.84 - 0.90	0.99	0.95 - 1.03
Darifenacin	0.82	0.68 - 0.99	0.89	0.74 - 1.08
Fesoterodine	0.79	0.66 - 0.94	0.98	0.82 - 1.16
Oxybutynin	0.68	0.47 - 0.98	0.72	0.50 - 1.04
Solifenacin	0.91	0.87 - 0.96	1.04	0.99 - 1.09
Trospium	0.75	0.66 - 0.85	0.84	0.74 - 0.96

Table CV5c. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.82	0.79 - 0.86	0.81	0.78 - 0.84
Darifenacin	0.62	0.48 - 0.81	0.43	0.33 - 0.56
Fesoterodine	0.74	0.61 - 0.90	0.74	0.61 - 0.90
Oxybutynin	0.79	0.54 - 1.16	0.76	0.52 - 1.12
Solifenacin	0.88	0.83 - 0.93	0.90	0.85 - 0.95
Trospium	0.73	0.62 - 0.85	0.72	0.62 - 0.84
MALES				
Any OAB drug (not tolterodine)	0.91	0.88 - 0.94	0.81	0.78 - 0.84
Darifenacin	0.80	0.65 - 0.99	0.60	0.49 - 0.74
Fesoterodine	0.67	0.57 - 0.79	0.53	0.45 - 0.62
Oxybutynin	1.23	0.89 - 1.71	2.57	1.85 - 3.57
Solifenacin	0.91	0.87 - 0.95	0.77	0.74 - 0.81
Trospium	1.04	0.94 - 1.14	0.94	0.85 - 1.03
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.90	0.87 - 0.93	0.77	0.74 - 0.80
Darifenacin	0.76	0.60 - 0.95	0.60	0.48 - 0.75
Fesoterodine	0.69	0.58 - 0.82	0.62	0.52 - 0.74
Oxybutynin	1.15	0.80 - 1.65	1.17	0.82 - 1.68
Solifenacin	0.90	0.86 - 0.94	0.75	0.71 - 0.79
Trospium	1.04	0.94 - 1.15	0.90	0.81 - 1.00
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.95	0.91 - 0.99	0.35	0.34 - 0.36
Darifenacin	0.87	0.68 - 1.12	0.24	0.19 - 0.31
Fesoterodine	0.68	0.56 - 0.82	0.19	0.16 - 0.23
Oxybutynin	1.33	0.92 - 1.93	15.08	10.38 - 21.92
Solifenacin	0.96	0.91 - 1.01	0.24	0.23 - 0.25
Trospium	1.05	0.93 - 1.18	0.24	0.21 - 0.27

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5d. Crude and Standardized Incidence Rate Ratios for Cardiovascular Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.87	0.84 - 0.90	0.75	0.72 - 0.78
Darifenacin	0.72	0.57 - 0.92	0.63	0.49 - 0.80
Fesoterodine	0.67	0.55 - 0.81	0.62	0.51 - 0.75
Oxybutynin	0.88	0.61 - 1.28	1.11	0.76 - 1.61
Solifenacin	0.90	0.85 - 0.95	0.78	0.74 - 0.82
Trospium	0.88	0.77 - 1.00	0.73	0.64 - 0.83
AGE OVER 65				
Any OAB drug (not tolterodine)	0.90	0.86 - 0.94	0.72	0.69 - 0.75
Darifenacin	0.72	0.56 - 0.93	0.54	0.42 - 0.70
Fesoterodine	0.74	0.60 - 0.91	0.57	0.46 - 0.70
Oxybutynin	0.87	0.57 - 1.32	0.98	0.65 - 1.48
Solifenacin	0.93	0.88 - 0.98	0.75	0.71 - 0.79
Trospium	0.89	0.77 - 1.02	0.72	0.63 - 0.83
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.90	0.86 - 0.94	0.87	0.83 - 0.91
Darifenacin	0.71	0.53 - 0.94	0.63	0.47 - 0.84
Fesoterodine	0.70	0.56 - 0.87	0.71	0.57 - 0.88
Oxybutynin	1.12	0.76 - 1.65	1.56	1.06 - 2.30
Solifenacin	0.93	0.88 - 0.99	0.91	0.86 - 0.96
Trospium	0.90	0.78 - 1.04	0.75	0.65 - 0.87
FEMALES				
Any OAB drug (not tolterodine)	0.87	0.82 - 0.92	1.07	1.01 - 1.13
Darifenacin	0.85	0.62 - 1.15	1.14	0.84 - 1.54
Fesoterodine	0.72	0.54 - 0.95	0.92	0.70 - 1.21
Oxybutynin	0.74	0.43 - 1.27	0.83	0.48 - 1.43
Solifenacin	0.92	0.85 - 0.99	1.15	1.06 - 1.24
Trospium	0.67	0.54 - 0.83	0.79	0.63 - 0.98
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.90	0.85 - 0.96	1.01	0.95 - 1.07
Darifenacin	0.84	0.61 - 1.16	0.86	0.62 - 1.19
Fesoterodine	0.84	0.63 - 1.12	0.94	0.70 - 1.25
Oxybutynin	0.77	0.43 - 1.39	0.67	0.37 - 1.21
Solifenacin	0.96	0.88 - 1.04	1.11	1.02 - 1.20
Trospium	0.65	0.51 - 0.83	0.69	0.54 - 0.88

Table CV5d. Crude and Standardized Incidence Rate Ratios for Cardiovascular Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.91	0.85 - 0.97	1.05	0.98 - 1.12
Darifenacin	0.74	0.50 - 1.09	0.57	0.38 - 0.84
Fesoterodine	0.79	0.58 - 1.07	0.83	0.61 - 1.12
Oxybutynin	0.90	0.50 - 1.62	0.77	0.43 - 1.39
Solifenacin	0.99	0.91 - 1.08	1.20	1.10 - 1.31
Trospium	0.67	0.51 - 0.87	0.67	0.51 - 0.87
MALES				
Any OAB drug (not tolterodine)	0.92	0.87 - 0.97	0.63	0.60 - 0.66
Darifenacin	0.68	0.46 - 1.00	0.43	0.29 - 0.63
Fesoterodine	0.66	0.50 - 0.87	0.50	0.38 - 0.66
Oxybutynin	1.42	0.86 - 2.35	1.22	0.74 - 2.02
Solifenacin	0.92	0.85 - 0.99	0.64	0.59 - 0.69
Trospium	1.08	0.92 - 1.26	0.71	0.61 - 0.83
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.91	0.86 - 0.96	0.60	0.57 - 0.63
Darifenacin	0.68	0.46 - 1.01	0.40	0.27 - 0.60
Fesoterodine	0.64	0.48 - 0.86	0.42	0.31 - 0.56
Oxybutynin	1.25	0.71 - 2.21	1.11	0.63 - 1.96
Solifenacin	0.92	0.85 - 0.99	0.60	0.55 - 0.65
Trospium	1.10	0.93 - 1.29	0.73	0.62 - 0.86
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.93	0.88 - 0.99	0.74	0.70 - 0.78
Darifenacin	0.78	0.52 - 1.17	0.67	0.44 - 1.01
Fesoterodine	0.65	0.48 - 0.88	0.63	0.46 - 0.85
Oxybutynin	1.71	1.03 - 2.83	2.09	1.26 - 3.45
Solifenacin	0.92	0.85 - 1.00	0.72	0.66 - 0.78
Trospium	1.10	0.92 - 1.31	0.79	0.66 - 0.94

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5e. Crude and Standardized Incidence Rate Ratios for MACE, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.88	0.85 - 0.91	0.82	0.79 - 0.85
Darifenacin	0.76	0.62 - 0.92	0.71	0.58 - 0.86
Fesoterodine	0.73	0.62 - 0.85	0.65	0.56 - 0.76
Oxybutynin	0.75	0.53 - 1.05	0.92	0.66 - 1.29
Solifenacin	0.90	0.86 - 0.94	0.87	0.83 - 0.91
Trospium	0.92	0.83 - 1.02	0.81	0.73 - 0.90
AGE OVER 65				
Any OAB drug (not tolterodine)	0.89	0.86 - 0.92	0.73	0.70 - 0.76
Darifenacin	0.74	0.60 - 0.92	0.62	0.50 - 0.77
Fesoterodine	0.78	0.66 - 0.93	0.63	0.53 - 0.75
Oxybutynin	0.82	0.57 - 1.18	1.05	0.73 - 1.52
Solifenacin	0.92	0.88 - 0.97	0.75	0.71 - 0.79
Trospium	0.93	0.83 - 1.04	0.78	0.69 - 0.87
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.90	0.87 - 0.93	0.91	0.88 - 0.94
Darifenacin	0.73	0.57 - 0.93	0.65	0.51 - 0.83
Fesoterodine	0.80	0.67 - 0.95	0.75	0.63 - 0.89
Oxybutynin	0.91	0.63 - 1.31	1.06	0.73 - 1.53
Solifenacin	0.92	0.87 - 0.97	1.00	0.95 - 1.05
Trospium	0.95	0.84 - 1.07	0.78	0.69 - 0.88
FEMALES				
Any OAB drug (not tolterodine)	0.89	0.85 - 0.93	1.06	1.01 - 1.11
Darifenacin	0.90	0.70 - 1.15	1.08	0.84 - 1.38
Fesoterodine	0.79	0.64 - 0.98	0.98	0.79 - 1.21
Oxybutynin	0.63	0.39 - 1.03	0.64	0.39 - 1.04
Solifenacin	0.91	0.85 - 0.97	1.09	1.02 - 1.16
Trospium	0.82	0.70 - 0.96	0.93	0.79 - 1.09
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.91	0.86 - 0.96	0.99	0.94 - 1.04
Darifenacin	0.86	0.66 - 1.12	1.01	0.77 - 1.32
Fesoterodine	0.90	0.71 - 1.14	0.90	0.71 - 1.14
Oxybutynin	0.70	0.41 - 1.18	0.58	0.34 - 0.98
Solifenacin	0.93	0.87 - 1.00	1.03	0.96 - 1.10
Trospium	0.79	0.66 - 0.95	0.86	0.71 - 1.03

Table CV5e. Crude and Standardized Incidence Rate Ratios for MACE, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.93	0.88 - 0.98	1.06	1.00 - 1.12
Darifenacin	0.79	0.57 - 1.09	0.59	0.43 - 0.81
Fesoterodine	0.96	0.76 - 1.21	1.07	0.85 - 1.34
Oxybutynin	0.69	0.39 - 1.22	0.52	0.30 - 0.92
Solifenacin	0.95	0.88 - 1.02	1.15	1.07 - 1.24
Trospium	0.83	0.68 - 1.01	0.83	0.68 - 1.01
MALES				
Any OAB drug (not tolterodine)	0.91	0.87 - 0.95	0.72	0.69 - 0.75
Darifenacin	0.70	0.51 - 0.96	0.55	0.40 - 0.76
Fesoterodine	0.69	0.55 - 0.86	0.51	0.41 - 0.64
Oxybutynin	1.23	0.78 - 1.95	1.03	0.65 - 1.63
Solifenacin	0.93	0.87 - 0.99	0.77	0.72 - 0.82
Trospium	1.04	0.91 - 1.19	0.76	0.66 - 0.87
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.89	0.85 - 0.93	0.62	0.59 - 0.65
Darifenacin	0.67	0.47 - 0.95	0.44	0.31 - 0.62
Fesoterodine	0.68	0.53 - 0.87	0.50	0.39 - 0.64
Oxybutynin	1.20	0.72 - 1.99	1.26	0.76 - 2.09
Solifenacin	0.90	0.84 - 0.96	0.62	0.58 - 0.66
Trospium	1.06	0.91 - 1.23	0.75	0.65 - 0.87
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.91	0.86 - 0.96	0.82	0.78 - 0.86
Darifenacin	0.77	0.54 - 1.10	0.69	0.48 - 0.98
Fesoterodine	0.69	0.54 - 0.89	0.55	0.43 - 0.71
Oxybutynin	1.46	0.91 - 2.34	1.41	0.88 - 2.26
Solifenacin	0.92	0.86 - 0.99	0.90	0.84 - 0.96
Trospium	1.07	0.92 - 1.24	0.76	0.65 - 0.88

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5f. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.88	0.84 - 0.93	0.65	0.62 - 0.68
Darifenacin	0.60	0.42 - 0.85	0.57	0.40 - 0.81
Fesoterodine	0.77	0.61 - 0.98	0.56	0.44 - 0.71
Oxybutynin	0.76	0.45 - 1.28	0.72	0.43 - 1.22
Solifenacin	0.92	0.86 - 0.99	0.69	0.64 - 0.74
Trospium	0.89	0.75 - 1.05	0.61	0.51 - 0.72
AGE OVER 65				
Any OAB drug (not tolterodine)	0.90	0.85 - 0.95	0.57	0.54 - 0.60
Darifenacin	0.55	0.37 - 0.81	0.38	0.26 - 0.56
Fesoterodine	0.87	0.68 - 1.11	0.52	0.40 - 0.67
Oxybutynin	0.79	0.45 - 1.40	0.62	0.35 - 1.10
Solifenacin	0.94	0.87 - 1.01	0.62	0.58 - 0.67
Trospium	0.90	0.75 - 1.08	0.54	0.45 - 0.65
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.96	0.91 - 1.01	0.87	0.82 - 0.92
Darifenacin	0.62	0.41 - 0.93	0.72	0.48 - 1.08
Fesoterodine	0.89	0.69 - 1.14	0.77	0.60 - 0.99
Oxybutynin	0.92	0.52 - 1.62	1.00	0.57 - 1.76
Solifenacin	1.01	0.94 - 1.09	0.93	0.86 - 1.00
Trospium	0.92	0.76 - 1.11	0.67	0.55 - 0.81
FEMALES				
Any OAB drug (not tolterodine)	0.93	0.86 - 1.00	1.17	1.09 - 1.26
Darifenacin	0.74	0.47 - 1.15	1.22	0.78 - 1.90
Fesoterodine	1.01	0.74 - 1.37	1.31	0.96 - 1.77
Oxybutynin	0.57	0.25 - 1.30	0.65	0.29 - 1.49
Solifenacin	1.01	0.91 - 1.11	1.26	1.14 - 1.39
Trospium	0.66	0.49 - 0.89	0.78	0.57 - 1.05
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.94	0.87 - 1.02	0.93	0.86 - 1.00
Darifenacin	0.67	0.41 - 1.09	0.54	0.33 - 0.88
Fesoterodine	1.21	0.88 - 1.65	1.25	0.91 - 1.71
Oxybutynin	0.56	0.23 - 1.40	0.47	0.19 - 1.18
Solifenacin	1.03	0.92 - 1.14	1.03	0.92 - 1.14
Trospium	0.63	0.45 - 0.88	0.57	0.41 - 0.79

Table CV5f. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	1.11	1.02 - 1.20	1.75	1.61 - 1.89
Darifenacin	0.76	0.44 - 1.31	0.85	0.49 - 1.46
Fesoterodine	1.34	0.97 - 1.83	1.91	1.38 - 2.61
Oxybutynin	0.55	0.20 - 1.56	0.50	0.18 - 1.42
Solifenacin	1.23	1.10 - 1.36	2.04	1.83 - 2.25
Trospium	0.65	0.44 - 0.95	0.82	0.56 - 1.20
MALES				
Any OAB drug (not tolterodine)	0.89	0.83 - 0.95	0.50	0.46 - 0.54
Darifenacin	0.57	0.33 - 0.98	0.38	0.22 - 0.65
Fesoterodine	0.61	0.42 - 0.88	0.34	0.23 - 0.49
Oxybutynin	1.35	0.70 - 2.61	0.74	0.38 - 1.43
Solifenacin	0.89	0.80 - 0.98	0.52	0.47 - 0.57
Trospium	1.10	0.90 - 1.34	0.56	0.46 - 0.68
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.89	0.82 - 0.96	0.45	0.42 - 0.48
Darifenacin	0.52	0.29 - 0.94	0.32	0.18 - 0.58
Fesoterodine	0.61	0.41 - 0.90	0.27	0.18 - 0.40
Oxybutynin	1.33	0.66 - 2.69	0.67	0.33 - 1.36
Solifenacin	0.88	0.79 - 0.97	0.48	0.43 - 0.53
Trospium	1.12	0.90 - 1.38	0.53	0.43 - 0.65
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.91	0.84 - 0.98	0.55	0.51 - 0.59
Darifenacin	0.62	0.34 - 1.12	0.67	0.37 - 1.21
Fesoterodine	0.64	0.43 - 0.94	0.37	0.25 - 0.54
Oxybutynin	1.63	0.85 - 3.15	1.18	0.61 - 2.28
Solifenacin	0.90	0.81 - 1.00	0.54	0.48 - 0.60
Trospium	1.11	0.89 - 1.38	0.62	0.49 - 0.77

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5g. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Death, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.86	0.81 - 0.91	0.95	0.89 - 1.01
Darifenacin	0.87	0.62 - 1.21	0.75	0.54 - 1.04
Fesoterodine	0.54	0.38 - 0.75	0.72	0.51 - 1.01
Oxybutynin	1.03	0.61 - 1.73	1.85	1.10 - 3.11
Solifenacin	0.88	0.81 - 0.96	0.96	0.88 - 1.04
Trospium	0.87	0.71 - 1.06	0.96	0.79 - 1.17
AGE OVER 65				
Any OAB drug (not tolterodine)	0.89	0.83 - 0.95	1.01	0.95 - 1.08
Darifenacin	0.95	0.68 - 1.33	0.86	0.61 - 1.20
Fesoterodine	0.56	0.39 - 0.81	0.68	0.47 - 0.98
Oxybutynin	0.98	0.54 - 1.77	1.71	0.95 - 3.10
Solifenacin	0.92	0.84 - 1.00	1.01	0.92 - 1.10
Trospium	0.88	0.71 - 1.09	1.08	0.87 - 1.33
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.83	0.77 - 0.89	0.86	0.80 - 0.92
Darifenacin	0.81	0.54 - 1.20	0.52	0.35 - 0.77
Fesoterodine	0.46	0.31 - 0.69	0.63	0.42 - 0.94
Oxybutynin	1.36	0.81 - 2.28	2.26	1.35 - 3.79
Solifenacin	0.84	0.76 - 0.92	0.89	0.81 - 0.98
Trospium	0.88	0.70 - 1.10	0.84	0.67 - 1.05
FEMALES				
Any OAB drug (not tolterodine)	0.80	0.73 - 0.87	0.97	0.88 - 1.06
Darifenacin	0.98	0.64 - 1.48	1.05	0.69 - 1.58
Fesoterodine	0.36	0.20 - 0.64	0.47	0.26 - 0.84
Oxybutynin	0.95	0.47 - 1.91	1.03	0.51 - 2.07
Solifenacin	0.83	0.73 - 0.94	1.03	0.91 - 1.16
Trospium	0.69	0.50 - 0.95	0.80	0.58 - 1.10
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.85	0.77 - 0.93	1.13	1.02 - 1.24
Darifenacin	1.05	0.68 - 1.60	1.30	0.85 - 1.98
Fesoterodine	0.38	0.20 - 0.73	0.51	0.27 - 0.98
Oxybutynin	1.02	0.48 - 2.16	0.94	0.45 - 1.99
Solifenacin	0.88	0.77 - 1.00	1.23	1.08 - 1.40
Trospium	0.68	0.48 - 0.96	0.85	0.59 - 1.20

Table CV5g. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Death, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Current Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.72	0.64 - 0.80	0.66	0.59 - 0.73
Darifenacin	0.73	0.42 - 1.26	0.41	0.24 - 0.71
Fesoterodine	0.27	0.13 - 0.57	0.21	0.10 - 0.44
Oxybutynin	1.23	0.62 - 2.45	0.92	0.46 - 1.83
Solifenacin	0.75	0.64 - 0.87	0.73	0.63 - 0.84
Trospium	0.69	0.48 - 0.99	0.59	0.41 - 0.85
MALES				
Any OAB drug (not tolterodine)	0.96	0.88 - 1.04	0.93	0.85 - 1.01
Darifenacin	0.86	0.50 - 1.46	0.55	0.32 - 0.93
Fesoterodine	0.74	0.49 - 1.10	0.87	0.58 - 1.30
Oxybutynin	1.53	0.73 - 3.25	2.37	1.12 - 5.04
Solifenacin	0.98	0.87 - 1.09	0.91	0.81 - 1.02
Trospium	1.06	0.82 - 1.35	1.07	0.83 - 1.37
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.95	0.87 - 1.03	0.94	0.86 - 1.02
Darifenacin	0.93	0.55 - 1.57	0.61	0.36 - 1.03
Fesoterodine	0.70	0.45 - 1.08	0.78	0.50 - 1.21
Oxybutynin	1.13	0.46 - 2.83	2.15	0.88 - 5.38
Solifenacin	0.97	0.86 - 1.09	0.89	0.79 - 1.00
Trospium	1.08	0.83 - 1.40	1.22	0.93 - 1.58
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.95	0.86 - 1.04	1.14	1.04 - 1.25
Darifenacin	1.02	0.59 - 1.77	0.67	0.38 - 1.16
Fesoterodine	0.66	0.41 - 1.05	1.19	0.74 - 1.89
Oxybutynin	1.83	0.87 - 3.87	4.05	1.92 - 8.57
Solifenacin	0.94	0.83 - 1.06	1.11	0.98 - 1.25
Trospium	1.09	0.82 - 1.43	1.17	0.88 - 1.53

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5h. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.80	0.70 - 0.91	0.74	0.65 - 0.84
Darifenacin	0.82	0.39 - 1.69	0.84	0.40 - 1.73
Fesoterodine	1.09	0.69 - 1.68	0.93	0.59 - 1.43
Oxybutynin	0.96	0.35 - 2.68	0.58	0.21 - 1.62
Solifenacin	0.76	0.62 - 0.92	0.69	0.56 - 0.83
Trospium	0.87	0.59 - 1.27	0.90	0.61 - 1.31
AGE OVER 65				
Any OAB drug (not tolterodine)	0.87	0.75 - 0.99	0.89	0.77 - 1.01
Darifenacin	0.83	0.38 - 1.82	1.27	0.57 - 2.78
Fesoterodine	1.37	0.86 - 2.12	1.60	1.01 - 2.48
Oxybutynin	1.28	0.47 - 3.54	1.17	0.43 - 3.23
Solifenacin	0.83	0.67 - 1.01	0.73	0.59 - 0.89
Trospium	0.76	0.47 - 1.20	0.79	0.49 - 1.25
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.81	0.69 - 0.94	0.87	0.74 - 1.01
Darifenacin	0.84	0.35 - 2.00	0.92	0.38 - 2.19
Fesoterodine	0.92	0.51 - 1.60	0.71	0.40 - 1.24
Oxybutynin	1.50	0.56 - 4.10	1.03	0.38 - 2.81
Solifenacin	0.80	0.63 - 0.99	0.96	0.75 - 1.19
Trospium	0.80	0.47 - 1.31	0.79	0.47 - 1.29
FEMALES				
Any OAB drug (not tolterodine)	0.75	0.60 - 0.91	0.86	0.69 - 1.04
Darifenacin	0.57	0.18 - 1.87	0.44	0.14 - 1.44
Fesoterodine	0.86	0.40 - 1.79	0.90	0.42 - 1.87
Oxybutynin	1.77	0.67 - 4.66	1.87	0.70 - 4.93
Solifenacin	0.66	0.46 - 0.90	0.75	0.53 - 1.02
Trospium	0.85	0.47 - 1.48	1.25	0.69 - 2.18
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.77	0.61 - 0.95	0.72	0.57 - 0.88
Darifenacin	0.64	0.20 - 2.07	0.47	0.15 - 1.52
Fesoterodine	0.90	0.38 - 2.04	0.73	0.31 - 1.65
Oxybutynin	2.27	0.86 - 5.91	3.03	1.15 - 7.88
Solifenacin	0.71	0.49 - 0.98	0.58	0.40 - 0.80
Trospium	0.76	0.38 - 1.45	0.88	0.44 - 1.68

Table CV5h. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.75	0.58 - 0.94	0.97	0.74 - 1.21
Darifenacin	0.41	0.10 - 2.01	0.28	0.07 - 1.38
Fesoterodine	0.71	0.27 - 1.79	0.56	0.21 - 1.41
Oxybutynin	2.52	0.96 - 6.37	2.48	0.95 - 6.26
Solifenacin	0.75	0.51 - 1.04	1.22	0.83 - 1.70
Trospium	0.64	0.28 - 1.41	0.45	0.19 - 0.99
MALES				
Any OAB drug (not tolterodine)	0.88	0.74 - 1.03	0.68	0.57 - 0.79
Darifenacin	1.24	0.52 - 2.93	1.02	0.43 - 2.41
Fesoterodine	1.27	0.74 - 2.12	0.95	0.55 - 1.59
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	0.85	0.66 - 1.07	0.66	0.51 - 0.83
Trospium	0.91	0.54 - 1.48	0.74	0.44 - 1.20
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.96	0.80 - 1.13	1.00	0.83 - 1.17
Darifenacin	1.16	0.44 - 3.08	1.78	0.67 - 4.72
Fesoterodine	1.68	0.99 - 2.74	2.15	1.26 - 3.51
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	0.92	0.70 - 1.17	0.82	0.63 - 1.04
Trospium	0.78	0.41 - 1.44	0.73	0.38 - 1.34
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.89	0.72 - 1.07	0.80	0.64 - 0.96
Darifenacin	1.46	0.55 - 3.82	1.37	0.52 - 3.58
Fesoterodine	1.10	0.55 - 2.11	0.82	0.41 - 1.57
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	0.85	0.62 - 1.12	0.77	0.56 - 1.01
Trospium	0.96	0.51 - 1.74	1.03	0.54 - 1.87

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5i. Crude and Standardized Incidence Rate Ratios for Stroke, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	1.50	1.26 - 1.73	0.11	0.09 - 0.13
Darifenacin	1.17	0.38 - 3.59	0.08	0.03 - 0.25
Fesoterodine	2.18	1.18 - 3.73	0.14	0.08 - 0.24
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	1.33	1.00 - 1.69	0.08	0.06 - 0.10
Trospium	1.77	1.05 - 2.78	0.17	0.10 - 0.27
AGE OVER 65				
Any OAB drug (not tolterodine)	2.14	1.76 - 2.46	2.53	2.09 - 2.91
Darifenacin	1.16	0.30 - 4.89	1.18	0.30 - 4.97
Fesoterodine	3.42	1.73 - 5.94	2.41	1.22 - 4.18
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	1.94	1.42 - 2.45	2.69	1.96 - 3.40
Trospium	2.45	1.33 - 3.97	2.60	1.42 - 4.22
HIGH CV RISK				
Any OAB drug (not tolterodine)	1.28	1.01 - 1.54	0.94	0.74 - 1.13
Darifenacin	1.69	0.56 - 4.91	2.01	0.66 - 5.84
Fesoterodine	2.05	1.00 - 3.79	2.75	1.35 - 5.08
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	1.13	0.77 - 1.54	0.58	0.40 - 0.79
Trospium	1.16	0.52 - 2.36	0.36	0.16 - 0.73
FEMALES				
Any OAB drug (not tolterodine)	1.36	1.06 - 1.64	1.19	0.93 - 1.43
Darifenacin	0.89	0.23 - 3.86	1.04	0.26 - 4.52
Fesoterodine	2.15	0.98 - 4.20	1.97	0.90 - 3.85
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	0.98	0.61 - 1.43	0.66	0.41 - 0.96
Trospium	2.33	1.33 - 3.67	2.34	1.33 - 3.68
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	1.65	1.20 - 2.04	1.12	0.81 - 1.38
Darifenacin	0.00	. - .	0.00	. - .
Fesoterodine	2.48	0.88 - 5.78	1.35	0.48 - 3.15
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	1.15	0.62 - 1.79	0.99	0.53 - 1.54
Trospium	3.46	1.86 - 5.37	1.84	0.99 - 2.86

Table CV5i. Crude and Standardized Incidence Rate Ratios for Stroke, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	1.18	0.86 - 1.49	0.84	0.61 - 1.06
Darifenacin	1.16	0.30 - 4.70	2.12	0.54 - 8.59
Fesoterodine	2.67	1.25 - 4.92	3.30	1.54 - 6.09
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	0.71	0.37 - 1.20	0.26	0.13 - 0.44
Trospium	1.82	0.85 - 3.36	0.46	0.22 - 0.85
MALES				
Any OAB drug (not tolterodine)	1.71	1.32 - 2.06	0.05	0.04 - 0.06
Darifenacin	1.81	0.46 - 7.33	0.03	0.01 - 0.12
Fesoterodine	2.23	0.92 - 4.69	0.04	0.02 - 0.08
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	1.81	1.26 - 2.35	0.05	0.03 - 0.06
Trospium	0.96	0.33 - 2.50	0.06	0.02 - 0.16
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	2.82	2.21 - 3.26	5.83	4.57 - 6.75
Darifenacin	3.50	0.95 - 11.28	3.94	1.07 - 12.70
Fesoterodine	4.54	2.02 - 8.01	4.89	2.18 - 8.62
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	2.96	2.10 - 3.65	6.68	4.74 - 8.25
Trospium	1.00	0.27 - 3.22	4.37	1.18 - 14.09
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	1.43	0.99 - 1.83	1.34	0.92 - 1.72
Darifenacin	2.82	0.74 - 10.10	1.61	0.42 - 5.77
Fesoterodine	1.06	0.28 - 3.80	0.56	0.15 - 2.01
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	1.79	1.15 - 2.42	1.84	1.18 - 2.49
Trospium	0.00	. - .	0.00	. - .

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5j. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.94	0.89 - 0.99	0.87	0.83 - 0.91
Darifenacin	1.01	0.75 - 1.35	0.82	0.61 - 1.09
Fesoterodine	0.86	0.69 - 1.07	0.78	0.62 - 0.97
Oxybutynin	0.71	0.41 - 1.22	0.87	0.51 - 1.50
Solifenacin	0.95	0.88 - 1.02	0.92	0.85 - 0.99
Trospium	0.97	0.83 - 1.13	0.85	0.72 - 0.99
AGE OVER 65				
Any OAB drug (not tolterodine)	0.98	0.93 - 1.03	0.95	0.90 - 1.00
Darifenacin	1.03	0.76 - 1.39	1.17	0.86 - 1.58
Fesoterodine	0.98	0.77 - 1.23	1.01	0.80 - 1.27
Oxybutynin	0.74	0.41 - 1.34	1.34	0.74 - 2.43
Solifenacin	0.97	0.90 - 1.05	0.91	0.84 - 0.98
Trospium	1.02	0.86 - 1.20	0.98	0.83 - 1.16
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.89	0.83 - 0.95	0.89	0.83 - 0.95
Darifenacin	1.08	0.76 - 1.52	0.90	0.64 - 1.27
Fesoterodine	0.75	0.56 - 0.99	0.65	0.49 - 0.86
Oxybutynin	0.73	0.38 - 1.41	1.09	0.57 - 2.11
Solifenacin	0.90	0.82 - 0.98	0.98	0.89 - 1.07
Trospium	0.93	0.76 - 1.14	0.71	0.58 - 0.87
FEMALES				
Any OAB drug (not tolterodine)	0.92	0.86 - 0.99	0.92	0.86 - 0.99
Darifenacin	1.10	0.76 - 1.58	1.01	0.70 - 1.45
Fesoterodine	0.80	0.57 - 1.11	0.92	0.66 - 1.28
Oxybutynin	0.57	0.27 - 1.21	0.53	0.25 - 1.13
Solifenacin	0.96	0.86 - 1.06	0.92	0.83 - 1.02
Trospium	0.88	0.69 - 1.11	0.97	0.76 - 1.22
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.94	0.87 - 1.01	0.91	0.84 - 0.98
Darifenacin	1.07	0.72 - 1.58	1.04	0.70 - 1.53
Fesoterodine	0.93	0.65 - 1.31	0.93	0.65 - 1.31
Oxybutynin	0.60	0.27 - 1.37	0.49	0.22 - 1.12
Solifenacin	0.98	0.87 - 1.09	0.93	0.83 - 1.04
Trospium	0.84	0.64 - 1.09	0.88	0.67 - 1.14

Table CV5j. Crude and Standardized Incidence Rate Ratios for All-Cause Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.89	0.81 - 0.97	1.02	0.93 - 1.11
Darifenacin	1.30	0.85 - 1.96	1.60	1.05 - 2.41
Fesoterodine	0.67	0.43 - 1.04	0.94	0.60 - 1.46
Oxybutynin	0.45	0.17 - 1.28	0.52	0.19 - 1.48
Solifenacin	0.94	0.82 - 1.07	1.03	0.90 - 1.17
Trospium	0.82	0.59 - 1.12	0.89	0.65 - 1.21
MALES				
Any OAB drug (not tolterodine)	0.99	0.92 - 1.06	0.84	0.78 - 0.90
Darifenacin	1.03	0.65 - 1.63	0.70	0.44 - 1.11
Fesoterodine	0.92	0.68 - 1.24	0.69	0.51 - 0.93
Oxybutynin	1.28	0.61 - 2.73	1.09	0.52 - 2.32
Solifenacin	0.96	0.86 - 1.06	0.92	0.83 - 1.02
Trospium	1.08	0.87 - 1.33	0.77	0.62 - 0.95
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	1.02	0.95 - 1.09	0.98	0.91 - 1.05
Darifenacin	1.09	0.68 - 1.74	1.29	0.80 - 2.06
Fesoterodine	1.00	0.73 - 1.36	1.08	0.79 - 1.47
Oxybutynin	1.16	0.52 - 2.65	2.07	0.92 - 4.72
Solifenacin	0.94	0.84 - 1.05	0.88	0.79 - 0.98
Trospium	1.22	0.98 - 1.50	1.07	0.86 - 1.32
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.92	0.84 - 1.00	0.82	0.75 - 0.89
Darifenacin	0.92	0.51 - 1.64	0.52	0.29 - 0.93
Fesoterodine	0.83	0.58 - 1.19	0.49	0.34 - 0.70
Oxybutynin	1.55	0.69 - 3.52	1.40	0.62 - 3.18
Solifenacin	0.87	0.76 - 0.98	0.95	0.83 - 1.07
Trospium	1.05	0.80 - 1.36	0.61	0.47 - 0.79

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5k. Crude and Standardized Incidence Rate Ratios for Cardiovascular Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.86	0.78 - 0.95	1.20	1.08 - 1.32
Darifenacin	1.34	0.84 - 2.11	1.57	0.99 - 2.47
Fesoterodine	0.85	0.56 - 1.28	1.05	0.69 - 1.58
Oxybutynin	0.83	0.34 - 2.06	1.04	0.43 - 2.58
Solifenacin	0.81	0.69 - 0.94	1.35	1.15 - 1.57
Trospium	0.87	0.63 - 1.18	0.91	0.66 - 1.24
AGE OVER 65				
Any OAB drug (not tolterodine)	0.81	0.72 - 0.90	0.92	0.82 - 1.02
Darifenacin	1.42	0.89 - 2.23	2.12	1.33 - 3.33
Fesoterodine	0.89	0.57 - 1.37	0.90	0.57 - 1.39
Oxybutynin	0.97	0.40 - 2.40	1.06	0.44 - 2.62
Solifenacin	0.72	0.60 - 0.85	0.86	0.72 - 1.02
Trospium	0.86	0.61 - 1.19	0.78	0.56 - 1.08
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.80	0.71 - 0.90	0.96	0.85 - 1.08
Darifenacin	1.52	0.93 - 2.46	1.52	0.93 - 2.46
Fesoterodine	0.51	0.28 - 0.92	0.57	0.31 - 1.03
Oxybutynin	0.84	0.31 - 2.36	1.12	0.41 - 3.15
Solifenacin	0.75	0.62 - 0.89	0.99	0.82 - 1.18
Trospium	0.89	0.62 - 1.26	0.94	0.65 - 1.34
FEMALES				
Any OAB drug (not tolterodine)	0.60	0.50 - 0.71	0.69	0.58 - 0.81
Darifenacin	1.11	0.59 - 2.04	1.25	0.67 - 2.30
Fesoterodine	0.67	0.36 - 1.23	0.79	0.42 - 1.46
Oxybutynin	0.58	0.18 - 1.99	0.63	0.20 - 2.17
Solifenacin	0.53	0.40 - 0.69	0.65	0.49 - 0.85
Trospium	0.63	0.38 - 1.02	0.63	0.38 - 1.02
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.56	0.46 - 0.67	0.61	0.50 - 0.73
Darifenacin	1.18	0.63 - 2.17	1.53	0.82 - 2.81
Fesoterodine	0.83	0.44 - 1.52	0.77	0.41 - 1.41
Oxybutynin	0.70	0.22 - 2.40	0.61	0.19 - 2.09
Solifenacin	0.44	0.31 - 0.61	0.55	0.39 - 0.76
Trospium	0.58	0.33 - 0.99	0.45	0.26 - 0.77

Table CV5k. Crude and Standardized Incidence Rate Ratios for Cardiovascular Mortality, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.64	0.52 - 0.77	0.79	0.64 - 0.95
Darifenacin	1.39	0.72 - 2.62	1.52	0.78 - 2.86
Fesoterodine	0.46	0.19 - 1.09	0.44	0.18 - 1.04
Oxybutynin	0.41	0.10 - 2.14	0.44	0.11 - 2.30
Solifenacin	0.61	0.45 - 0.81	0.85	0.62 - 1.12
Trospium	0.62	0.33 - 1.11	0.64	0.35 - 1.15
MALES				
Any OAB drug (not tolterodine)	1.22	1.08 - 1.36	1.81	1.60 - 2.02
Darifenacin	1.86	0.95 - 3.54	1.96	1.01 - 3.73
Fesoterodine	1.09	0.63 - 1.84	1.35	0.78 - 2.28
Oxybutynin	1.77	0.56 - 6.02	1.54	0.48 - 5.24
Solifenacin	1.17	0.97 - 1.38	2.18	1.81 - 2.57
Trospium	1.20	0.80 - 1.75	1.24	0.83 - 1.81
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	1.14	1.00 - 1.28	1.31	1.14 - 1.48
Darifenacin	1.94	1.00 - 3.67	2.91	1.50 - 5.51
Fesoterodine	0.95	0.51 - 1.72	1.07	0.58 - 1.93
Oxybutynin	1.76	0.55 - 5.96	1.66	0.52 - 5.62
Solifenacin	1.05	0.85 - 1.26	1.28	1.04 - 1.54
Trospium	1.27	0.84 - 1.87	1.20	0.79 - 1.77
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.97	0.83 - 1.12	1.14	0.97 - 1.31
Darifenacin	1.83	0.89 - 3.66	1.53	0.75 - 3.06
Fesoterodine	0.57	0.26 - 1.23	0.71	0.32 - 1.53
Oxybutynin	2.06	0.65 - 6.96	1.87	0.59 - 6.32
Solifenacin	0.90	0.71 - 1.11	1.14	0.90 - 1.41
Trospium	1.19	0.76 - 1.81	1.26	0.80 - 1.92

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5l. Crude and Standardized Incidence Rate Ratios for MACE, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.94	0.87 - 1.01	0.39	0.36 - 0.42
Darifenacin	1.04	0.67 - 1.61	0.38	0.24 - 0.59
Fesoterodine	1.20	0.90 - 1.58	0.44	0.33 - 0.58
Oxybutynin	1.00	0.50 - 2.01	0.31	0.15 - 0.62
Solifenacin	0.85	0.75 - 0.96	0.38	0.33 - 0.43
Trospium	1.09	0.87 - 1.36	0.44	0.35 - 0.55
AGE OVER 65				
Any OAB drug (not tolterodine)	0.97	0.89 - 1.05	1.07	0.98 - 1.16
Darifenacin	1.08	0.67 - 1.71	1.42	0.89 - 2.25
Fesoterodine	1.36	1.00 - 1.83	1.47	1.08 - 1.98
Oxybutynin	1.29	0.65 - 2.58	1.31	0.66 - 2.62
Solifenacin	0.85	0.74 - 0.97	0.96	0.84 - 1.09
Trospium	1.06	0.82 - 1.36	1.05	0.81 - 1.35
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.93	0.85 - 1.02	0.97	0.88 - 1.06
Darifenacin	1.24	0.76 - 1.99	1.34	0.83 - 2.15
Fesoterodine	0.86	0.58 - 1.26	1.14	0.77 - 1.68
Oxybutynin	1.25	0.60 - 2.63	1.08	0.51 - 2.27
Solifenacin	0.86	0.74 - 0.99	0.92	0.79 - 1.06
Trospium	1.07	0.80 - 1.41	0.90	0.68 - 1.18
FEMALES				
Any OAB drug (not tolterodine)	0.73	0.64 - 0.82	0.84	0.74 - 0.95
Darifenacin	0.82	0.43 - 1.54	0.88	0.46 - 1.65
Fesoterodine	0.93	0.59 - 1.44	1.13	0.71 - 1.76
Oxybutynin	1.07	0.48 - 2.39	1.05	0.47 - 2.34
Solifenacin	0.60	0.48 - 0.74	0.64	0.51 - 0.79
Trospium	0.89	0.62 - 1.25	1.21	0.85 - 1.70
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.72	0.62 - 0.83	0.75	0.65 - 0.86
Darifenacin	0.82	0.42 - 1.60	1.03	0.52 - 2.01
Fesoterodine	0.99	0.59 - 1.62	0.88	0.53 - 1.44
Oxybutynin	1.39	0.63 - 3.08	1.66	0.75 - 3.68
Solifenacin	0.59	0.46 - 0.74	0.64	0.50 - 0.81
Trospium	0.83	0.55 - 1.22	0.78	0.52 - 1.15

Table CV5l. Crude and Standardized Incidence Rate Ratios for MACE, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.73	0.62 - 0.84	0.82	0.70 - 0.95
Darifenacin	0.87	0.42 - 1.77	1.17	0.57 - 2.38
Fesoterodine	0.75	0.42 - 1.32	1.33	0.74 - 2.35
Oxybutynin	1.18	0.49 - 2.84	1.00	0.42 - 2.41
Solifenacin	0.65	0.51 - 0.82	0.72	0.56 - 0.91
Trospium	0.80	0.50 - 1.24	0.55	0.35 - 0.85
MALES				
Any OAB drug (not tolterodine)	1.21	1.10 - 1.32	0.30	0.27 - 0.33
Darifenacin	1.50	0.82 - 2.69	0.28	0.15 - 0.50
Fesoterodine	1.51	1.05 - 2.13	0.31	0.22 - 0.44
Oxybutynin	1.12	0.35 - 3.89	0.16	0.05 - 0.56
Solifenacin	1.13	0.97 - 1.30	0.32	0.28 - 0.37
Trospium	1.33	0.98 - 1.77	0.29	0.21 - 0.38
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	1.26	1.13 - 1.38	1.38	1.24 - 1.52
Darifenacin	1.57	0.84 - 2.90	1.80	0.96 - 3.32
Fesoterodine	1.72	1.18 - 2.45	2.04	1.40 - 2.91
Oxybutynin	1.26	0.39 - 4.34	0.97	0.30 - 3.34
Solifenacin	1.14	0.97 - 1.32	1.27	1.08 - 1.47
Trospium	1.36	0.97 - 1.87	1.30	0.93 - 1.78
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	1.16	1.03 - 1.29	1.17	1.04 - 1.30
Darifenacin	1.91	1.02 - 3.50	1.56	0.83 - 2.86
Fesoterodine	0.99	0.58 - 1.64	0.90	0.53 - 1.49
Oxybutynin	1.63	0.51 - 5.58	1.17	0.37 - 4.01
Solifenacin	1.08	0.90 - 1.27	1.18	0.98 - 1.39
Trospium	1.40	0.97 - 1.96	1.36	0.95 - 1.90

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

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5m. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Death, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	0.76	0.66 - 0.87	1.22	1.06 - 1.39
Darifenacin	1.36	0.77 - 2.35	1.71	0.97 - 2.96
Fesoterodine	1.23	0.81 - 1.84	1.55	1.02 - 2.32
Oxybutynin	0.64	0.20 - 2.22	0.85	0.27 - 2.94
Solifenacin	0.65	0.52 - 0.80	1.36	1.08 - 1.68
Trospium	0.69	0.44 - 1.06	0.74	0.47 - 1.14
AGE OVER 65				
Any OAB drug (not tolterodine)	0.70	0.60 - 0.81	0.78	0.66 - 0.90
Darifenacin	1.43	0.81 - 2.47	2.54	1.45 - 4.38
Fesoterodine	1.26	0.80 - 1.94	1.31	0.83 - 2.01
Oxybutynin	0.74	0.23 - 2.56	0.86	0.27 - 2.97
Solifenacin	0.54	0.41 - 0.70	0.58	0.44 - 0.75
Trospium	0.70	0.44 - 1.10	0.66	0.41 - 1.03
HIGH CV RISK				
Any OAB drug (not tolterodine)	0.66	0.55 - 0.77	0.80	0.67 - 0.94
Darifenacin	1.37	0.73 - 2.52	1.45	0.77 - 2.66
Fesoterodine	0.67	0.36 - 1.23	0.77	0.41 - 1.42
Oxybutynin	0.82	0.26 - 2.81	1.02	0.32 - 3.50
Solifenacin	0.59	0.45 - 0.76	0.77	0.59 - 0.99
Trospium	0.65	0.38 - 1.08	0.71	0.42 - 1.18
FEMALES				
Any OAB drug (not tolterodine)	0.48	0.36 - 0.61	0.59	0.45 - 0.76
Darifenacin	1.42	0.70 - 2.80	1.75	0.86 - 3.45
Fesoterodine	1.00	0.52 - 1.86	1.20	0.62 - 2.23
Oxybutynin	0.49	0.12 - 2.54	0.61	0.15 - 3.16
Solifenacin	0.38	0.24 - 0.58	0.50	0.32 - 0.76
Trospium	0.27	0.10 - 0.72	0.24	0.09 - 0.64
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.45	0.33 - 0.59	0.49	0.36 - 0.64
Darifenacin	1.47	0.72 - 2.89	2.08	1.02 - 4.08
Fesoterodine	1.20	0.62 - 2.22	1.08	0.56 - 2.00
Oxybutynin	0.58	0.14 - 3.00	0.55	0.13 - 2.84
Solifenacin	0.28	0.16 - 0.48	0.33	0.19 - 0.56
Trospium	0.29	0.11 - 0.77	0.22	0.08 - 0.59

Table CV5m. Crude and Standardized Incidence Rate Ratios for Coronary Heart Disease Death, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.51	0.37 - 0.67	0.69	0.50 - 0.91
Darifenacin	1.65	0.77 - 3.38	1.93	0.90 - 3.95
Fesoterodine	0.57	0.22 - 1.48	0.54	0.20 - 1.40
Oxybutynin	0.68	0.17 - 3.42	0.71	0.18 - 3.57
Solifenacin	0.44	0.27 - 0.68	0.75	0.46 - 1.16
Trospium	0.26	0.08 - 0.84	0.22	0.07 - 0.71
MALES				
Any OAB drug (not tolterodine)	1.08	0.92 - 1.24	1.82	1.55 - 2.09
Darifenacin	1.45	0.61 - 3.38	1.68	0.71 - 3.92
Fesoterodine	1.48	0.86 - 2.44	1.90	1.11 - 3.13
Oxybutynin	1.21	0.30 - 6.26	1.08	0.26 - 5.59
Solifenacin	0.94	0.73 - 1.18	2.20	1.70 - 2.76
Trospium	1.16	0.72 - 1.81	1.23	0.76 - 1.92
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.97	0.81 - 1.14	1.12	0.93 - 1.31
Darifenacin	1.50	0.63 - 3.48	3.10	1.31 - 7.19
Fesoterodine	1.29	0.70 - 2.27	1.59	0.87 - 2.80
Oxybutynin	1.20	0.29 - 6.18	1.23	0.30 - 6.34
Solifenacin	0.79	0.59 - 1.03	0.90	0.67 - 1.17
Trospium	1.18	0.71 - 1.88	1.20	0.72 - 1.91
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.80	0.65 - 0.96	0.90	0.73 - 1.08
Darifenacin	1.21	0.45 - 3.22	1.02	0.38 - 2.71
Fesoterodine	0.76	0.35 - 1.60	0.98	0.45 - 2.06
Oxybutynin	1.36	0.33 - 7.01	1.30	0.32 - 6.70
Solifenacin	0.70	0.51 - 0.93	0.80	0.58 - 1.07
Trospium	1.01	0.57 - 1.71	1.16	0.66 - 1.96

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV5n. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Death, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
OVERALL				
Any OAB drug (not tolterodine)	1.04	0.89 - 1.19	1.18	1.01 - 1.35
Darifenacin	1.28	0.59 - 2.73	1.32	0.60 - 2.81
Fesoterodine	0.14	0.03 - 0.73	0.14	0.03 - 0.73
Oxybutynin	1.20	0.38 - 4.01	1.39	0.44 - 4.65
Solifenacin	1.10	0.89 - 1.33	1.32	1.06 - 1.60
Trospium	1.20	0.77 - 1.80	1.21	0.78 - 1.82
AGE OVER 65				
Any OAB drug (not tolterodine)	1.03	0.87 - 1.19	1.17	0.99 - 1.35
Darifenacin	1.41	0.65 - 2.98	1.36	0.63 - 2.87
Fesoterodine	0.16	0.04 - 0.83	0.14	0.03 - 0.72
Oxybutynin	1.44	0.46 - 4.78	1.43	0.45 - 4.75
Solifenacin	1.06	0.83 - 1.31	1.37	1.08 - 1.69
Trospium	1.18	0.73 - 1.84	0.99	0.61 - 1.54
HIGH CV RISK				
Any OAB drug (not tolterodine)	1.09	0.92 - 1.26	1.27	1.07 - 1.47
Darifenacin	1.83	0.85 - 3.78	1.65	0.77 - 3.41
Fesoterodine	0.18	0.04 - 0.91	0.17	0.04 - 0.86
Oxybutynin	0.87	0.21 - 4.41	1.34	0.33 - 6.79
Solifenacin	1.10	0.85 - 1.37	1.41	1.09 - 1.76
Trospium	1.39	0.85 - 2.17	1.39	0.85 - 2.17
FEMALES				
Any OAB drug (not tolterodine)	0.77	0.61 - 0.94	0.84	0.66 - 1.03
Darifenacin	0.68	0.22 - 2.19	0.56	0.18 - 1.81
Fesoterodine	0.20	0.05 - 1.01	0.22	0.05 - 1.11
Oxybutynin	0.71	0.18 - 3.57	0.65	0.16 - 3.27
Solifenacin	0.75	0.53 - 1.02	0.86	0.60 - 1.17
Trospium	1.14	0.66 - 1.88	1.17	0.67 - 1.93
FEMALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	0.72	0.55 - 0.91	0.82	0.62 - 1.03
Darifenacin	0.75	0.24 - 2.39	0.61	0.20 - 1.95
Fesoterodine	0.26	0.06 - 1.29	0.24	0.06 - 1.19
Oxybutynin	0.88	0.22 - 4.38	0.70	0.17 - 3.48
Solifenacin	0.68	0.45 - 0.97	0.92	0.61 - 1.32
Trospium	1.02	0.54 - 1.81	0.84	0.45 - 1.49

Table CV5n. Crude and Standardized Incidence Rate Ratios for Cerebrovascular Death, With Tolterodine as Reference, by Sex, Age Group, and Level of Cardiovascular Risk: Recent Exposure

	Crude Incidence Rate Ratio	(95% CI)	Standardized Incidence Rate Ratio[a]	(95% CI)
FEMALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	0.83	0.63 - 1.04	0.95	0.73 - 1.19
Darifenacin	0.99	0.32 - 3.04	0.86	0.28 - 2.64
Fesoterodine	0.29	0.07 - 1.39	0.29	0.07 - 1.39
Oxybutynin	0.00	. - .	0.00	. - .
Solifenacin	0.85	0.58 - 1.18	1.01	0.68 - 1.40
Trospium	1.17	0.60 - 2.12	1.30	0.67 - 2.35
MALES				
Any OAB drug (not tolterodine)	1.60	1.31 - 1.87	1.77	1.45 - 2.07
Darifenacin	2.97	1.16 - 7.04	2.66	1.04 - 6.31
Fesoterodine	0.00	. - .	0.00	. - .
Oxybutynin	3.29	0.82 - 15.19	2.70	0.68 - 12.47
Solifenacin	1.81	1.39 - 2.23	2.12	1.63 - 2.61
Trospium	1.32	0.64 - 2.48	1.29	0.63 - 2.42
MALES OVER 65 YEARS				
Any OAB drug (not tolterodine)	1.64	1.34 - 1.92	1.70	1.39 - 1.99
Darifenacin	3.16	1.25 - 7.37	2.51	0.99 - 5.85
Fesoterodine	0.00	. - .	0.00	. - .
Oxybutynin	3.35	0.84 - 15.21	2.55	0.64 - 11.58
Solifenacin	1.78	1.35 - 2.21	2.08	1.58 - 2.58
Trospium	1.50	0.74 - 2.77	1.22	0.60 - 2.26
MALES WITH HIGH CV RISK				
Any OAB drug (not tolterodine)	1.53	1.21 - 1.82	1.76	1.40 - 2.10
Darifenacin	3.77	1.50 - 8.62	2.84	1.13 - 6.50
Fesoterodine	0.00	. - .	0.00	. - .
Oxybutynin	4.24	1.07 - 18.87	3.35	0.84 - 14.91
Solifenacin	1.49	1.07 - 1.94	2.02	1.44 - 2.62
Trospium	1.75	0.87 - 3.18	1.52	0.75 - 2.76

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

a. The reference for standardization was the Danish population on January 1, 2008.

Table CV6a. Adjusted Hazard Rate Ratio for Cardiovascular Endpoints, With Tolterodine as Reference, Current Exposure

	Adjusted Hazard Rate Ratio[a]	(95% CI)
Acute myocardial infarction		
Any OAB drug except tolterodine	0.93	0.80 - 1.08
Darifenacin	0.91	0.62 - 1.35
Fesoterodine	0.83	0.60 - 1.15
Oxybutynin	0.58	0.26 - 1.30
Solifenacin	0.94	0.80 - 1.11
Trospium	1.11	0.87 - 1.41
Stroke		
Any OAB drug except tolterodine	1.10	0.86 - 1.39
Darifenacin	1.22	0.71 - 2.11
Fesoterodine	1.06	0.64 - 1.74
Oxybutynin	0.48	0.12 - 1.94
Solifenacin	1.08	0.84 - 1.41
Trospium	1.07	0.73 - 1.57
Cardiovascular death		
Any OAB drug except tolterodine	1.03	0.93 - 1.14
Darifenacin	1.00	0.76 - 1.30
Fesoterodine	0.98	0.77 - 1.23
Oxybutynin	1.11	0.73 - 1.69
Solifenacin	1.05	0.94 - 1.17
Trospium	1.05	0.89 - 1.24
Composite endpoint		
Any OAB drug except tolterodine	1.00	0.92 - 1.09
Darifenacin	0.97	0.78 - 1.21
Fesoterodine	0.95	0.79 - 1.15
Oxybutynin	0.90	0.62 - 1.32
Solifenacin	1.01	0.92 - 1.11
Trospium	1.06	0.93 - 1.22
All-cause death		
Any OAB drug except tolterodine	0.99	0.93 - 1.05
Darifenacin	0.95	0.81 - 1.11
Fesoterodine	0.89	0.78 - 1.02
Oxybutynin	0.96	0.74 - 1.24
Solifenacin	1.00	0.94 - 1.07
Trospium	1.00	0.91 - 1.10

CI = confidence interval; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder.

a. From Cox regression models. The variables included were Charlson items 1-4 (cardiovascular history); any prior hospital diagnosis of renal failure or dialysis, arthritis, diabetes, COPD, obesity, hypertension, atrial fibrillation; and any prior prescription of NSAIDs, lipid-lowering drugs, low-dose aspirin, anti-gout drugs, drugs against COPD, nicotine preparations, drugs for alcohol abstinence, antihypertensives, or antidiabetics; and the patient's disposable income as a crude marker of socioeconomic status.

Table CV6b. Adjusted Hazard Rate Ratio for Cardiovascular Endpoints, With Tolterodine as Reference, Recent Exposure

	Adjusted Hazard Rate Ratio[a]	(95% CI)
Acute myocardial infarction		
Any OAB drug except tolterodine	0.95	0.68 - 1.31
Darifenacin	1.22	0.60 - 2.47
Fesoterodine	1.26	0.74 - 2.15
Oxybutynin	1.38	0.55 - 3.48
Solifenacin	0.81	0.56 - 1.19
Trospium	0.84	0.49 - 1.42
Stroke		
Any OAB drug except tolterodine	1.51	0.85 - 2.69
Darifenacin	1.02	0.23 - 4.53
Fesoterodine	2.10	0.85 - 5.18
Oxybutynin	0.99	0.13 - 7.64
Solifenacin	1.19	0.62 - 2.31
Trospium	2.06	0.97 - 4.37
Cardiovascular death		
Any OAB drug except tolterodine	0.93	0.72 - 1.20
Darifenacin	1.28	0.74 - 2.21
Fesoterodine	0.91	0.56 - 1.49
Oxybutynin	0.67	0.24 - 1.82
Solifenacin	0.81	0.60 - 1.08
Trospium	1.04	0.71 - 1.52
Composite endpoint		
Any OAB drug except tolterodine	1.01	0.82 - 1.24
Darifenacin	1.20	0.76 - 1.91
Fesoterodine	1.23	0.87 - 1.76
Oxybutynin	1.16	0.61 - 2.22
Solifenacin	0.84	0.66 - 1.07
Trospium	1.10	0.81 - 1.50
All-cause death		
Any OAB drug except tolterodine	0.98	0.86 - 1.12
Darifenacin	0.98	0.71 - 1.36
Fesoterodine	0.90	0.69 - 1.17
Oxybutynin	0.65	0.37 - 1.14
Solifenacin	0.97	0.83 - 1.12
Trospium	0.97	0.79 - 1.19

CI = confidence interval; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder.

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. From Cox regression models. The variables included were Charlson items 1-4 (cardiovascular history); any prior hospital diagnosis of renal failure or dialysis, arthritis, diabetes, COPD, obesity, hypertension, atrial fibrillation; and any prior prescription of NSAIDs, lipid-lowering drugs, low-dose aspirin, anti-gout drugs, drugs against COPD, nicotine preparations, drugs for alcohol abstinence, antihypertensives, or antidiabetics; and the patient's disposable income as a crude marker of socioeconomic status.

Table CV6c. Adjusted Hazard Rate Ratio for Cardiovascular Endpoints, With Any Other OAB Drug as Reference, Current Exposure

	Adjusted Hazard Rate Ratio[a]	(95% CI)
Acute myocardial infarction		
Darifenacin	0.94	0.64 - 1.39
Fesoterodine	0.84	0.61 - 1.15
Oxybutynin	0.68	0.30 - 1.51
Solifenacin	0.95	0.82 - 1.10
Tolterodine	1.08	0.92 - 1.25
Trospium	1.13	0.90 - 1.43
Stroke		
Darifenacin	1.21	0.72 - 2.04
Fesoterodine	1.00	0.62 - 1.59
Oxybutynin	0.54	0.13 - 2.18
Solifenacin	1.07	0.85 - 1.35
Tolterodine	0.91	0.72 - 1.16
Trospium	1.03	0.72 - 1.48
Cardiovascular death		
Darifenacin	1.00	0.77 - 1.29
Fesoterodine	0.88	0.70 - 1.11
Oxybutynin	1.03	0.66 - 1.60
Solifenacin	1.04	0.94 - 1.15
Tolterodine	0.97	0.87 - 1.07
Trospium	1.05	0.90 - 1.22
Composite endpoint		
Darifenacin	0.98	0.79 - 1.21
Fesoterodine	0.89	0.75 - 1.07
Oxybutynin	0.90	0.60 - 1.33
Solifenacin	1.00	0.92 - 1.09
Tolterodine	1.00	0.92 - 1.09
Trospium	1.07	0.94 - 1.22
All-cause death		
Darifenacin	0.98	0.84 - 1.14
Fesoterodine	0.90	0.79 - 1.02
Oxybutynin	0.94	0.72 - 1.24
Solifenacin	1.01	0.96 - 1.08
Tolterodine	1.01	0.95 - 1.07
Trospium	1.02	0.93 - 1.12

CI = confidence interval; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder.

Note: reference is current treatment with any other OAB drug.

a. From Cox regression models. The variables included were Charlson items 1-4 (cardiovascular history); any prior hospital diagnosis of renal failure or dialysis, arthritis, diabetes, COPD, obesity, hypertension, atrial fibrillation; and any prior prescription of NSAIDs, lipid-lowering drugs, low-dose aspirin, anti-gout drugs, drugs against COPD, nicotine preparations, drugs for alcohol abstinence, antihypertensives, or antidiabetics; and the patient's disposable income as a crude marker of socioeconomic status.

Table CV6d. Adjusted Hazard Rate Ratio for Cardiovascular Endpoints, With Any Other OAB Drug as Reference, Recent Exposure

	Adjusted Hazard Rate Ratio[a]	(95% CI)
Acute myocardial infarction		
Darifenacin	1.25	0.61 - 2.56
Fesoterodine	1.51	0.92 - 2.47
Oxybutynin	1.69	0.69 - 4.13
Solifenacin	0.79	0.57 - 1.10
Tolterodine	1.06	0.76 - 1.47
Trospium	0.85	0.51 - 1.40
Stroke		
Darifenacin	0.79	0.19 - 3.25
Fesoterodine	1.70	0.77 - 3.75
Oxybutynin	0.84	0.12 - 6.05
Solifenacin	0.91	0.53 - 1.56
Tolterodine	0.66	0.37 - 1.18
Trospium	1.75	0.93 - 3.31
Cardiovascular death		
Darifenacin	1.46	0.86 - 2.46
Fesoterodine	1.02	0.65 - 1.62
Oxybutynin	0.81	0.30 - 2.17
Solifenacin	0.81	0.63 - 1.05
Tolterodine	1.07	0.84 - 1.38
Trospium	1.15	0.81 - 1.63
Composite endpoint		
Darifenacin	1.25	0.79 - 1.96
Fesoterodine	1.34	0.97 - 1.86
Oxybutynin	1.32	0.70 - 2.48
Solifenacin	0.79	0.64 - 0.98
Tolterodine	0.99	0.81 - 1.22
Trospium	1.15	0.87 - 1.52
All-cause death		
Darifenacin	1.06	0.77 - 1.45
Fesoterodine	0.96	0.75 - 1.23
Oxybutynin	0.71	0.41 - 1.23
Solifenacin	1.00	0.87 - 1.14
Tolterodine	1.02	0.89 - 1.17
Trospium	1.01	0.84 - 1.23

CI = confidence interval; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder.

Note: reference is current treatment with any other OAB drug.

a. From Cox regression models. The variables included were Charlson items 1-4 (cardiovascular history); any prior hospital diagnosis of renal failure or dialysis, arthritis, diabetes, COPD, obesity, hypertension, atrial fibrillation; and any prior prescription of NSAIDs, lipid-lowering drugs, low-dose aspirin, anti-gout drugs, drugs against COPD, nicotine preparations, drugs for alcohol abstinence, antihypertensives, or antidiabetics; and the patient's disposable income as a crude marker of socioeconomic status.

Table CV6e. Adjusted Hazard Rate Ratio for Cardiovascular Endpoints, With No Current/Recent Exposure to Any OAB Drug as a Reference, Current Exposure

	Adjusted Hazard Rate Ratio[a]	(95% CI)
Acute myocardial infarction		
Darifenacin	0.94	0.65 - 1.37
Fesoterodine	0.83	0.61 - 1.14
Oxybutynin	0.54	0.24 - 1.20
Solifenacin	0.98	0.85 - 1.12
Tolterodine	1.05	0.92 - 1.21
Trospium	1.13	0.91 - 1.41
Stroke		
Darifenacin	1.20	0.71 - 2.02
Fesoterodine	1.05	0.66 - 1.67
Oxybutynin	0.63	0.20 - 1.98
Solifenacin	1.16	0.93 - 1.44
Tolterodine	1.10	0.88 - 1.38
Trospium	1.13	0.79 - 1.62
Cardiovascular death		
Darifenacin	0.95	0.74 - 1.24
Fesoterodine	0.90	0.73 - 1.12
Oxybutynin	1.06	0.71 - 1.57
Solifenacin	1.09	0.99 - 1.20
Tolterodine	1.08	0.98 - 1.19
Trospium	1.07	0.91 - 1.24
Composite endpoint		
Darifenacin	0.96	0.78 - 1.19
Fesoterodine	0.92	0.77 - 1.09
Oxybutynin	0.90	0.63 - 1.28
Solifenacin	1.06	0.98 - 1.14
Tolterodine	1.08	1.00 - 1.17
Trospium	1.10	0.97 - 1.25
All-cause death		
Darifenacin	0.88	0.76 - 1.02
Fesoterodine	0.81	0.71 - 0.92
Oxybutynin	0.89	0.69 - 1.13
Solifenacin	0.99	0.93 - 1.04
Tolterodine	1.04	0.98 - 1.09
Trospium	0.98	0.90 - 1.07

CI = confidence interval; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder.

a. From Cox regression models. The variables included were Charlson items 1-4 (cardiovascular history); any prior hospital diagnosis of renal failure or dialysis, arthritis, diabetes, COPD, obesity, hypertension, atrial fibrillation; and any prior prescription of NSAIDs, lipid-lowering drugs, low-dose aspirin, anti-gout drugs, drugs against COPD, nicotine preparations, drugs for alcohol abstinence, antihypertensives, or antidiabetics; and the patient's disposable income as a crude marker of socioeconomic status.

Table CV6f. Adjusted Hazard Rate Ratio for Cardiovascular Endpoints, With No Current/Recent Exposure to Any OAB Drug as a Reference, Recent Exposure

	Adjusted Hazard Rate Ratio[a]	(95% CI)
Acute myocardial infarction		
Darifenacin	1.61	0.83 - 3.13
Fesoterodine	1.66	1.03 - 2.67
Oxybutynin	1.84	0.76 - 4.46
Solifenacin	1.07	0.80 - 1.43
Tolterodine	1.34	1.01 - 1.76
Trospium	1.13	0.71 - 1.79
Stroke		
Darifenacin	0.90	0.22 - 3.65
Fesoterodine	1.77	0.82 - 3.83
Oxybutynin	0.87	0.12 - 6.27
Solifenacin	1.09	0.68 - 1.77
Tolterodine	0.94	0.56 - 1.60
Trospium	1.87	1.03 - 3.41
Cardiovascular death		
Darifenacin	1.41	0.84 - 2.35
Fesoterodine	1.06	0.68 - 1.63
Oxybutynin	0.75	0.28 - 2.01
Solifenacin	0.92	0.73 - 1.15
Tolterodine	1.10	0.89 - 1.37
Trospium	1.12	0.80 - 1.56
Composite endpoint		
Darifenacin	1.30	0.84 - 2.00
Fesoterodine	1.34	0.98 - 1.84
Oxybutynin	1.25	0.67 - 2.32
Solifenacin	0.93	0.77 - 1.11
Tolterodine	1.09	0.91 - 1.30
Trospium	1.20	0.92 - 1.56
All-cause death		
Darifenacin	1.19	0.88 - 1.62
Fesoterodine	1.10	0.86 - 1.39
Oxybutynin	0.74	0.43 - 1.28
Solifenacin	1.16	1.03 - 1.30
Tolterodine	1.19	1.06 - 1.34
Trospium	1.14	0.95 - 1.37

CI = confidence interval; COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder.

Note: all follow-up containing current use of any OAB drugs was removed from the analysis.

a. From Cox regression models. The variables included were Charlson items 1-4 (cardiovascular history); any prior hospital diagnosis of renal failure or dialysis, arthritis, diabetes, COPD, obesity, hypertension, atrial fibrillation; and any prior prescription of NSAIDs, lipid-lowering drugs, low-dose aspirin, anti-gout drugs, drugs against COPD, nicotine preparations, drugs for alcohol abstinence, antihypertensives, or antidiabetics; and the patient's disposable income as a crude marker of socioeconomic status.

Table CV7a. Results of Propensity Score–Matched Analysis for Cardiovascular Endpoints and Overall Mortality, With Tolterodine as Reference, Current Exposure

	Incidence Rate Ratio	(95% CI)
Acute myocardial infarction		
Any OAB drug except tolterodine	0.94	0.80 - 1.11
Darifenacin	0.89	0.57 - 1.39
Fesoterodine	0.83	0.56 - 1.25
Oxybutynin	0.43	0.11 - 1.73
Solifenacin	0.93	0.78 - 1.12
Trospium	1.02	0.77 - 1.35
Stroke		
Any OAB drug except tolterodine	1.06	0.82 - 1.36
Darifenacin	1.03	0.52 - 2.03
Fesoterodine	1.17	0.65 - 2.12
Oxybutynin	0.42	0.06 - 3.02
Solifenacin	1.05	0.79 - 1.39
Trospium	0.93	0.60 - 1.45
Cardiovascular death		
Any OAB drug except tolterodine	1.04	0.93 - 1.16
Darifenacin	0.90	0.65 - 1.23
Fesoterodine	1.10	0.84 - 1.44
Oxybutynin	1.13	0.63 - 2.01
Solifenacin	1.08	0.95 - 1.22
Trospium	0.99	0.82 - 1.19
Composite endpoint		
Any OAB drug except tolterodine	1.00	0.92 - 1.10
Darifenacin	0.87	0.67 - 1.13
Fesoterodine	1.03	0.83 - 1.29
Oxybutynin	0.96	0.57 - 1.61
Solifenacin	1.02	0.92 - 1.13
Trospium	0.99	0.85 - 1.16
All-cause death		
Any OAB drug except tolterodine	0.95	0.90 - 1.02
Darifenacin	0.96	0.81 - 1.14
Fesoterodine	0.93	0.79 - 1.09
Oxybutynin	1.22	0.88 - 1.68
Solifenacin	0.97	0.90 - 1.04
Trospium	0.97	0.87 - 1.08

CI = confidence interval; OAB = overactive bladder.

All characteristics presented in Table A6 were included in the propensity score model.

Table CV7b. Results of Propensity Score–Matched Analysis for Cardiovascular Endpoints and Overall Mortality, With Tolterodine as Reference, Recent Exposure

	Incidence Rate Ratio	(95% CI)
Acute myocardial infarction		
Any OAB drug except tolterodine	0.94	0.67 - 1.32
Darifenacin	0.90	0.32 - 2.59
Fesoterodine	1.50	0.82 - 2.72
Oxybutynin	1.39	0.32 - 6.05
Solifenacin	0.90	0.61 - 1.35
Trospium	0.96	0.55 - 1.66
Stroke		
Any OAB drug except tolterodine	1.53	0.83 - 2.84
Darifenacin	1.01	0.12 - 8.43
Fesoterodine	2.56	0.91 - 7.19
Oxybutynin	1.59	0.19 - 12.99
Solifenacin	1.33	0.63 - 2.83
Trospium	2.35	1.09 - 5.06
Cardiovascular death		
Any OAB drug except tolterodine	0.95	0.73 - 1.25
Darifenacin	0.97	0.45 - 2.11
Fesoterodine	1.24	0.70 - 2.20
Oxybutynin	1.51	0.55 - 4.16
Solifenacin	0.89	0.64 - 1.22
Trospium	1.22	0.81 - 1.84
Composite endpoint		
Any OAB drug except tolterodine	1.06	0.85 - 1.32
Darifenacin	1.05	0.56 - 1.97
Fesoterodine	1.72	1.16 - 2.56
Oxybutynin	1.83	0.84 - 4.01
Solifenacin	0.97	0.75 - 1.26
Trospium	1.35	0.97 - 1.86
All-cause death		
Any OAB drug except tolterodine	0.99	0.86 - 1.14
Darifenacin	0.94	0.63 - 1.41
Fesoterodine	0.96	0.70 - 1.33
Oxybutynin	1.20	0.63 - 2.26
Solifenacin	1.01	0.86 - 1.19
Trospium	1.05	0.84 - 1.31

CI = confidence interval; OAB = overactive bladder.

All characteristics presented in Table A6 were included in the propensity score model.