Postauthorization Safety Program Using the Swedish National Registers—A Validation Study of Cardiovascular and Cancer Events in Users of Pharmacological Treatments for Overactive Bladder

Prepared for:

Astellas Pharma Global Development, Inc.

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Final Swedish Study Report

ISN/Protocol No.178-CL-118:

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

Version 1.0, February 16, 2016

NDA Number: 202611

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Title	Postauthorization Safety Program Using the Swedish National Registers—A Validation Study of Cardiovascular and Cancer Events in Users of Pharmacological Treatments for Overactive Bladder
Version identifier of the final study report	1.0
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Active substance	Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine
Medicinal product	Detrusitol, Ditropan, Emselex, Gelnique, Kentera, Oxibutynin, Tolterodin, Toviaz, Vesicare
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 and tolterodine). ▪ 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) among new users of antimuscarinic drugs used in the treatment of OAB.
Country(-ies) of study	Sweden
Author	[redacted]

Marketing Authorization Holder(s)

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

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1 Abstract

Title

Postauthorization Safety Program Using the Swedish National Registers—A Validation Study of Cardiovascular and Cancer Events in Users of Pharmacological Treatments for Overactive Bladder

Version / Date

Version 1.0 / February 16, 2016

Keywords: overactive bladder, pharmacoepidemiology, antimuscarinics, national health registers

Rationale and Background

Mirabegron is a beta-3 adrenergic agonist indicated for the symptomatic treatment of urgency, increased micturition frequency, and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Astellas obtained marketing authorization for mirabegron on June 28, 2012, in the United States (US)[1] and on December 20, 2012, in the European Union (EU). The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) included a postapproval requirement to evaluate cardiovascular safety.[2] The FDA also required a postapproval commitment to evaluate cancer risks.[3]

To prepare for a postapproval safety assessment of cardiovascular and cancer risk, this study has been designed to describe drug-use patterns among new users of antimuscarinic drugs, calculate background rates of cardiovascular and cancer endpoints among antimuscarinic drug users, map the availability of data on covariates, and explore proxies for missing covariates. This is part of a multinational study in Sweden, Denmark, the United Kingdom, and the United States.

Research Question and Objectives

The objectives of this study are as follows:

- To characterize new users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, and tolterodine) with respect to selected covariates.
- To describe the patterns of usage of OAB medications, including duration of treatments, drug switching, and use of medications as add-on therapy to each other.
- To describe the availability of potential confounders in the Swedish national registers.
- To estimate the incidence rates of four different cardiovascular events plus all-cause mortality in new users of antimuscarinic drugs indicated for the treatment of OAB.

- To estimate the incidence rate ratio (IRR) of four different cardiovascular endpoints plus all-cause mortality in new users of each of the OAB medications compared with tolterodine, a frequently used OAB medication across the populations of the research program.
- To estimate the incidence rate 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.

Study Design

This was a retrospective cohort study.

Setting

We used data from the national registers in Sweden. The study period was July 1, 2005, through December 31, 2012, using the first year as run-in to assess new users of OAB treatment.

Subjects and Study Size, Including Dropouts

The cohort consisted of new users of any of the following medications for OAB: oxybutynin, tolterodine, darifenacin, solifenacin, and fesoterodine. New users were defined at the time of the first dispensing of one of the medications of interest (prescription index date) with at least 1 year of information and without any recorded dispensing of the current study drug that qualified the subject for cohort entry during the preceding 12 months. Each patient was allowed to contribute exposure time to more than one individual OAB medication.

For each subject, follow-up started on the date of the first dispensing for a drug of interest and finished at the earliest of the following events: end of the study period (December 31, 2012), death, emigration, occurrence of an exclusion diagnosis, or occurrence of a study endpoint (at the time of an AMI individuals would stop contributing person-time for AMI analyses, but would continue for all other endpoints; likewise for other endpoints).

The study was conducted in the cohort of 130,944 new users of any individual OAB medication during the study period.

Variables and Data Sources

Person-time was classified based on individual OAB medication dispensing.

The endpoints of interest in the cardiovascular component were as follows:

- Acute myocardial infarction (AMI), including coronary heart disease deaths
- Stroke, including cerebrovascular disease death
- Cardiovascular mortality (comprising coronary heart disease death and cerebrovascular disease death)

- The composite endpoint major adverse cardiac events (MACE)— AMI, stroke, or cardiovascular mortality
- All-cause mortality

One overall composite cancer endpoint and two sex-specific composite cancer endpoints were evaluated. The cancers included in the overall composite endpoint are the 10 cancers with the highest incidence rates in the general population, excluding non-melanoma skin cancer:

- Overall: 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 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 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 range of characteristics, including demographics and others that define elevated cancer or cardiovascular risk, relevant diagnoses related to OAB, number of outpatient visits, number of hospitalizations, and use of other medications, were evaluated.

In Sweden, the Prescribed Drug Register contains all prescriptions dispensed in community and hospital pharmacies, recorded on an individual level with a personal registration number. The Prescribed Drug Register has approximately 6.4 million individuals with at least one dispensing in 2012. The coverage is close to 100% of all prescribed medicines dispensed to the Swedish population. The Prescribed Drug Register started July 1, 2005.

For all patients, Prescribed Drug Register data are linkable with hospital records, the cancer register, and national mortality data. Starting from January 1, 1997, for inpatients and in 2001 for outpatients, diagnoses in hospital records (inpatients and outpatients) have been coded according to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10). Procedures are coded according to the Nordic Classification of Surgical Procedures (NCSP), using also the Swedish adaptation "KVÅ."

Results

The study population comprised 130,944 patients with 1.8 therapy episodes per patient during the study period. Of all 240,141 therapy episodes, 37% were with tolterodine, 35% with solifenacin, 13% with fesoterodine, 8% with darifenacin, 5% with oxybutynin, and 3% with more than one drug. Trospium was not available in Sweden in this period.

The prevalences of smoking, hypertension, dyslipidemia, and OAB are lower than expected in this population, which we attribute to underrecording of these conditions in hospital discharge records.

In the cardiovascular analysis, of 130,944 patients, 4% had an AMI, 5% had a stroke, 3% died of cardiovascular causes, 8% experienced a MACE, and 8% died of any cause. In general, we observed higher risks of AMI, stroke, cardiovascular mortality, MACE, and all-cause mortality with tolterodine than with other study drugs. Increasing analytical complexity resulted in stronger control of confounding, taking the IRRs from propensity score–adjusted analyses closer to the null than analyses with less adjustment. In propensity score–adjusted analyses, results reflected that current use of tolterodine is associated with higher cardiovascular risks than current use of either solifenacin or fesoterodine. Among non-tolterodine study drugs, there was little variation in risk, with fesoterodine generally having the lowest IRRs and darifenacin the highest.

In the cancer analyses, of the 130,944 patients, 4.3% of the study population was diagnosed with 1 of the 10 study cancers. Also, 3,242 nonstudy first cancer events were noted. Prostate, breast, and colorectal cancer were the three most common cancers, contributing 27%, 17%, and 16% of cases, respectively. No drug seemed to carry an increased risk of cancer. Standardized incidence rates (SIRs) were generally similar across drug-use groups, and the drugs with the maximum and the minimum SIRs varied for the 10 study cancers. Analyses of cancer incidence rates by dose and by time since initiation of exposure showed that risk was higher with lower cumulative doses and during early treatment, which is consistent with protopathic bias or surveillance bias. The effect on the composite cancer endpoint was driven by prostate and bladder cancers, the specific cancers that had the highest rates in the earliest periods.

Discussion

In this cohort of patients with at least one prescription for an OAB medication, 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 with a lag time before clinical manifestation, the ability to detect associated events depends on the length of drug use and follow-up for each individual OAB medication. The validity of the endpoints in the source of information has been documented over the long history of the Swedish registries.

Current use of tolterodine was associated with higher risk for targeted cardiovascular events than current use of either solifenacin or fesoterodine.

Among the study drugs, none seemed to carry an increased risk of cancer. Analyses showed that risk was higher with lower cumulative doses and during early treatment, driven by prostate and bladder cancers, which is consistent with protopathic bias or surveillance bias.

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

Names and affiliations of principal investigators:

- [redacted] MD, PhD, [redacted]

Milestones

- Final protocol submission to the FDA: September 24, 2014; Amendment submitted February 27, 2015
- Final statistical analysis plan submission to the FDA: February 27, 2015
- Progress report submission to the FDA: March 31, 2015
- Final report submission: February 2016

2 List of Abbreviations

AMI	acute myocardial infarction
ATC	Anatomical Therapeutic Chemical
CPE	Centre for Pharmacoepidemiology, Karolinska Institutet
DDD	defined daily dose
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
HIV	human immunodeficiency virus
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
NPR	Swedish National Patient Register
MACE	major adverse cardiac events
NBHW	National Board of Health and Welfare
NCSP	Nordic Classification of Surgical Procedures
NSAIDs	nonsteroidal anti-inflammatory drugs
OAB	overactive bladder
PPV	positive predictive value
RTI-HS	RTI Health Solutions, a business unit of RTI International
SD	standard deviation
SEER	Surveillance, Epidemiology and End Results Program (US)
US	United States

3 Investigators

Karolinska Institutet, Department of Medicine, Solna, Centre for Pharmacoepidemiology, is responsible for conducting the study in the Swedish national registers. The core research team is listed below.

- Principal Investigator: [redacted] MD, PhD, [redacted]
- Project Leader/Biostatistician: [redacted] MSc, PhD, statistician

- Medical advisor: [redacted] MD, PhD, research coordinator
- Administrator: [redacted] project coordinator
- Database manager: [redacted] database manager
- Epidemiologist: [redacted] MD, PhD, [redacted] senior researcher

RTI Health Solutions coordinates the European studies and supports Karolinska Institutet:

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

4 Other Responsible Parties

- Funding for this research is provided by Astellas, the manufacturer of mirabegron.

5 Milestones and Activities Completed

Task/Milestone	Anticipated Timing	Actual Timing
Protocol submission to the FDA	September 2014	September 2014
Amended protocol (V1.1) submitted to the FDA	—	February 2015
Swedish ethics approval	October 2014	October 2014
Development of statistical analysis plan	October 2014	February 2015
Application for data	October 2014	October 2014
NBHW data delivery	January 2015	January 2015
Submission of study status report to the FDA (regulatory milestone)	March 2015	March 31, 2015
Statistics Sweden data delivery	April 2015	May 2015
Analytic data set completely available	July 2015	July 2015
Study report submission to the FDA	February 2016	

FDA = United States Food and Drug Administration; NBHW = National Board of Health and Welfare (Sweden).

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 (US)[4] and on December 20, 2012, in the European Union (EU).[5] The US Food and Drug Administration (FDA)[4] and the European Medicines Agency (EMA) included a postapproval requirement to evaluate cardiovascular safety. The FDA also required a postapproval commitment to evaluate cancer risk.[4]

To prepare for a postmarketing safety assessment of cardiovascular and cancer risk associated with mirabegron use, a study has been designed to describe drug-use patterns among users of antimuscarinic drugs for the treatment of OAB and to calculate background rates of cardiovascular and cancer endpoints in this population. This is part of a multinational study in Sweden, Denmark, the United Kingdom, and the United States.

The present report presents methods and results for the entire study and completes the progress report dated March 26, 2015.

6.1 Literature Review

6.1.1 Drug Utilization

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

In an earlier drug utilization study, Altman et al.[6] concluded "from 2000 to 2007, there was a 68.8% increase in dispensed anticholinergic drugs in a population of 9 million. More than 93 million defined daily doses (DDDs) (calculated average maintenance dose per day) of anticholinergic drugs were dispensed, corresponding to an overall quantity of 3.5 DDD per 1,000 persons per year. Approximately two-thirds of anticholinergic drugs were prescribed to women, regardless of drug type."[6]

Linnér et al. reported low adherence to anticholinergic drugs: "Based on the analysis it appears that the adherence rate to continuous treatment with anticholinergics in Sweden is similar to the rate in Denmark.[7] Of the 47,685 individuals who received their first prescription of anticholinergics during 2007 and 2008, less than 50% filled their second prescription within 120 days…After one year the adherence rate was less than 20 percent."[8]

Johnell and Fastbom identified a potential interaction in the elderly (aged 75 or more years): "Anticholinergic drug use was more common among cholinesterase inhibitor users than nonusers, particularly in men, of whom 9% who were taking cholinesterase inhibitors were dispensed anticholinergic drugs compared with 5% who were not taking cholinesterase inhibitors."[9]

6.1.2 Cardiovascular Risk Factors in Users of Drugs for Overactive Bladder

In a study performed in the HealthCore Integrated Research Database and GE Healthcare database, baseline cardiovascular comorbidity was higher in subjects with an OAB diagnosis or treated with OAB antimuscarinic drugs (39%) than in age- and sex-matched subjects without either OAB codes or OAB antimuscarinic treatment (21%).[10] 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 OAB codes or OAB antimuscarinic treatment. Prevalence of cardiovascular comorbidity was similar in OAB patients treated with OAB antimuscarinic drugs (39%) and age- and sex-matched OAB patients with no such treatment (38%); use of non-OAB medications with antimuscarinic effect was higher in treated subjects (37% vs. 29% for untreated subjects).

A related study, also in the US (GE Healthcare database), found that OAB patients treated with OAB antimuscarinics had baseline heart rate distributions similar to those with no such treatment.[11] In this study, treated OAB patients 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 OAB patients (median age, 66 years; 17% men) and untreated OAB patients (median age, 59 years; 14% men).

6.1.3 Endpoint Identification and Validation in the Proposed Data Sources

Information on the endpoints for the Swedish component was extracted from the national health registers, which have high diagnostic accuracy.[12] Reporting to the Swedish national health registers is mandatory. Appendix A includes a list of validation studies on the endpoints in the data sources.

6.1.3.1 Acute Myocardial Infarction

We found three studies on the validity of acute myocardial infarction (AMI) diagnoses in the Swedish National Patient Register. Tables with results of these validation studies are included in Appendix A. All of these studies showed the validity of the AMI endpoint to be high, with positive predictive values (PPVs) between 86% and 98%.

6.1.3.2 Stroke

We found two studies on the validity of stroke diagnoses in the Swedish National Patient Register. Tables with results of these validation studies are included in Appendix A. Both of these studies showed the validity of the stroke endpoint to be reasonably high, with PPVs of 68.5% and 94%.

6.1.3.3 Cancer

The source of data on cancer endpoints was the Swedish Cancer Register, which is population based and contains records of all incidences of malignant neoplasms in the

Swedish population from 1958 onward. The Swedish Cancer Register is considered to be of good quality, as 99% of the cases are histologically verified, and completeness is high (96.3% in 1998).[13]

7 Research Question and Objectives

The objectives of this study are as follows:

- To characterize new users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, or tolterodine) with respect to selected covariates.
- To describe the patterns of usage of OAB medications, including duration of treatments (based on DDDs), drug switching, and use of medications as add-on therapy.
- To describe the availability of potential confounders in the Swedish national registers.
- To estimate the incidence rates of four different cardiovascular events plus all-cause mortality in new users of antimuscarinic drugs indicated for the treatment of OAB.
- To estimate the incidence rate ratio of four different cardiovascular endpoints plus all-cause mortality in new users of each of the OAB medications compared with tolterodine, a frequently used OAB medication across the populations of the research program.
- To estimate the incidence rates of one overall composite cancer endpoint and two sex-specific composite endpoints (one for men and one for women), during the first year after start of treatment and during subsequent years, among new users of antimuscarinic drugs used in the treatment of OAB.

8 Amendments and Updates

Not applicable.

9 Research Methods

9.1 Study Design

Patients exposed to selected drugs used in the treatment of OAB (darifenacin, fesoterodine, oxybutynin, solifenacin, or tolterodine) were identified from the population during the study period of July 1, 2006, through December 31, 2012. The latter is consistent across databases in the program.

We described the characteristics of the patients belonging to the overall exposed cohort and to each category of new users of individual OAB medications, allowing each patient to belong to more than one category. Major risk factors for cardiovascular and cancer endpoints that could act as potential confounders were described, and the incidence rates of

the four cardiovascular endpoints, all-cause mortality, and the three composite cancer endpoints in new users of the drugs of interest were estimated.

9.2 Setting

The study was conducted in Sweden using data from the Swedish national health care registers; the Swedish Prescribed Drug Register, the Swedish Cancer Register, the National Patient Register, and the Cause of Death Register constitute the primary sources of data. A unique personal registration number is issued to all residents in Sweden upon birth or immigration and is used throughout life. The unique personal registration number is used to link patients' data from the different registers, as described below.[14]

9.3 Subjects

Subjects in the program are required to meet all of the following inclusion criteria:

- Be a resident in Sweden for at least 12 months before the first dispensing of an OAB medication of interest (thereby providing medical and prescription history data).
- Have a first recorded dispensing for oxybutynin, tolterodine, darifenacin, solifenacin, or fesoterodine.
- Be aged 18 years or older at the time of first dispensing of a drug of interest.

Patients were excluded if they met any of the following criteria at any time prior to cohort entry:

- Had a diagnosis of cancer other than non-melanoma skin cancer between 1997 and cohort entry.
- Had a diagnosis of human immunodeficiency virus (HIV) infection between 1997 and cohort entry.

The latter exclusion criterion was included in the protocol for consistency with components of the program that use other data sources. In other data sources, it was expected that the diagnosis of HIV infection would modify the provision of a patient's health care so that it would no longer be captured in the data source. In the Swedish health registers, health care utilization of subjects with a diagnosis of HIV infection would continue to be captured.

A new user of any drug of interest was defined as a patient who received a first dispensing for any of the OAB medications of interest during the study period without a dispensing for the same medication in the previous 12 months. All new users of OAB medications of interest that met the inclusion criteria were included in the study.

9.3.1 Follow-up

Follow-up of eligible subjects started on the date of the first dispensing of an OAB medication (cohort entry date). For the analyses based on individual endpoints or composite

endpoints (either cardiovascular or cancer), follow-up finished at the earliest of the following dates:

- End of the study period (December 31, 2012).
- Death.
- Emigration.
- Occurrence of a diagnosis of HIV or cancer (except non-melanoma skin cancer).
- For all cancer analyses (for all three composite endpoints), the first incident targeted cancer was considered to be the cancer endpoint of interest; 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.
- In the cardiovascular analysis, person-time allocation was different for the composite major adverse cardiac events (MACE) endpoint and for sequential targeted cardiovascular events occurring in the same individual.
  - For the composite MACE endpoint, person-time follow-up terminated at the date of occurrence of the first targeted cardiovascular event.
  - For sequential targeted cardiovascular endpoints occurring in the same individual, person-time of follow-up accumulated until the date of occurrence of a subsequent targeted cardiovascular event. Patients may experience multiple endpoints (e.g., first a stroke and then cancer). Each of these events, and the associated person-time, were captured.

9.4 Variables

9.4.1 Time at Risk and Exposure

9.4.1.1 Cardiovascular Study

To define time at risk, it is assumed that any cardiovascular effects of OAB medications will present shortly after first use, continue while patients continue the use, and decline after the medication is discontinued.

Each day of exposed person-time was classified in mutually exclusive categories based on specific drug use and recency of use—current, recent, or past use. Patients contributed person-time to different exposure categories if they switched treatment. Current use included the days covered in the prescription plus 7 days, in the understanding that patients may forget doses and use the drug dispensed a few days beyond the days of supply noted in the prescription. Recent use included the first 60 days after current use, and past use included person-time after the end of recent use.

The Swedish Prescribed Drug Register does not hold numerical or complete data on the dosing instructions; therefore, the prescription's period of usage may not be inferred directly from the information available. Instead, filled prescriptions were assigned a period

of usage based on the dispensed quantity and the recommended DDD. We assumed use of 1 pill/day, 2 transdermal patches/week, and 30 mL of intravesical solution/day.

9.4.1.2 Cancer Study

It was assumed that effects of OAB medications on the incidence of cancers will continue for a long period of time after the medication is discontinued. Time at risk was defined as starting with the first dispensing for new use of any of the OAB medications. Follow-up time thus extended beyond the end of exposure time. Exposure was categorized by duration and recency.

Patients who entered the OAB medication–exposed cohort were considered "ever-exposed" to OAB medications. For the construction of user categories for single OAB medications, patients who entered the cohort with exposure to OAB medication A were considered ever-exposed to OAB medication A.

For single exposure, patients in the OAB medication A category who subsequently began treatment with OAB medication B had their person-time in the OAB medication A category censored at the start of treatment with OAB medication B, and from the date of the first filled prescription of OAB medication B, their person-time was entered into the category of those exposed to multiple OAB medications (the multiple-exposure category). Also, from the first the dispensing of OAB medication B the patient was considered ever-exposed to B.

9.4.2 Endpoints

9.4.2.1 Cardiovascular Endpoints

The endpoints of interest in the cardiovascular component were as follows:

- Acute myocardial infarction (AMI), including coronary heart disease death
- Stroke, including cerebrovascular disease death
- Cardiovascular mortality (comprised of coronary heart disease death and cerebrovascular disease death)
- The composite endpoint major adverse cardiac events (MACE)—AMI, stroke, or cardiovascular mortality
- All-cause mortality

The operational definition is described in Section 6.10.3.1 of the protocol.

9.4.2.2 Cancer Endpoints

The cancers observed in the mirabegron clinical development program were those that occur commonly in the general population; therefore, the present study focused on an overall composite endpoint consisting of the 10 most commonly occurring malignancies. Ranking cancers by the highest age-adjusted incidence rate for each sex in the US Surveillance, Epidemiology, and End Results (SEER) data, 2005-2009,[15] these cancers (incidence rate per 100,000, adjusted to the 2000 US standard population) are prostate

(69.4), breast (67.2), lung and bronchus (62.6), colon and rectum (46.3), melanoma of skin (21.0), urinary bladder (20.8), non-Hodgkin lymphoma (19.6), kidney and renal pelvis (15.1), corpus uteri (12.6), and pancreas (12.1).

For all cancer analyses (for all three composite endpoints), only the first incident targeted cancer was considered to be the cancer endpoint of interest; 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.

The primary cancer endpoint was the overall composite cancer endpoint. However, because some of these cancers occur exclusively (or nearly exclusively) in either males or females, the sex-specific composite cancer incidence rates were calculated.

9.4.3 Endpoint Ascertainment and Validation

9.4.3.1 Cardiovascular Endpoints

For cardiovascular endpoints, the Swedish National Patient Register contains all cases of AMI and stroke that are diagnosed during hospitalizations. The register collects all information contained in the list of discharge diagnoses for each hospitalization of a Swedish resident with a personal registration number. In addition, fatal cases of AMI and stroke that occur in or out of the hospital are obtained from the national Cause of Death Register, where diagnoses from autopsy reports and death certificates are recorded. As an entry of a cause of death is mandatory for every fatality that occurs in the country, the register can be considered to contain all fatal cases of AMI and stroke in Sweden. See Table 1 for high-level *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes to be used to identify endpoints in the cardiovascular study. Appendix B of the study protocol contains the ICD-10 codes contained in the definition of each of the endpoints.

Table 1. High-Level ICD-10 Codes Used to Identify Endpoints in the Cardiovascular Study

Endpoint	National Patient Register	Cause of Death Register
Acute myocardial infarction	I21	Coronary heart disease death: I20–I25, I46, I47.0, I47.2, I49.0, I49.8, I49.9, I51.6, I51.9, I70.9, R96.1, R98
Stroke	I60-I61, I63–I64	Cerebrovascular disease death: I60, I61, I63,I64, I65, I66, I67, I68, I69, G45
Cardiovascular mortality		Codes for coronary heart disease death or cerebrovascular disease death
All-cause mortality		Any

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

Note: Detailed codes can be found in Appendix B of the study protocol.

The validity of the Swedish National Patient Register (NPR) is high. The long follow-up makes the register particularly suitable for large-scale population-based research. Ludvigsson et al.[12] reviewed 132 papers that had validated the NPR. With few exceptions, validation of ICD codes from the NPR was made by comparing registered diagnoses in the NPR with information in medical records. The PPV was found to differ between diagnoses but was generally 85%-95%.

We found three studies on the validity of AMI diagnoses and two studies on the validity of stroke in the Swedish National Patient Register. Tables with results of these validation studies are included in Appendix A. All of these studies showed the validity of these endpoints to be high, with PPVs between 86% and 98% for AMI and 68% and 94% for stroke.

- Linnersjö et al.[16] evaluated the diagnostic quality of the hospital discharge and death records for 2,403 cases of first AMI identified using ICD-9* code 410. Of the 2,101 cases with available medical records (gold standard), 2,053 cases (98%) were classified as AMI according to the diagnostic criteria. A total of 302 fatal cases died outside the hospital. Among the autopsied cases, 93% (193 cases) had died with AMI as an underlying or contributory cause of death. Of 94 unhospitalized fatal cases without autopsy, 80% (75 cases) had AMI as the underlying or contributory cause of death.
- Hammar et al.[17] collected incident cases of AMI by using ICD-9 code 410 for hospital discharges and deaths. About 40,000 new cases of AMI per year were recorded in Sweden in 1987-1995. Examination of medical records (gold standard) for a national sample of patients with ischemic heart disease (713 with a discharge diagnosis of AMI and 1,135 with a discharge diagnosis of other ischemic heart disease) revealed a PPV of 86% and a sensitivity of 94% for this one code.
- Lindblad et al.[18] validated diagnoses of AMI and acute stroke by following 3,240 hypertensive patients aged 40-69 years and matched population controls from 1977-1987. The first event suggested in the Swedish National Patient Register identified by ICD-8† or ICD-9* coding could be confirmed by medical records (gold standard) in 96% (395 of 413) of AMI cases and 94% (236 of 251) of acute stroke cases. The underlying cause of death as identified by ICD-8 or ICD-9 coding in the Cause of Death Register was confirmed by hospital records for 96% (88 of 92) of patients with AMI and 92% (36 of 39) of patients with acute stroke.
- Stegmayr et al.[19] validated stroke diagnoses from mortality statistics, hospital discharges, and a population-based MONICA stroke register for a total of 309,806 Swedish patients aged 25 to 74 years during the years 1985-1989. The PPV for ICD-9 code 430-438 was found to be 68.5% (3,492 of 5,101).

* ICD-9 = *International Classification of Diseases, 9th Revision.*

† ICD-8 = *International Classification of Diseases, 8th Revision.*

9.4.3.2 Cancer Endpoints

The source of data on cancer endpoints was the Swedish Cancer Register. The Swedish Cancer Register is population based and contains records of all incidences of malignant neoplasms in the Swedish population from 1958 onward. Reporting to the Swedish Cancer Register is mandatory. The Swedish Cancer Register is generally considered to be of good quality: 99% of the cases are histologically verified, and completeness is high (96.3% in 1998).[13]

9.4.4 Potential Confounding Factors

In the main analyses of the mirabegron core studies, we will control for potential differences in distribution of determinants of cardiovascular endpoints or in cancer risk between users of antimuscarinic drugs.

The relevant confounding factors and covariates for cardiovascular disease (such as those outlined in Graham et al.[20]) are as follows:

- Age
- Sex
- Geographic area of residence
- Characteristics that define high cardiovascular risk (history of cerebrovascular disease, coronary artery disease, angina, myocardial infarction, heart failure, arrhythmias, use of antiarrhythmic drugs, hypertension, use of antihypertensive drugs, hyperlipidemia, use of lipid-lowering drugs, diabetes mellitus)
- OAB status. 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
- Number of outpatient visits and number of hospitalizations
- Use of other medications (nitrates, other drugs used to treat angina, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, antiplatelets, nonsteroidal anti-inflammatory drugs, estrogen, thyroid hormone replacement)
- Comorbidities (chronic obstructive pulmonary disease, dementia, gout, forms of arthritis, renal impairment, malignancy, peptic ulcer disease, organ transplantation)

Proxies for characteristics not captured in electronic data, such as smoking, body mass index, alcohol abuse, menopausal status, and occupational exposures or frailty, were used whenever possible. To address time-varying confounding, the status information for important confounders (such as number of outpatient visits and number of hospitalizations) was updated during follow-up for the analyses described in Section 9.9. Details are given in the statistical analysis plan.

In addition to potential cardiovascular confounding factors, characteristics that define elevated risk of malignancies, use of other medications (e.g., potent immunomodulators),

and comorbidities (e.g., chronic obstructive pulmonary disease, forms of arthritis, renal impairment) were evaluated.

For most covariates (e.g., history of medical conditions, history of bilateral mastectomy, use of hormone replacement therapy), all available information from 1997 (the start of ICD-10) was used, but within a limited time window depending on cohort entry date and with equal length for all patients (5 years); however, the 12-month period prior to the cohort entry date was used to estimate the medical history for conditions identified by Anatomical Therapeutic Chemical (ATC) codes, the number of outpatient visits, and the number of hospitalizations. Data on drug dispensing are available from July 1, 2005, and diagnoses coded in ICD-10 from January 1, 1997.

Appendix B summarizes the patient characteristic variables available in the Swedish national registers and their format.

9.5 Data Sources and Measurement

The data sources used in this study were linked by use of the personal registration number, a unique identifier assigned to all Swedish residents at birth or upon immigration and kept throughout life.

All linkage between data sources occurred within the Swedish National Board of Health and Welfare, and anonymized data were delivered to CPE.

9.5.1 Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register is a nationwide database covering the entire Swedish population. It includes data that fall into four main categories: (1) patient-specific data, (2) prescriber data, (3) drug data, and (4) pharmacy data. Drug data include the trade name, pharmaceutical form, strength and package size, number of packages, ATC classification code, amount in defined daily dose (DDD), and the prescribing and dispensing dates. The information is updated monthly. It does not include the majority of sales of nonprescription over-the-counter medicines, medicines administered at hospitals and nursing homes, or medicines prescribed but not dispensed.

9.5.2 Swedish National Patient Register

The Swedish National Patient Register (NPR) includes more than 99% of all somatic (including surgery) and psychiatric hospital discharges. It is mandatory for all physicians, private and publicly funded, to deliver data to the NPR (except for visits in primary care). Previous validation of the NPR by the National Board of Health and Welfare showed that 85%-95% of all diagnoses in the NPR are valid.

9.5.3 Swedish Cancer Register

The Swedish Cancer Register covers the whole Swedish population. Approximately 50,000 neoplasms are registered every year in Sweden. It is compulsory for every health care

provider to report new cases to the registry. The report informs about every cancer diagnosed at clinical, morphological, or other laboratory examinations, as well as cases diagnosed at autopsy. Since 2005, the site and histological type of the cases have been coded in ICD-O-3 codes. A quality study published in Acta Oncologica in 2008 estimated that underreporting was approximately 4%.

9.5.4 Swedish Cause of Death Register

The Swedish Cause of Death Register comprises all deaths among Swedish residents, whether occurring in Sweden or abroad. The causes of death are coded according to the international (English) version of ICD-10. The register is updated yearly. In 1994, the non-reporting rate was 0.45% of all deaths.

9.6 Bias

The main limitation of this study is the lack of data from primary health care. The strategy implemented to overcome the lack of this data source for patient characteristics that may not be well recorded in hospital data (alcohol use, obesity) was to search for these diagnoses in secondary hospital discharge records. Also, prescriptions for drugs to help with these conditions 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 would have missed the mild and moderate cases and those that did not require hospital care.

9.7 Study Size

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

9.8 Data Transformation

Raw data delivered by the National Board of Health and Welfare (NBHW) and Statistics Sweden were transformed into a common data model developed at the Centre for Pharmacoepidemiology, Karolinska Institutet (CPE). Analysis data sets were derived from these data.

In the estimation of OAB medication dose, returned packages were subtracted from the number of dispensed prescriptions (returns were entered into the system as a negative number of packages). Pills were assumed to be taken once daily; two transdermal patches were assumed to be consumed every 7 days; and for instillation, 30 mL/day was the assumed consumption.

9.9 Statistical Methods

All data management and analysis was performed in SAS software, version 9.4 [redacted] at the CPE.

The data analysis included the following activities:

- Characterization of new users of OAB medications according to baseline covariates.
- Description of drug-use patterns (e.g., discontinuation and switching between antimuscarinic drugs).
- Estimation of the incidence rate of four different cardiovascular endpoints plus all-cause mortality during periods of OAB treatment among new users of individual OAB medications. Subgroup analyses targeted the population aged 65 years or older and individuals with high cardiovascular risk.
- Estimation of the adjusted incidence rate ratio of four different cardiovascular endpoints plus all-cause mortality of each of the OAB medications compared with the most prevalent OAB medication in the Prescribed Drug Register (tolterodine).
- Estimation of the incidence rate of the overall composite cancer endpoint and the two sex-specific composite cancer endpoints following initiation of OAB treatment for new users (ever use).
- Estimation of the incidence rate of the overall composite cancer endpoint and the two sex-specific composite cancer endpoints following initiation of OAB treatment among new users of darifenacin, fesoterodine, oxybutynin, solifenacin, and tolterodine while they were not exposed to other OAB medications (that is, exposed to a single OAB).
- Description of completeness and distribution of a range of potential confounders for cardiovascular and cancer endpoints.

9.9.1 Main Summary Measures

Continuous variables, such as age, were summarized with the mean and standard deviation (SD), while categorical variables, such as education or hypertension, were summarized with number and percentage. We calculated the crude and age-sex–standardized incidence rate (SIR) of cardiovascular and cancer endpoints and incidence rate ratios (IRRs) for cardiovascular endpoints. The reference for standardization was the distribution of years of follow-up in the study population.

9.9.2 Main Statistical Methods

9.9.2.1 Drug Utilization Study

First, data were cleaned by subtracting returns from total dispensings. Then, all incident dispensings within the study period were identified, and the first eligible dispensing of each drug for each patient was set as the index dispensing (allowing up to five index dates per patient, one for each study OAB medication, up to five OAB medications).

Drug Episodes

Within each patient-drug combination, adjacent, nonoverlapping drug episodes covering the whole time period from the index date until the end of follow-up were established. Each drug episode was denoted current, recent, or past. The drug episodes were constructed as described below.

For all dispensings, starting at the index dispensing and ending at the last dispensing before end of follow-up, duration was set to number of pills or 7*(number of patches)/2 or (total amount)/30 mL, depending on route of administration. Durations longer than 14 days were extended by 7 days to allow for nonadherence. For durations of 14 days or less (prepackaged dosing), no such grace period was added.

Each dispensing of another OAB medication during current use was classified as an add-on or a switch. Add-ons were defined as the new drug dispensed within 7 days of the ongoing dispensing or the duration of the new dispensing ending before the current duration. All other dispensings of another OAB medication during current use were classified as switches. Dispensing of the same OAB medication during current use cut the ongoing exposure short and started the new exposure.

All use starting at dispensing and ending at duration plus grace period was denoted as current use. Gaps of 60 days or less between end of current use and the next dispensing of the same OAB medication were denoted as recent use. Time periods following recent use without new dispensing of the same OAB medication were denoted past use.

Therapy Episodes

Within each patient, adjacent nonoverlapping therapy episodes covering the whole time period from the first index date until the end of follow-up were established. Each therapy episode was characterized as single or multiple use. Therapy episodes were constructed using the drug episodes described above.

Within each patient-drug pair, continuous use was defined as time periods covered by current and recent use (i.e., with an allowable maximum gap of 60 days). Time not covered by continuous use was set as unexposed.

At each add-on, as defined above, the ATC code of the added drug (or drugs in case of dispensing of more than one drug on the same date) was recorded. At add-ons to a single continuous exposure, the exposure type changed from single to multiple, whereas the exposure type stayed multiple at add-ons to ongoing multiple use.

At each switch as defined above, the ongoing exposure was cut short and the new exposure started and was assigned to the drug (or drugs in case of dispensing of more than one drug on the same date) switched to.

Patterns of Drug Use

Baseline characteristics of the study population at the time of cohort entry, overall and by drug of index prescription, were summarized, including demographic information and data on cardiovascular and cancer risk factors, comorbidities, use of other medications, and

health care resource utilization. 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.

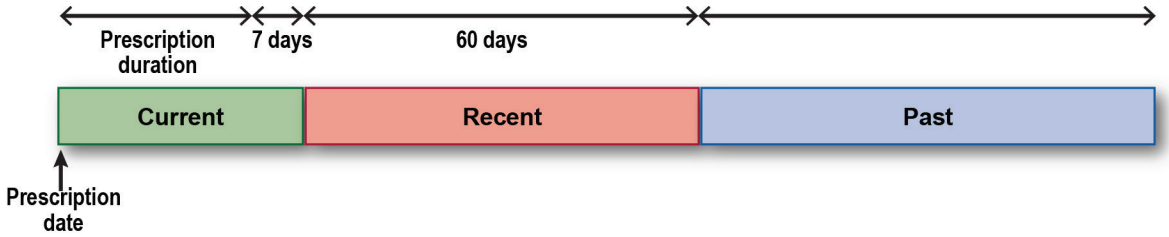
9.9.2.2 Cardiovascular Study

Time at Risk and Exposure Classification

In the cardiovascular study, we were mostly interested in current exposure to individual drugs, with the assumption 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 (Figure 1):

- *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.

Figure 1. Recency of Exposure



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 as they changed treatment.

Statistical Analysis in the Cardiovascular Study

Descriptive Analysis

We showed baseline characteristics of the study population at the time of cohort entry stratified by whether they experienced AMI, stroke, cardiovascular mortality, or the

composite cardiovascular endpoint, along with results of a separate analysis of all-cause death.

Incidence Rates: Crude and Standardized

Person-time accumulated separately for each endpoint, delimiting five different person-time populations: AMI, stroke, cardiovascular mortality, the composite endpoint (any of these individual endpoints), and all-cause mortality.

For each endpoint, we reported event count, person-years, crude and age-sex–standardized incidence rates (SIRs) with 95% confidence intervals (CIs). We also reported incidence rates for each exposure category.

Increased cardiovascular risk was defined by the presence of one or more of the diagnoses in the first group or two or more of the second group of diagnoses at baseline

One or more of the following:

- Diabetes (diagnostic codes or medications)
- Prior history of AMI
- Prior history of stroke
- Prior history of heart failure
- Peripheral arterial disease (PAD)
- Coronary heart disease (CHD)
- Transient ischemic attack (TIA)

Two or more of the following

- Current smoking (diagnoses or medications)
- Dyslipidemia (diagnoses or medications)
- Hypertension (diagnoses or medications)

All incidence rates and 95% CIs were calculated per 1,000 person-years, using Byar's formula for confidence limits.[21]

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: Standardized and Adjusted

We used Cox regression models to compare patients in each of the exposure-endpoint combinations; separate models were constructed to explore, for example, the association of current use of solifenacin relative to current use of tolterodine for the endpoint stroke, and the association of current use of darifenacin relative to current use of tolterodine for the same endpoint. This allowed the covariates in each model to take different coefficients and thus better address confounding for each exposure-endpoint association. For this analysis,

we focused on current and recent use. Hazard ratios can be thought of as incidence rate ratios.[22] For simplicity, given that other results presented in this report are incidence rate ratios and to be consistent with other parts of this research program, we will use the term "incidence rate ratio" in all instances.

To compare the risk of cardiovascular endpoints 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 overall distribution of person-time in the study population.

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.

Covariates considered for adjustment were organ transplant, PAD, polycystic ovarian syndrome, renal impairment, renal disease, sigmoidoscopies, TIA, age, alcohol abuse, AMI, antiplatelet use, arthritis, cancer, cerebrovascular disease, cohort entry year, CHD, dementia, diabetes, diabetes with complications, diabetes without complications, dialysis, digoxin use, drug abuse, dyslipidemia, education, endometriosis, fractures, gout, heart failure, HIV, hormone replacement therapy, hypertension, immunosuppressive treatment, income, low-dose aspirin, mammograms, metastases, mild liver disease, moderate liver disease, use of nitrates, NSAID use, number of OAB medications during follow-up, number of hospitalizations, number of outpatient visits, number of OAB medications before the index date, OAB diagnosis, obesity, para-/hemiplegia, peptic ulcer disease, pulmonary disease, peripheral vascular disease, rheumatic disease, sex, smoking, statin use, stroke, tamoxifen use, use of thyroid hormone.

Covariates to include in the Cox regression models were selected by first constructing individual Cox regression models for each covariate and the exposure variable (current OAB medication exposure) for each endpoint. Then, for each endpoint, the effect (if any) of each individual covariate on the effect estimate (IRR) of current OAB medication exposure compared with tolterodine was measured. The selection of candidate confounders or effect modifiers to be included in the adjusted models were based on results of the univariate regression models for each of the covariates. The selection of variables for regression models was based on the change-in-estimate criterion for any OAB medication relative to tolterodine, comparing adjusted to crude estimates and looking for changes in the point estimate of at least 5%. A covariate that modified the adjusted IRR relative to the crude IRR for an endpoint for any of the OAB medications compared to tolterodine in the univariate analysis by 5% or more was included in the adjusted model for that endpoint in the full cohort analysis and all subgroup analyses. Age and sex were included in all models regardless of change-in-estimate effect.

We estimated risks for current and recent drug use. Models were repeated with reference to use of any OAB medication (e.g., for analysis of 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).

Propensity Score Analysis

For each comparison, e.g., current use of darifenacin versus tolterodine, a multiple logistic regression model was established that had use of darifenacin (i.e., the nontolterodine OAB medication) as the dependent variable. The independent variables included in the model were all the baseline characteristics listed in Analysis Table A3.

A new model was established for each pairwise comparison of OAB medications, but the same propensity score model was applied for all endpoints (AMI, stroke, 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, 10 different propensity score models were constructed representing exposure propensity at cohort entry (five 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. In brief, two propensity score limits were set, corresponding to the 2.5th percentile of propensity scores for those exposed to tolterodine and the 97.5th percentile for those unexposed to tolterodine (nontolterodine). All patients with propensity scores outside the range established by these two limits, whether exposed or unexposed, were 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

We calculated incidence rates for the following strata:

- Females
- Males
- Patients aged 65 or more years
- Patients with increased risk for cardiovascular disease
- Females aged 65 or more years
- Females with increased risk for cardiovascular disease
- Males aged 65 or more years
- Males with increased risk for cardiovascular disease

9.9.3 Missing Values

The issue of missing values is generally a limited problem in the National Swedish health care registers since missing information is rare on key variables such as cancer and prescribed drugs. Age and sex are never missing since these are derived from the unique personal identifier. As a register-based study, if a patient does not have a diagnosis or drug code recorded, it is assumed that patient does not have the disease or drug use, and no missing values are involved. A very small fraction of dates are imprecise, with only year or year and month given. Imprecise dates were imputed.

We also noted underrecording of smoking and other lifestyle variables. Although we used proxies (e.g., medication use) to capture information as completely as the source allowed, residual confounding may be a concern due to missing data.

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

Not applicable.

9.10 Quality Control

Routine procedures included checking electronic files, maintaining security and data confidentiality, following statistical analysis plans, and performing quality-control checks of all programs.

Security processes were in place to ensure the safety of all systems and data and that data could not be accessed by anyone except selected study staff.

Appropriate data storage and archiving procedures were followed, with periodic backup of files to tape. Standard procedures to restore files in the event of a hardware or software failure were in place.

CPE conducted quality control for data management and statistical analysis by following its internal guideline, [redacted] The guideline covers verification of data sets delivered from the National Board of Health and Welfare and from Statistics Sweden, checks of inclusion and exclusion criteria when preparing the analysis data set, and plausibility and consistency checks of output. All programs were checked and issues resolved. Senior team members from CPE and RTI Health Solutions conducted the final quality control for the deliverables. The programs, data sets, logs, and lists associated with this study, as well as all study deliverables, have been archived by CPE.

10 Results

10.1 Participants

10.1.1 Study Population

The study population included of 130,944 patients aged 18 years or older with a first dispensing of darifenacin, fesoterodine, oxybutynin, solifenacin, or tolterodine between July 1, 2006, and December 31, 2012, without history of cancer or HIV at the time of cohort entry.

10.2 Descriptive Data

The mean (SD) age at cohort entry was 66 (15.3) years, and 58% were aged 65 years or older (Table 2 and Analysis Table A1). Females comprised 60% of the cohort. The mean duration of enrollment prior to cohort entry was 4 years; duration of enrollment was less than 2 years for 20% of the population, 2 to 4 years for 33% of the population, and 4 or more years (up to 8 years) for 47% of the population.

Of the patients in the population, 48% had hypertension, 24% had dyslipidemia, 5% had a history of AMI, 6% had a history of stroke, 1.3% had a history of transient ischemic attack; 10% had a history of coronary heart disease, and 3.7% had a history of heart failure. Overall, 53% had no hospitalizations the year before cohort entry, and 64% had fewer than five outpatient visits in the same period. At cohort entry, based on hospitalizations and visits to hospital outpatient clinics, about 18% of study patients had a recorded diagnosis of OAB.

At cohort entry, 42% of the patients were newly exposed to tolterodine, 36% to solifenacin, and 10% to fesoterodine (Analysis Table A2). Less than 7% were newly exposed at cohort entry to darifenacin, and only 4% were exposed to oxybutynin.

Characteristics of the patients by OAB medication at study cohort entry are shown in Analysis Table A3. All medications were available during the entire study period except fesoterodine, which was first available in 2008. The percentage of use of darifenacin and tolterodine was lower in 2010-2012 than in 2006-2007, while the opposite was true for the other medications.

Oxybutynin users were younger and generally healthier at cohort entry than the users of the other study medications: mean age 55 years, 63% females, less cardiovascular disease, and fewer hospitalizations and outpatient visits the year before cohort entry. The profile of users of the other individual study drugs—darifenacin, fesoterodine, solifenacin, and tolterodine—was more homogeneous, with mean age 65-68 years, prevalence of female sex 60%-64% (except tolterodine, 55%), prevalence of hypertension (47%-49%) and prevalence of dyslipidemias (24%-27%). The prevalence of cardiovascular conditions at cohort entry was also quite homogeneous across drugs: 3%-4% had heart failure, 5%-7% stroke, 4%-5% had had AMI, and 7%-11% had coronary heart disease.

At cohort entry, recorded history of OAB ranged from 11% (tolterodine) to 24% (fesoterodine), with 15% for oxybutynin.

Table 2. Characteristics of Exposed Patients, Overall and by Overactive Bladder Drug at Study Cohort Entry

	All patients (n = 130,944)		Darifenacin (n = 9,093)		Fesoterodine (n = 13,536)		Oxybutynin (n = 5,420)		Solifenacin (n = 47,313)		Tolterodine (n = 55,510)	
Variable	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Age at cohort entry (years)												
18-24	2,170	1.7	91	1.0	205	1.5	559	10.3	618	1.3	697	1.3
25-34	3,813	2.9	198	2.2	358	2.6	636	11.7	1,282	2.7	1,335	2.4
35-44	7,349	5.6	420	4.6	731	5.4	572	10.6	2,815	5.9	2,806	5.1
45-54	14,361	11.0	943	10.4	1,535	11.3	692	12.8	5,588	11.8	5,595	10.1
55-64	26,975	20.6	1,954	21.5	2,964	21.9	878	16.2	10,266	21.7	10,895	19.6
65-74	35,924	27.4	2,544	28.0	4,124	30.5	1,061	19.6	13,414	28.4	14,762	26.6
75-84	29,438	22.5	2,194	24.1	2,872	21.2	782	14.4	9,956	21.0	13,620	24.5
85+	10,914	8.3	749	8.2	747	5.5	240	4.4	3,374	7.1	5,800	10.4
Mean (SD)	66	(15.3)	67	(14.2)	65	(14.5)	55	(20.2)	65	(14.8)	68	(15.1)
Female sex	77,992	59.6	5,748	63.2	8,075	59.7	3,409	62.9	30,457	64.4	30,259	54.5
Calendar year at cohort entry												
2006	13,223	10.1	1,441	15.8	0	0	761	14.0	2,996	6.3	8,010	14.4
2007	24,173	18.5	2,763	30.4	0	0	908	16.8	6,615	14.0	13,872	25.0
2008	21,860	16.7	1,766	19.4	841	6.2	501	9.2	7,440	15.7	11,303	20.4
2009	18,942	14.5	710	7.8	3,140	23.2	486	9.0	6,656	14.1	7,942	14.3
2010	18,289	14.0	937	10.3	3,155	23.3	740	13.7	7,423	15.7	6,028	10.9
2011	17,839	13.6	856	9.4	3,314	24.5	858	15.8	7,989	16.9	4,814	8.7
2012	16,618	12.7	620	6.8	3,086	22.8	1,166	21.5	8,194	17.3	3,541	6.4
Duration of enrollment prior to cohort entry												
< 2 years	25,986	19.8	3,134	34.5	0	0.0	1,329	24.5	6,253	13.2	15,245	27.5
2-4 years	43,277	33.1	3,266	35.9	2,501	18.5	1,086	20.0	14,176	30.0	22,229	40.0
4-8 years	61,681	47.1	2,693	29.6	11,035	81.5	3,005	55.4	26,884	56.8	18,036	32.5

	All patients		Darifenacin		Fesoterodine		Oxybutynin		Solifenacin		Tolterodine	
Hypertension	62,492	47.7	4,331	47.6	6,448	47.6	1,905	35.1	22,385	47.3	27,391	49.3
Dyslipidemia	31,900	24.4	2,228	24.5	3,647	26.9	937	17.3	11,691	24.7	13,380	24.1
History of acute myocardial infarction	5,867	4.5	448	4.9	617	4.6	163	3.0	1,949	4.1	2,689	4.8
History of stroke	7,445	5.7	563	6.2	724	5.3	159	2.9	2,322	4.9	3,673	6.6
History of transient ischemic attack	1,733	1.3	153	1.7	217	1.6	31	0.6	602	1.3	729	1.3
History of coronary heart disease	12,699	9.7	995	10.9	1,326	9.8	367	6.8	4,270	9.0	5,734	10.3
History of heart failure	4,850	3.7	366	4.0	480	3.5	109	2.0	1,576	3.3	2,315	4.2
Diagnosis of overactive bladder	23,210	17.7	2,105	23.1	3,214	23.7	816	15.1	10,870	23.0	6,190	11.2

SD = standard deviation.

Note: Patients who entered the cohort on more than one study medication (n = 72) are included in the column for all patients, but not in other columns.

Source: Analysis Tables A1 and A3.

10.3 Outcome Data

Outcome data for the cardiovascular and cancer endpoints 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 130,944 index therapy episodes (one per patient), of which 72 were for more than one OAB medication. Of the 130,872 index episodes for individual study drugs, 42% were for tolterodine, 36% for solifenacin, 10% for fesoterodine, 7% for darifenacin, and 4% for oxybutynin. The mean duration of completed episodes ranged from 6 months (fesoterodine) to 8 months (darifenacin, solifenacin, and tolterodine) (Analysis Table A8). Overall, 11.6% of the index therapy episodes were ongoing at the end of the study period, with mean duration between 10 months (oxybutynin) and 21 months (tolterodine). Of completed and ongoing index therapy episodes, 37% lasted 1 to 3 months, 29% lasted 4 to 6 months, and 24% lasted more than 9 months. Overall, 52% of the episodes consisted of one prescription. For index therapy episodes with individual drugs, there was no prior recorded exposure to other study drugs in 77% (darifenacin) to 90% (tolterodine) of episodes. Next, the most common prior recorded exposure was to more than one study drug. For all individual drugs except tolterodine, tolterodine was the most common previous exposure.

10.4.1.2 All Therapy Episodes

There were 240,141 therapy episodes during follow-up: 37% with tolterodine, 35% with solifenacin, 13% with fesoterodine, 8% with darifenacin, 5% with oxybutynin, and 3% with more than one drug (Analysis Table A9). Each subject had, on average, 1.8 therapy episodes during the study period.

Of all completed therapy episodes, 83% finished a therapy episode because the prescription was not renewed or refilled, 14% ended with a medication switch, and 3% ended with a medication add-on. The most common drug switched to or added was solifenacin. For solifenacin therapy episodes, the most common drug switched to or added was tolterodine.

10.4.1.3 Prescriptions and Route of Administration

In general, subjects had dispensings for a single strength of tablets, commonly the lowest strength available. Of subjects who had dispensings of darifenacin, 79% had dispensings only for 7.5-mg tablets (available in 7.5 and 15 mg) (Analysis Table A10). Similarly, for subjects with dispensings for fesoterodine, 76% had dispensings only for 4-mg tablets (available in 4 and 8 mg). Oxybutynin was available in patches (3.9 mg/24 hours), solutions

with different concentrations, and tablets (5 mg); 53% of subjects with oxybutynin dispensings had dispensings for tablets only and 42% for patches only. For solifenacin, 82% of patients had dispensings only for 5-mg tablets (available in 5 and 10 mg). For tolterodine, 46% of subjects had dispensings only for 4-mg tablets and 37% for only 2-mg tablets (available in 1, 2, and 4 mg).

Of 5,420 patients with an index therapy episode for oxybutynin, 4% entered the cohort with an index therapy episode for intravesical oxybutynin, with a mean age of 56 years and 56% females. Other characteristics are shown in Analysis Table CV3(2).

10.4.2 Cardiovascular Results

Of the 130,944 subjects in the study, 4% had an AMI, 5% had a stroke, 3% died of cardiovascular causes, 8% experienced a MACE, and 8% died of any cause (Analysis Table CV1).

Of the study population without cardiovascular endpoints, 54% was aged 65 years or older and 61% was female. Patients with cardiovascular endpoints were older and included a larger proportion of males. Patients who developed cardiovascular events during follow-up were sicker at baseline than patients who remained event-free.

10.4.2.1 Incidence Rates

The crude and age-sex–standardized incidence rates of the cardiovascular endpoints for current exposure to the study drugs are summarized in Analysis Table CV3, and the same rates, for recent exposure to the study drugs, are summarized in Analysis Table CV4. The population for standardization was the study population person-time. Strata for stratified analyses include age over 65 years, female and male sex, high baseline cardiovascular risk, and combinations of these variables. Within each stratum of current use, the highest incident rates were generally among users of tolterodine; in some cases, among users of darifenacin. In general, crude and standardized incidence rates were similar, with the exception of oxybutynin and darifenacin, the standardized incidence rates of which were higher in some analyses. In the paragraphs below, we report SIRs (95% CI) per 1,000 person-years.

For AMI (Analysis Tables CV3 and CV4), the SIR was 11.4 (10.8-12.0) for current use of any OAB medication and 13.7 (12.5-14.9) for recent use. Of the three most commonly used OAB medications—tolterodine, solifenacin and fesoterodine—the SIR for current use was lowest for fesoterodine, 8.2 (6.6-9.8), and greatest for tolterodine, 13.3 (12.3-14.3). For recent use, the ranking was the same, but SIRs were higher. In patients with high cardiovascular risk, the SIR for current use of any OAB medication, 21.3 (19.9-22.8), was higher than in the overall cohort. SIRs in males and in patients over 65 years old were higher than in the overall cohort.

For stroke (Analysis Tables CV3 and CV4), the SIR for any OAB medication was 18.7 (17.9-19.5) for current use and 17.2 (15.8-18.6) for recent use. Of the three most commonly used OAB medications—tolterodine, solifenacin and fesoterodine—the SIR for current use was lowest for solifenacin, 16.9 (15.6-18.1), and greatest for tolterodine, 21.0 (19.7-22.3).

The SIR for current use of any OAB medication among patients with high cardiovascular risk was approximately double that in the overall cohort and was also higher in males and patients aged over 65 years than in the overall cohort. SIRs for stroke were higher than for AMI.

For cardiovascular mortality, the SIR for any OAB medication was 6.4 (5.9-6.8) for current use and 8.7 (7.7-9.7) for recent use. Among the three most commonly used OAB medications—tolterodine, solifenacin and fesoterodine—the SIR for current use was lowest of fesoterodine, 4.2 (3.0-5.4), and greatest for tolterodine, 7.8 (7.0-8.5). Among patients with high cardiovascular risk, the SIR was approximately twice that in the cohort overall. SIRs in males and patients aged older than 65 years were also higher than in the overall population.

We included the composite endpoint MACE for consideration in case the effect of OAB medications was homogeneous on the components of MACE (Analysis Tables CV3 and CV4). The SIR for any OAB medication was 29.2 (28.2-30.1) for current use and 29.1 (27.3-30.9) for recent use. Among the three most commonly used OAB medications—tolterodine, solifenacin and fesoterodine—the SIR for current use was lowest for fesoterodine, 25.0 (22.2-27.7), and greatest for tolterodine, 33.0 (31.4-34.6). Among patients with high cardiovascular risk, the SIR was approximately twice that in the cohort overall. SIRs in males and patients aged older than 65 years were also higher.

For all-cause mortality (Analysis Tables CV3 and CV4), the SIR for any OAB medication was 17.9 (17.1-18.7) for current use and 24.9 (23.3-26.5) for recent use. Among the three most commonly used OAB medications—tolterodine, solifenacin and fesoterodine—the SIR for current use was lowest for fesoterodine, 12.4 (10.4-14.4), and greatest for tolterodine, 21.4 (20.1-22.6). The SIR for current use of any OAB medication among patients with high cardiovascular risk was 31.5 (29.7-33.2), higher in males and in patients aged over 65 years than the cohort overall.

Results on cumulative dose, duration of use, and time since first exposure for the three most commonly used OAB medications—tolterodine, solifenacin and fesoterodine—for AMI seem to be approximate stable [Analysis Table CV3(2)]. For stroke, the SIRs are highest in the first quartile and then decrease. For cardiovascular mortality, there is no clear pattern, but there is a tendency toward increasing SIRs over increasing cumulative measurements. For MACE, SIRs are also highest in the first quartile and decrease thereafter. For all-cause mortality, SIRs generally increased over cumulative measurements. Overall, no consistent pattern was identified.

Based on these results, among users of the three most common drugs—tolterodine, solifenacin and fesoterodine—current use of fesoterodine seems to generally have the lowest incidence rate for cardiovascular endpoints and current use of tolterodine the highest.

10.4.2.2 Age-and-Sex-Standardized Incidence Rate Ratios

Age-sex–standardized incidence rate ratios for current exposure with reference to tolterodine are shown in Analysis Table CV5a. Similar results for recent exposure are shown in Analysis Table CV5b. The standard was the study population person-time. For AMI and

current exposure to OAB medications, standardized IRRs were generally a little under the null, suggesting risks slightly lower than tolterodine's. Worth mentioning are the results for fesoterodine, with a standardized IRR consistently between 0.6 and 0.7, and upper bound of the 95% CI around 0.8 in most strata. In women, solifenacin also seemed to be associated with a lower incidence rate of AMI than tolterodine. Standardized IRRs were more unstable for oxybutynin and had lower precision. This was also true for recent exposure. For stroke and current or recent exposure to OAB medications, standardized IRRs were slightly below or around the null in most cases, but solifenacin and oxybutynin seemed to have lower IRRs than other medications and were lower than the null. Findings for cardiovascular mortality, MACE, and all-cause mortality were similar, with most standardized IRRs slightly below the null; fesoterodine and solifenacin seemed to be generally protective, and oxybutynin had less precise estimates.

Based on these results, solifenacin seemed to have a lower risk for all studied endpoints than tolterodine. Effects of other drugs varied across endpoints, but most point estimates suggested risk for other drugs might also be lower than tolterodine's.

10.4.2.3 Incidence Rate Ratios From Propensity Score Analyses

Incidence rate ratios from propensity score analyses for current exposure, with current use of tolterodine as the reference, were below 1, except for current use of darifenacin for all-cause mortality (IRR, 1.04; 95% CI, 0.88-1.23; Table 3); IRRs for current use of individual drugs were between 0.69 and 0.96. Fesoterodine was the individual drug with the lowest point estimates, and darifenacin the highest.

Based on propensity score analyses, current use of the combined OAB medications except tolterodine was associated with lower risk for all endpoints than current use of tolterodine. Among the individual drugs, fesoterodine had the lowest IRRs and darifenacin the highest.

Table 3. Incidence Rate Ratios for Cardiovascular Endpoints From Propensity Score Analysis

Endpoint and Current Exposure	IRR	95% CI
Acute myocardial infarction		
Tolterodine	Ref.	
Any OAB medication (except tolterodine)	0.80	(0.71-0.90)
Darifenacin	0.96	(0.77-1.19)
Fesoterodine	0.72	(0.56-0.92)
Oxybutynin	0.79	(0.53-1.19)
Solifenacin	0.84	(0.73-0.96)

Endpoint and Current Exposure	IRR	95% CI
Stroke		
Tolterodine	Ref.	
Any OAB medication (except tolterodine)	0.87	(0.80-0.96)
Darifenacin	0.94	(0.79-1.12)
Fesoterodine	0.87	(0.73-1.03)
Oxybutynin	0.87	(0.65-1.16)
Solifenacin	0.88	(0.79-0.98)
Cardiovascular mortality		
Tolterodine	Ref.	
Any OAB medication (except tolterodine)	0.83	(0.70-0.98)
Darifenacin	0.96	(0.71-1.28)
Fesoterodine	0.69	(0.48-0.99)
Oxybutynin	0.79	(0.43-1.45)
Solifenacin	0.84	(0.69-1.01)
MACE		
Tolterodine	Ref.	
Any OAB medication (except tolterodine)	0.86	(0.79-0.92)
Darifenacin	0.96	(0.83-1.10)
Fesoterodine	0.82	(0.71-0.94)
Oxybutynin	0.85	(0.67-1.08)
Solifenacin	0.87	(0.80-0.95)
All-cause mortality		
Tolterodine	Ref.	
Any OAB medication (except tolterodine)	0.83	(0.75-0.92)
Darifenacin	1.04	(0.88-1.23)
Fesoterodine	0.73	(0.60-0.90)
Oxybutynin	0.90	(0.64-1.25)
Solifenacin	0.85	(0.76-0.95)

10.4.2.4 Comparison of Results From Various Analyses

Increasing analytical complexity resulted in point estimates closer to the null, likely representing better control of confounding. Crude point estimates are farther from the null than age-sex adjusted point estimates, which are in turn farther from the null than point estimates from multivariate analysis and from propensity score-analyses. For this reason, we prefer to focus on results from propensity score analysis as this analysis had the most adjustment and likely the most control of confounding.

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 person-time in the Swedish 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

A total of 5,653 occurrences of the overall composite endpoint were identified (4.3% of the study population). Additionally, 3,242 nonstudy first cancer events were noted (Table 4 and Analysis Table N1). While 40% of patients who did not develop cancer were males, 55% of those who did develop cancer were males. Patients who developed cancer were older at cohort entry (mean [SD], 71 [10.2] years) than those who did not (mean [SD], 66 [15.5] years). The health profile of patients who developed a composite cancer endpoint and those who did not develop cancer was generally similar.

Prostate, breast, and colorectal cancer were the three most common cancers, contributing 27%, 17% and 16%, respectively, of the 5,653 cases.

Table 4. Standardized Incidence Rates for Cancer for Ever Exposure to Any Overactive Bladder Drug

	Events	Individuals Contributing Person-time	Person-time (Years)	Standardized Incidence Rate[a]	(95% CI)	
Composite cancer endpoint						
Any OAB medication	5,653	130,944	417,795	13.52	13.17	13.88
Darifenacin	606	12,335	45,153	13.57	12.48	14.66
Fesoterodine	598	21,922	45,193	13.26	12.19	14.33
Oxybutynin	273	8,142	23,686	14.14	12.41	15.88
Solifenacin	2,177	57,112	159,876	14.08	13.49	14.68
Tolterodine	2,996	59,805	215,270	13.37	12.89	13.85

	Events	Individuals Contributing Person-time	Person-time (Years)	Standardized Incidence Rate[a]	(95% CI)	
Composite cancer endpoint (females)						
Any OAB medication	2,532	77,992	256,053	9.96	9.57	10.35
Darifenacin	323	7,894	30,547	10.43	9.29	11.57
Fesoterodine	277	13,674	29,187	9.42	8.30	10.53
Oxybutynin	154	5,327	16,330	10.27	8.63	11.91
Solifenacin	1,078	36,948	105,737	10.30	9.68	10.92
Tolterodine	1,225	33,076	122,874	9.90	9.35	10.46
Composite cancer endpoint (males)						
Any OAB medication	3,121	52,952	161,742	19.41	18.72	20.09
Darifenacin	283	4,441	14,606	18.75	16.56	20.94
Fesoterodine	321	8,248	16,005	19.61	17.45	21.77
Oxybutynin	119	2,815	7,356	20.55	16.82	24.27
Solifenacin	1,099	20,164	54,139	20.33	19.13	21.53
Tolterodine	1,771	26,729	92,396	19.10	18.21	19.99
Prostate cancer (males)						
Any OAB medication	1,530	52,952	161,742	9.50	9.03	9.98
Darifenacin	140	4,441	14,606	9.31	7.77	10.86
Fesoterodine	160	8,248	16,005	9.74	8.22	11.26
Oxybutynin	50	2,815	7,356	8.57	6.17	10.97
Solifenacin	557	20,164	54,139	10.24	9.39	11.09
Tolterodine	850	26,729	92,396	9.18	8.56	9.80
Breast cancer (females)						
Any OAB medication	961	77,992	256,053	3.77	3.53	4.01
Darifenacin	125	7,894	30,547	4.01	3.30	4.71
Fesoterodine	99	13,674	29,187	3.40	2.72	4.07
Oxybutynin	55	5,327	16,330	3.61	2.65	4.57
Solifenacin	424	36,948	105,737	4.01	3.63	4.39
Tolterodine	455	33,076	122,874	3.72	3.38	4.06

	Events	Individuals Contributing Person-time	Person-time (Years)	Standardized Incidence Rate[a]	(95% CI)	
Colorectal cancer						
Any OAB medication	888	130,944	417,795	2.14	2.00	2.28
Darifenacin	107	12,335	45,153	2.34	1.89	2.78
Fesoterodine	73	21,922	45,193	1.61	1.24	1.99
Oxybutynin	47	8,142	23,686	2.39	1.69	3.09
Solifenacin	322	57,112	159,876	2.08	1.85	2.31
Tolterodine	487	59,805	215,270	2.20	2.00	2.39
Colorectal cancer (females)						
Any OAB medication	459	77,992	256,053	1.81	1.65	1.98
Darifenacin	66	7,894	30,547	2.13	1.61	2.64
Fesoterodine	39	13,674	29,187	1.33	0.91	1.75
Oxybutynin	30	5,327	16,330	2.06	1.32	2.81
Solifenacin	176	36,948	105,737	1.70	1.45	1.95
Tolterodine	240	33,076	122,874	1.91	1.67	2.16
Colorectal cancer (males)						
Any OAB medication	429	52,952	161,742	2.67	2.42	2.93
Darifenacin	41	4,441	14,606	2.68	1.86	3.51
Fesoterodine	34	8,248	16,005	2.07	1.37	2.78
Oxybutynin	17	2,815	7,356	2.93	1.53	4.34
Solifenacin	146	20,164	54,139	2.72	2.27	3.16
Tolterodine	247	26,729	92,396	2.66	2.33	2.99

OAB = overactive bladder.

Source: Analysis Table N3.

[a] Standardized to the sex and age distribution of person-time in the Swedish study population.

10.4.3.2 Cancer Incidence Rates by Ever Exposure to Study OAB Medications

The 5,653 counts of the cancers included in the composite endpoints occurred during 417,795 person-years of follow-up, for a crude incidence rate of 13.5 (13.2-13.9) (Table 4 and Analysis Table N3). The SIR for the composite endpoint combining all medications was 13.5 (13.2-13.9). SIRs in females were lower than in males. For all study drugs combined, the SIR was 10.0 (9.6-10.4) for the composite endpoint in females and 19.4 (18.7-20.1) for the composite endpoint in males. SIRs for the sex-specific composite endpoints were similar across individual drugs.

For prostate cancer, the SIR in males was 9.5 (9.0-10.0) for all drugs combined, and ranged from 8.6 (oxybutynin) to 10.2 (solifenacin). For breast cancer, the SIR in females was 3.8

(3.5-4.0) for the combined study drugs and ranged from 3.4 (fesoterodine) to 4.0 (darifenacin and solifenacin). For colorectal cancer, the SIR was 2.1 (2.0-2.3) for all drugs combined and ranged from 1.6 (fesoterodine) to 2.4 (oxybutynin). For some of the less common cancers, there were larger variations in the SIR by individual drugs (e.g., the SIR for pancreatic cancer in males was 0.2 for darifenacin and 0.8 for oxybutynin, but confidence intervals were relatively wide).

In summary, no drug seemed to carry an increased risk of cancer. SIRs were generally similar across drug-use groups, and the drugs with the maximum and the minimum SIRs varied for the 10 study cancers.

10.4.3.3 Cancer Incidence Rates by Single Exposure to Study OAB Medications

Of 5,653 occurrences of the overall composite cancer event, 5,190 (92%) occurred during 384,096 (92%) person-years of ever exposure to a single drug (Analysis Table N4). The SIR for the overall composite cancer endpoint for the combined study drugs was 13.5 (13.1-13.9). For the combined drugs, the SIR was 9.8 (9.4-10.3) in females and 19.2 (18.5-19.9) in males. These numbers are practically identical to those for the overall person-time. Figures for prostate, breast, and colorectal cancer are also very similar to those found for ever exposure to study medications.

10.4.3.4 Cancer Incidence Rates by Cumulative Dose, Duration of Exposure, and Time From Start of Treatment

Tolterodine, the most commonly used study drug, showed a pattern of monotonically decreasing SIRs over cumulative duration of current exposure and cumulative time since first exposure [Analysis Table N4 (2)]. For cumulative dose, the second quartile showed a small increase relative to the first quartile, and SIRs decreased monotonically thereafter; point estimates from the first to the fourth quartile were 13.4, 14.1, 12.9 and 12.6. The steepest decline was for time since first exposure, reflecting that there are many more cancer cases identified early during therapy than later; point estimates from the first to the fourth quartile were 20.7, 13.5, 12.2 and 12.0.

For solifenacin, the second most commonly used study drug, SIRs also decreased with cumulative dose, duration of current exposure, and time since first exposure, although there was a slight rebound of SIRs in the last quartile for the three measures of cumulative use. Again, the steepest decline was for time since first exposure.

For the third most commonly used study drug, fesoterodine, SIRs also declined over quartiles of cumulative dose, current exposure, and time since first exposure, although not monotonically. The steepest decline was for time since first exposure.

Oxybutynin, the least commonly used drug, showed a different pattern: an initial decrease followed by increasing SIRs at the highest quartile of all three measures.

Incidence rates for the composite endpoint were highest in the first 6 months after the start of treatment and decreased until approximately 2 years after the start of treatment (see figures in Appendix C). Incidence rates were approximately stable thereafter. This effect was driven by bladder and prostate cancer.

Overall, we saw a general decline in the SIRs going from lower to higher cumulative dose. The incidence rate of the composite endpoint (driven by prostate and bladder cancer) was highest shortly after the start of treatment.

10.5 Other Analyses

Not applicable.

10.6 Adverse Events/Adverse Reactions

For studies in which a 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."*[23]

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."*[24]

Module VIII – Post-Authorisation Safety Studies, of the same document echoes this approach.[25] 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 comprised 130,944 patients with 1.8 therapy episodes per patient during the study period. Of all 240,141 therapy episodes, 37% were with tolterodine, 35% with solifenacin, 13% with fesoterodine, 8% with darifenacin, 5% with oxybutynin, and 3% with more than one drug. Trospium was not available in Sweden in this period.

The prevalences of smoking, hypertension, dyslipidemia, and OAB are lower than expected in this population, which we attribute to underrecording of these conditions in hospital discharge records.

In the cardiovascular analysis, of 130,944 patients, 4% had an AMI, 5% had a stroke, 3% died of cardiovascular causes, 8% experienced a MACE, and 8% died of any cause. In general, we observed higher risks with tolterodine than with other study drugs. Increasing analytical complexity resulted in stronger control of confounding, taking the IRRs from propensity score analyses closer to the null than less adjusted analyses. In propensity score analyses, results reflected that current use of tolterodine is associated with higher cardiovascular risks than current use of either solifenacin or fesoterodine. Among nontolterodine study drugs, there was little variation in risk, with fesoterodine generally having the lowest IRRs and darifenacin the highest.

In the cancer analyses, of the 130,944 patients, 4.3% of the study population was diagnosed with 1 of the 10 study cancers. Additionally, 3,242 nonstudy first cancer events were noted. Prostate, breast, and colorectal cancer were the three most common cancers, contributing with 27%, 17%, and 16% of cases, respectively. No study drug seemed to carry an increased risk of cancer. SIRs were generally similar across drug-use groups, and the drugs with the maximum and the minimum SIRs varied for the 10 study cancers. Dose analyses showed that risk was higher with lower cumulative doses, which is consistent with protopathic bias or surveillance bias. Analyses of cancer incidence rates by time since start of treatment showed highest rates in the earliest periods, driven by prostate and bladder cancer and consistent with protopathic or surveillance bias.

11.2 Limitations

One limitation in this study is the lack of primary care data. As a result, information on patient characteristics such as smoking, obesity, and OAB is limited. As a strategy to overcome this, we used proxies when available. Comparing users of one drug to users of another drug or other drugs minimized residual confounding arising from this underascertainment; comparisons to nonusers would be less reliable. Tolterodine is first-line treatment in Sweden, and there may be a healthy user effect influencing the results for this medication, which could be used in a healthier population than other OAB medications.

Information on dispensed prescriptions does not include dose or instructions for use. Thus, duration of exposure was estimated from the total amount of substance in the prescription, as recorded in the Prescribed Drug Register, and the DDD. The DDD is defined by the World Health Organization as the assumed average maintenance dose per day for a drug used for its main indication in adults.[26] However, actual prescribing may not follow DDDs.

We noted that incidence rates for cardiovascular ailments and recent drug exposure were generally higher than incidence rates for current drug use. We speculate that this may be related to treated patients stopping OAB drug treatment when their health declines. If cardiovascular events take place then, this would be captured as increased risk in the period of recent exposure, in agreement with our observation.

In cancer analysis, we estimated incidence rates and did not estimate measures of association. We acknowledge that comparisons of the risk of one drug relative to another are limited in this setting. However, given that the profile of users of the different drugs are not too divergent, especially for the most commonly used drugs—tolterodine, solifenacin, and fesoterodine—an informal comparison of age-and-sex-standardized incidence rates should provide an approximate indication of relative risks.

Use of the Swedish registries is a strength of this study because these data sources have complete population coverage in the country and have been found to be valid in several validation studies.

11.3 Interpretation

In this cohort of 130,944 patients with prescriptions for drugs to treat OAB in 2006 to 2012, the mean age at cohort entry was 66 years, and 60% were women. Of 240,141 therapy episodes during the study period, 37% were with tolterodine, 35% with solifenacin, 13% with fesoterodine, 8% with darifenacin, 5% with oxybutynin, and 3% with more than one drug.

Results from propensity score analyses reflected that current use of tolterodine is associated with higher cardiovascular risks than current use of either solifenacin or fesoterodine. Among nontolterodine study drugs, there was little variation in risk.

None of the study drugs seemed to carry an increased risk of cancer. SIRs were generally similar across drug-use groups, and the drugs with the maximum and the minimum SIRs varied for the 10 study cancers. Dose analyses and analyses on time since start of treatment showed that risk was higher with lower doses and during early treatment, driven by prostate and bladder cancer, which is consistent with protopathic bias or surveillance bias.

11.4 Generalizability

Generalizations from these findings depend on the category of the finding.[27,28] Findings that relate to drug utilization and patient characterization apply to the patient population in Sweden. Relative risks of events among patients using OAB medications should be generalizable to all patients using these medications, apart from the effect of any residual confounding and any as-yet-unidentified biological mediators.

12 Other Information

Not applicable.

13 Conclusion

In this cohort of 130,944 patients aged 18 years or older with at least one prescription for an OAB medication, 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 with a lag time before clinical manifestation, the ability to detect an event will depend on the length of drug use and follow-up for each individual OAB medication.

Current use of tolterodine was associated with higher risk for targeted cardiovascular events than current use of either solifenacin or fesoterodine.

Among the study drugs, none seemed to carry an increased risk of cancer. Analyses showed that risk was higher with lower cumulative doses and during early treatment, driven by prostate and bladder cancers, which is consistent with protopathic bias or surveillance bias.

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15 Appendix A: Validation Studies Conducted in the Swedish National Registers

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Table A-1. Acute Myocardial Infarction

Reference (AMI)	Study Period Endpoint	Inclusion Criteria and Population	Exclusion Criteria	Positive Predictive Value
Hammar N, Alfredsson L, Rosén M, Spetz CL, Kahan T, Ysberg AS. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. Int J Epidemiol. 2001 Oct;30 Suppl 1:S30-4	1987, 1995 AMI	▪ Study base: a national sample of hospital-treated patients, age 30-89 years, discharged between 1987 and 1995 ▪ Incident cases of AMI by record linkage of national hospital discharges and deaths ▪ 2,065 patients with AMI or other ischemic heart disease ▪ 1,848 patients (713 with AMI; ICD-9 410, and 1,135 with other ischemic heart disease; ICD-9 411-414) with medical records	▪ Recurrent event in the same subject within 28 days	PPV (ICD-9 410): 86% (612 of 713) Sensitivity (ICD-9 410): 94% NPV (ICD-9 411-414): 97% (1,098 of 1,135) PPV (ICD-9 411-414); 3% (37 of 1,135)
Linnersjö A, Hammar N, Gustavsson A, Reuterwall C. Recent time trends in acute myocardial infarction in Stockholm, Sweden. Int J Cardiol. 2000 Oct;76(1):17-21.	1992–1994 AMI	▪ Study base: aged 30-89 years in 1984–1996 in Stockholm County ▪ Evaluated: all first AMI cases that occurred in those aged 45–70 years during1992–1994 ▪ 2,403 cases identified by combining information from hospital discharges and deaths ▪ 2,101 cases with available medical records	▪ Case considered as a first AMI if not registered for a hospital discharge due to AMI in the previous 8 or more years ▪ Two discharge registrations for the same person were considered to belong to the same AMI episode if the dates differed less than 28 days	PPV (ICD-9 410): 98% (2,053 of 2,101)

Reference (AMI)	Study Period Endpoint	Inclusion Criteria and Population	Exclusion Criteria	Positive Predictive Value
Lindblad U, Råstam L, Ranstam J, Peterson M. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. Scand J Soc Med. 1993 Mar;21(1):3-9.	1977-1987 AMI, stroke	▪ Follow-up of 3,240 hypertensive outpatients aged 40-69 years (index), matched (age, sex, residency, cohort entry year) population controls (census), and normotensive subjects from 1977	▪ Only the first nonfatal AMI/stroke events were used ▪ Fatal if death occurred within 28 days after the onset; otherwise nonfatal	PPV (ICD-8 410.00 or 410.99 or ICD-9 410A-X): 96% (395 of 413) for AMI

AMI = acute myocardial infarction; CI = confidence interval; ICD-9 = *International Classification of Diseases, 9th Revision*; PPV = positive predictive value.

Table A-2. Stroke

Reference (Stroke)	Study Period Endpoint	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value
Lindblad U, Råstam L, Ranstam J, Peterson M. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. Scand J Soc Med. 1993 Mar;21(1):3-9..	1977-1987 AMI, stroke	▪ Follow-up of 3,240 hypertensive outpatients aged 40-69 years (index), matched (age, sex, residency, cohort entry year) population controls (census), and normotensive subjects from 1977	▪ Only the first nonfatal AMI/stroke events were used ▪ Fatal if death occurred within 28 days after the onset; otherwise nonfatal	PPV (ICD-8 436 or ICD-9 430-131): 94% (236 of 251) for stroke
Stegmayr B, Asplund K. Measuring stroke in the population: quality of routine statistics in comparison with a population-based stroke registry. Neuroepidemiology. 1992;11(4-6):204-13.	1985-1989 Nonfatal stroke	▪ Patients aged 25-74 years and discharged from two of the nine acute care hospitals, representing 32% of the total target population in the area covered by the MONICA registry (northern Sweden) ▪ 5,101 patients discharged alive from hospital ▪ WHO MONICA stroke criteria ▪ True number extrapolated to the entire MONICA population from case-finding in subsamples	▪ 10-20 nonfatal cases with insufficient data (1.6% of all nonfatal cases) ▪ 114 nonfatal out-of-hospital stroke events (3.2% of all accepted nonfatal cases in the MONICA registry)	PPV (ICD-9 430-438): 68.5% (3,492 of 5,101)

PPV = positive predictive value.

16 Appendix B: Description of Patient Characteristic Variables Available in the Swedish National Registers

Patient Characteristic	Type of Variable	Time Window of Assessment	Proxy/Derived/Covered
Birth, cohort entry, cohort exit, death	Date	Specific date	Covered
Cause of death	ICD-10 or other medical codes	Specific date	Covered
Duration of enrollment prior to cohort entry (days)	Number (start date of cohort minus date of enrollment in data source)	Specific period	Derived (enrollment in database at birth or immigration)
Duration of follow-up (days)	Number (date of cohort exit minus the date of cohort entry)	Specific period	Derived
Demographics: age, sex	Age: numerical Sex: binary	Specific date	Covered
Socioeconomic characteristics: education, income	Categorical: specific categories depend on the data structure	Baseline (just before the cohort entry date)	Covered by Statistics Sweden
Menopause	Binary, women only	Baseline (5 years before the cohort entry date)	Estimated based on age (above/below 50 years)
Hypertension	Binary	Baseline (12 months before the cohort entry date)	Derived from ICD-10 and/or ATC
Dyslipidemia	Binary	Baseline (12 months before the cohort entry date)	Derived from ICD-10 and/or ATC
History of AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, pulmonary artery disease	Binary	Baseline (12 months before the cohort entry date)	Derived from ICD-10 and/or ATC and/or NCSP

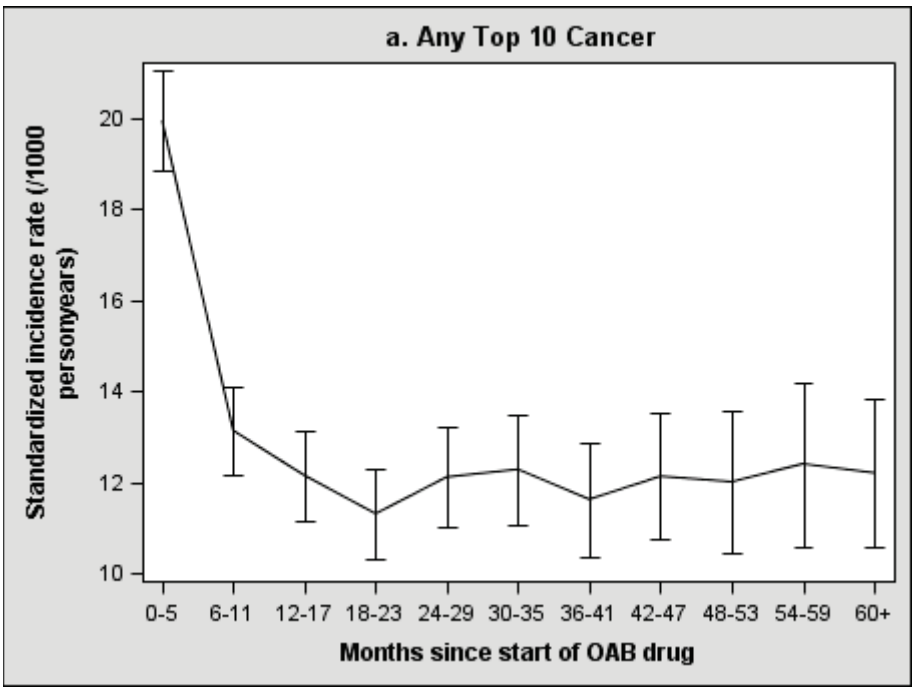
Patient Characteristic	Type of Variable	Time Window of Assessment	Proxy/Derived/Covered
Diabetes without complications (diabetes with complications is included with the Charlson score)	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10 and/or ATC
Alcohol abuse and related conditions	Binary	Baseline (5 years before the cohort entry date)	Weak proxy from ICD-10 and/or ATC and/or NCSP
Drug abuse	Binary	Baseline (5 years before the cohort entry date)	Proxy from ICD-10 and/or ATC and/or NCSP
Comorbidities included in the Charlson Index	Each comorbidity: binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10
Renal impairment	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10 and/or NCSP
Dialysis	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10 and/or NCSP
Fractures	Binary	Time varying (5 years before the cohort entry date)	Derived from ICD-10 and/or NCSP
Gout	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10 and/or ATC and/or NCSP
Arthritis	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10
Overactive bladder	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10
Organ transplantation	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10 and/or NCSP
Polycystic ovary syndrome	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10 and/or NCSP
Endometrial polyps or other benign growths of the uterine lining	Binary	Baseline (5 years before the cohort entry date)	Derived from ICD-10 and/or NCSP
Filled prescriptions Hormone replacement therapy Tamoxifen use	Binary	Baseline (12 months before the cohort entry date)	Covered

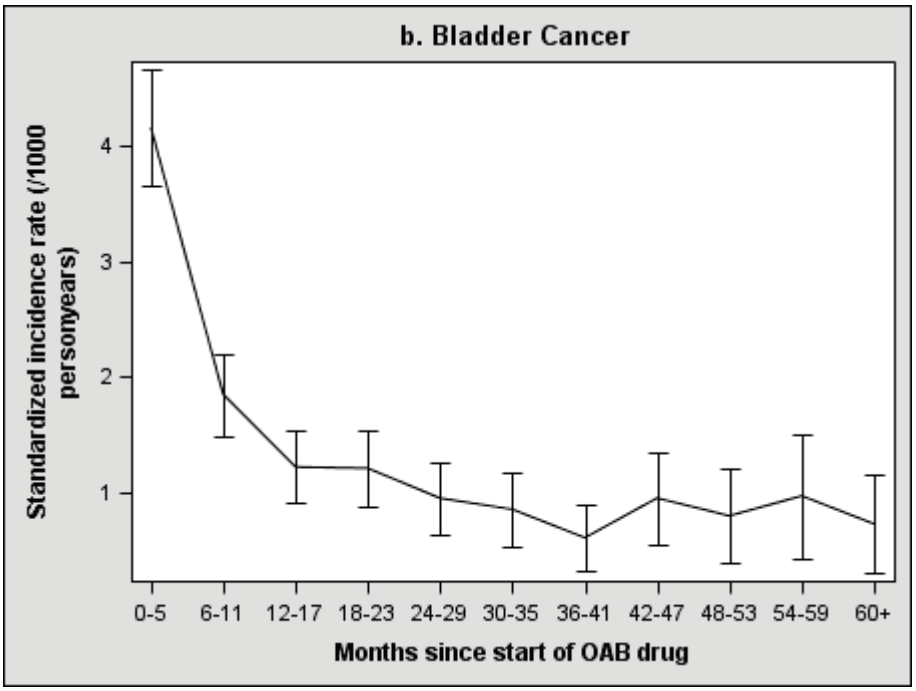
Patient Characteristic	Type of Variable	Time Window of Assessment	Proxy/Derived/Covered
Thyroid hormone replacement Nitrates, digoxin, antidiabetic drugs, statins Non-aspirin NSAIDs Low-dose aspirin[a] Antiplatelets (including aspirin in low doses[a]) Immunosuppressive agents)			
Health services utilization: outpatient visits	Numerical	Baseline (12 months before the cohort entry date)	Covered
Health services utilization: hospitalizations	Numerical	Baseline (12 months before the cohort entry date)	Covered
Sigmoidoscopies	Numerical	Baseline (12 months before the cohort entry date)	NCSP code UJF42 and UJF45

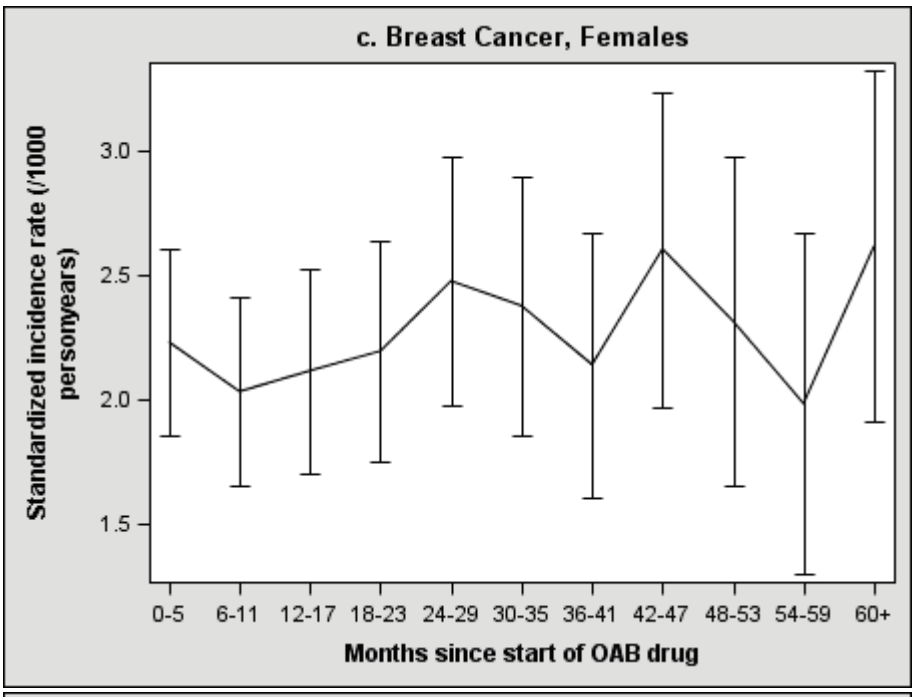
AMI = acute myocardial infarction; ATC = Anatomical Therapeutic Chemical; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; NCSP = Nordic Classification of Surgical Procedures; NSAIDs = nonsteroidal anti-inflammatory drugs.

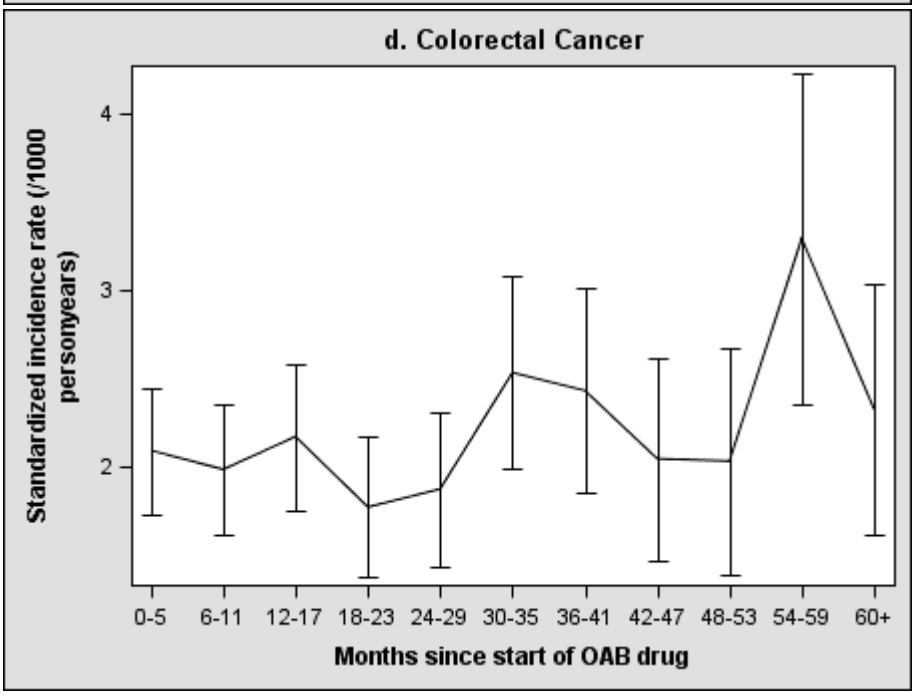
[a] Up to 325 mg per tablet.

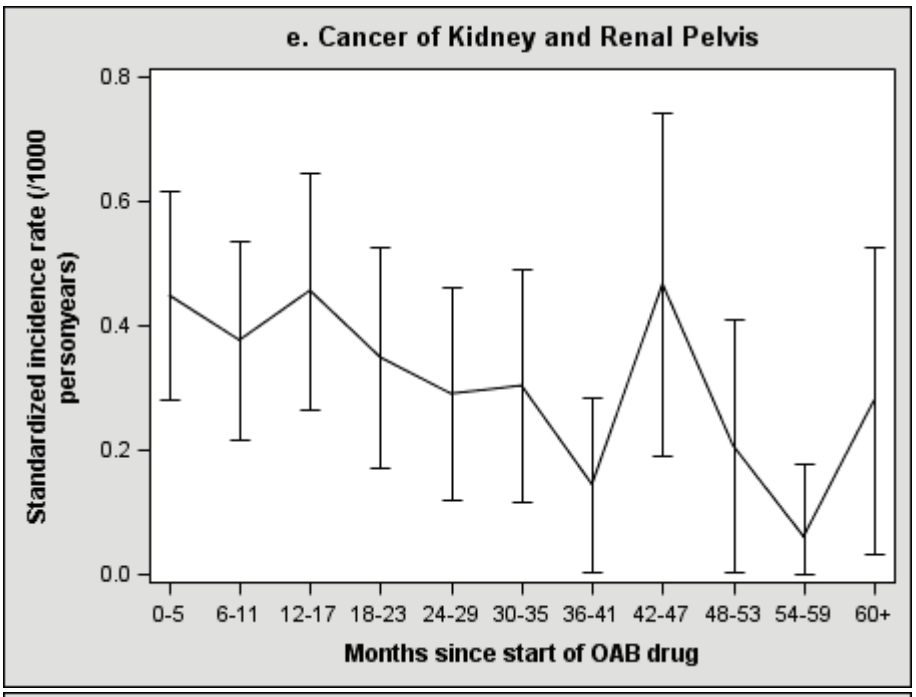
17 Appendix C: Cancer Standardized Incidence Rates by Time Since Cohort Entry at 6-Month Intervals. Swedish National Registers

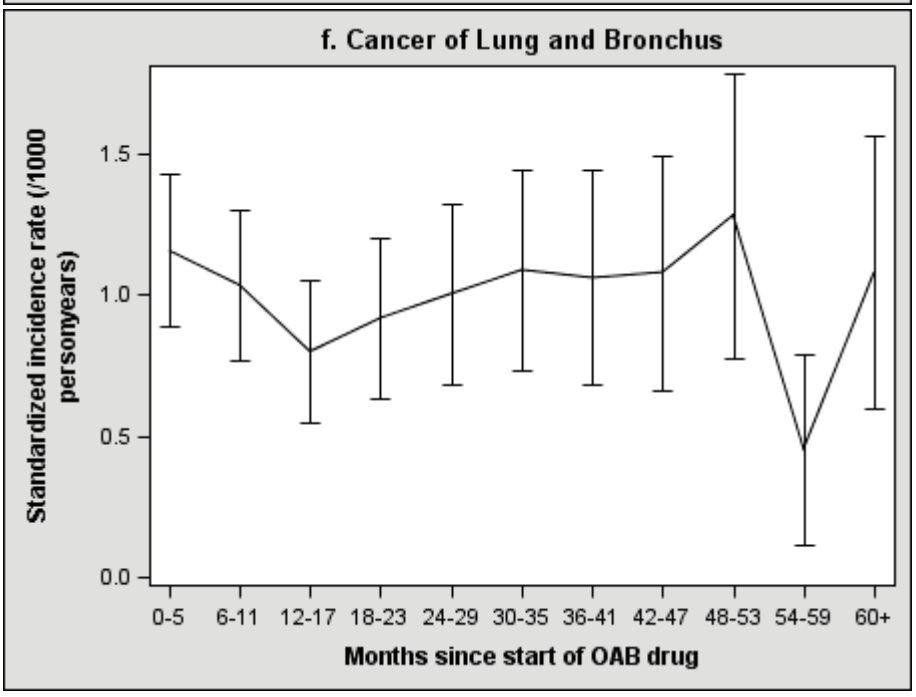


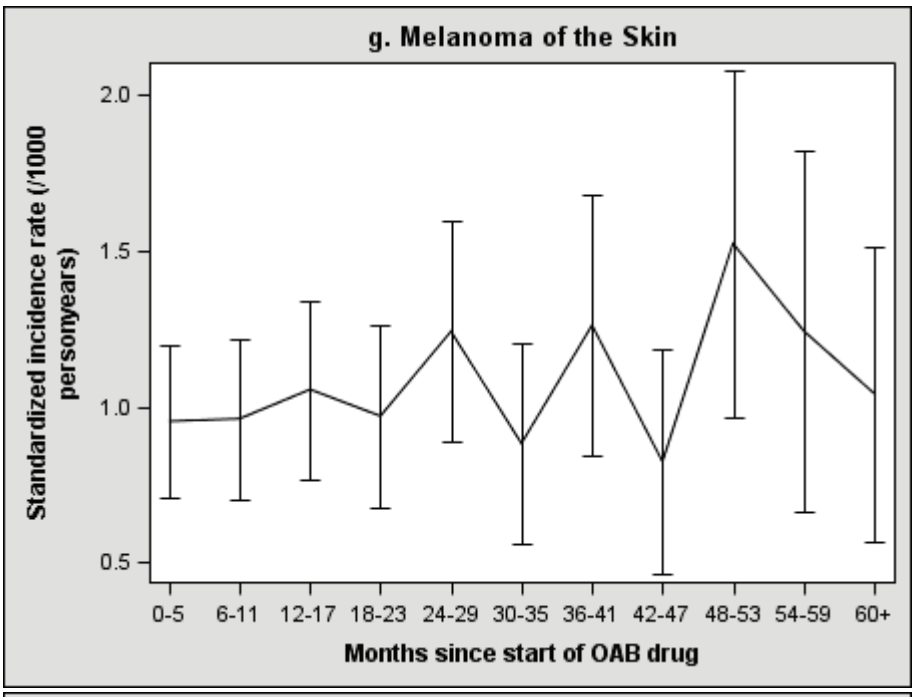


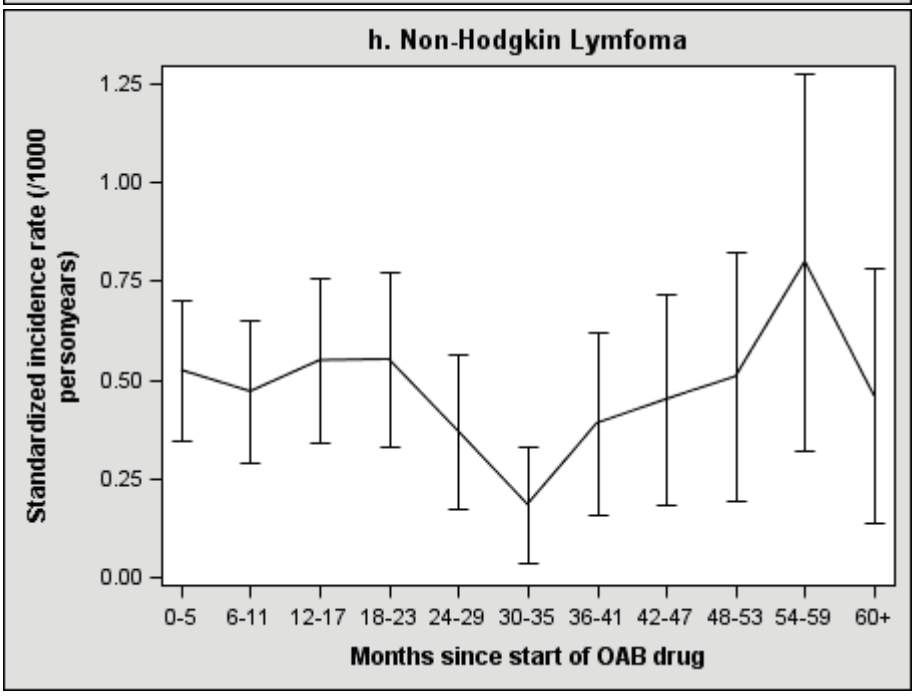

c. Breast Cancer, Females
Standardized incidence rate (/1000 personyears)
3.0
2.5
2.0
1.5
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug

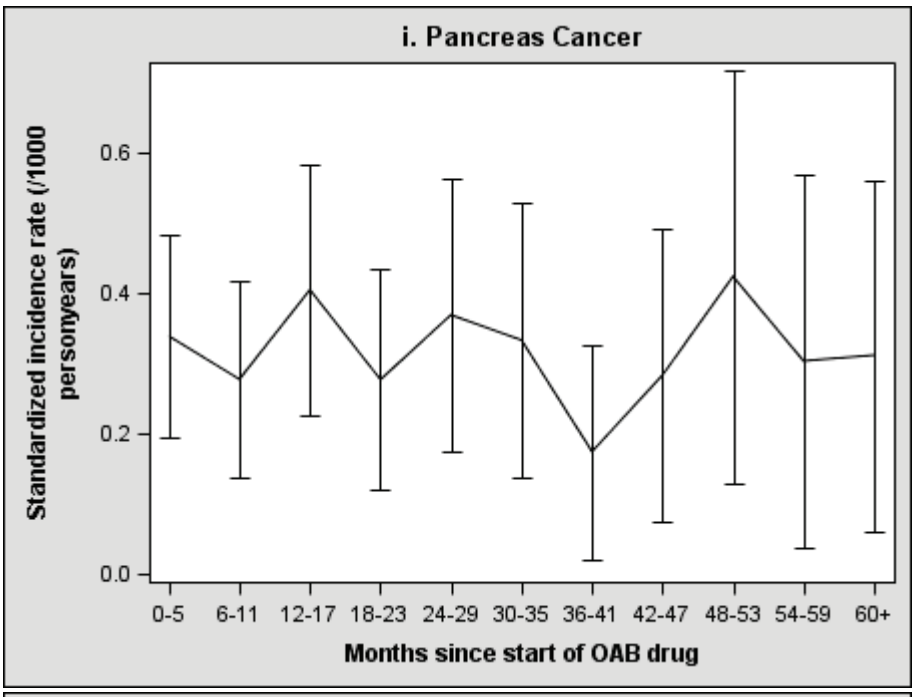

d. Colorectal Cancer
Standardized incidence rate (/1000 personyears)
4
3
2
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug

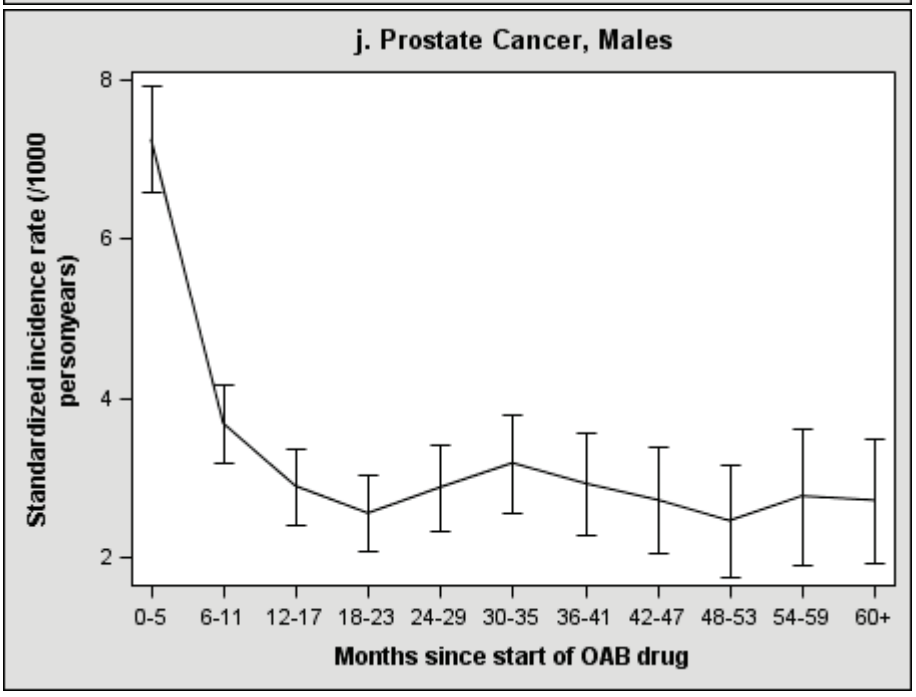

e. Cancer of Kidney and Renal Pelvis
Standardized incidence rate (/1000 personyears)
0.0
0.2
0.4
0.6
0.8
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug

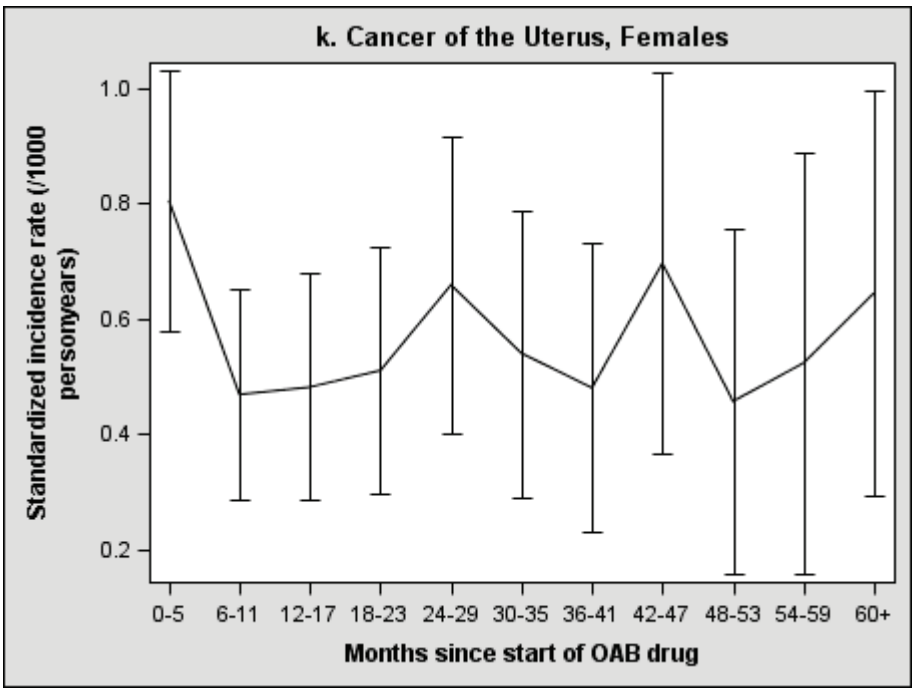

f. Cancer of Lung and Bronchus
Standardized incidence rate (/1000 personyears)
0.0
0.5
1.0
1.5
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug


g. Melanoma of the Skin
Standardized incidence rate (/1000 personyears)
2.0
1.5
1.0
0.5
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug


h. Non-Hodgkin Lymfoma
Standardized incidence rate (/1000 personyears)
1.25
1.00
0.75
0.50
0.25
0.00
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug


i. Pancreas Cancer
Standardized incidence rate (/1000 personyears)
0.0
0.2
0.4
0.6
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug


j. Prostate Cancer, Males
Standardized incidence rate (/1000 personyears)
2
4
6
8
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug


k. Cancer of the Uterus, Females
Standardized incidence rate (/1000 personyears)
1.0
0.8
0.6
0.4
0.2
0-5
6-11
12-17
18-23
24-29
30-35
36-41
42-47
48-53
54-59
60+
Months since start of OAB drug

18 Appendix D: Analysis Results Tables

Table A1. Characteristics of Those Exposed to Any OAB Medication at FIRST Study Cohort Entry (N = 130,944)

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Age at cohort entry (years)							
	Mean (SD)	*52*	*11.5*	*76*	*7.4*	*66*	*15.3*
	18-24	2,170	4.0	0	0.0	2,170	1.7
	25-34	3,813	7.0	0	0.0	3,813	2.9
	35-44	7,349	13.4	0	0.0	7,349	5.6
	45-54	14,361	26.3	0	0.0	14,361	11.0
	55-64	26,975	49.3	0	0.0	26,975	20.6
	65-74	0	0.0	35,924	47.1	35,924	27.4
	75-84	0	0.0	29,438	38.6	29,438	22.5
	85+	0	0.0	10,914	14.3	10,914	8.3
Sex							
	Female	33,640	61.5	44,352	58.1	77,992	59.6
	Male	21,028	38.5	31,924	41.9	52,952	40.4
Calendar year at cohort entry							
	2006	5,410	9.9	7,813	10.2	13,223	10.1
	2007	9,888	18.1	14,285	18.7	24,173	18.5
	2008	9,084	16.6	12,776	16.7	21,860	16.7
	2009	7,819	14.3	11,123	14.6	18,942	14.5
	2010	7,711	14.1	10,578	13.9	18,289	14.0
	2011	7,449	13.6	10,390	13.6	17,839	13.6
	2012	7,307	13.4	9,311	12.2	16,618	12.7
Duration of enrollment prior to cohort entry							
	Mean (SD)	*1,466*	*(694.3)*	*1,446*	*(687.6)*	*1,454*	*(690.5)*
	1 to < 2 years	10,759	19.7	15,227	20.0	25,986	19.8
	2 to < 4 years	17,735	32.4	25,542	33.5	43,277	33.1
	4 to < 8 years	26,174	47.9	35,507	46.6	61,681	47.1
Duration of follow-up							
	Mean (SD)	*1,230*	*(697.2)*	*1,119*	*(686.4)*	*1,165*	*(693.1)*
	< 1 year	8,090	14.8	13,510	17.7	21,600	16.5
	1 to < 2 years	7,857	14.4	12,955	17.0	20,812	15.9
	2 to < 4 years	15,783	28.9	23,126	30.3	38,909	29.7
	4 to < 8 years	22,938	42.0	26,685	35.0	49,623	37.9

Table A1. Characteristics of Those Exposed to Any OAB Medication at FIRST Study Cohort Entry (N = 130,944)

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Menopause	Yes	20,872	38.2	44,352	58.1	65,224	49.8
Number of study drugs during follow-up							
	1	44,695	81.8	61,447	80.6	106,142	81.1
	2	8,013	14.7	12,047	15.8	20,060	15.3
	3	1,624	3.0	2,325	3.0	3,949	3.0
	4	294	0.5	398	0.5	692	0.5
	5	42	0.1	59	0.1	101	0.1
						130,944	100
Number of different study drugs to which patient was exposed in the 12 months before this study							
	1	49,159	89.9	65,347	85.7	114,506	87.4
	2	4,940	9.0	9,785	12.8	14,725	11.2
	3	511	0.9	1,054	1.4	1,565	1.2
	4	53	0.1	85	0.1	138	0.1
	5	5	0.0	5	0.0	10	0.0
						130,944	100
Education (years)							
	Missing	8,775	16.1	12,422	16.3	21,197	16.2
	≤ 9	13,441	24.6	18,751	24.6	32,192	24.6
	< 9 to ≤ 12	19,412	35.5	26,891	35.3	46,303	35.4
	> 12	13,040	23.9	18,212	23.9	31,252	23.9
Income (in quartiles)							
	Missing	1,219	2.2	1,688	2.2	2,907	2.2
	Low	8,143	14.9	11,416	15.0	19,559	14.9
	Midlow	11,797	21.6	16,426	21.5	28,223	21.6
	Midhigh	12,638	23.1	17,396	22.8	30,034	22.9
	High	20,871	38.2	29,350	38.5	50,221	38.4

Table A1. Characteristics of Those Exposed to Any OAB Medication at FIRST Study Cohort Entry (N = 130,944)

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Hospitalizations							
	None	34,412	62.9	34,777	45.6	69,189	52.8
	< 5	17,821	32.6	34,853	45.7	52,674	40.2
	5-10	1,938	3.5	5,695	7.5	7,633	5.8
	11-25	435	0.8	910	1.2	1,345	1.0
	26-50	59	0.1	39	0.1	98	0.1
	> 50	3	0.0	2	0.0	5	0.0
Outpatient visits							
	None	12,127	22.2	13,073	17.1	25,200	19.2
	< 5	23,899	43.7	34,338	45.0	58,237	44.5
	5-10	11,717	21.4	19,188	25.2	30,905	23.6
	11-25	5,609	10.3	8,309	10.9	13,918	10.6
	26-50	1,103	2.0	1,186	1.6	2,289	1.7
	> 50	213	0.4	182	0.2	395	0.3
Comorbidities							
Mild liver disease, Charlson	Yes	492	0.9	415	0.5	907	0.7
AIDS/HIV, Charlson	No	54,668	100.0	76,276	100.0	130,944	100.0
Cancer, Charlson	No	54,668	100.0	76,276	100.0	130,944	100.0
Metastatic carcinoma, Charlson	No	54,668	100.0	76,276	100.0	130,944	100.0
Diabetes without complications, Charlson	Yes	2,230	4.1	7,666	10.1	9,896	7.6
Diabetes with complications, Charlson	Yes	770	1.4	2,662	3.5	3,432	2.6
Alcohol abuse and related conditions	Yes	1,270	2.3	848	1.1	2,118	1.6
Polycystic ovary syndrome	Yes	96	0.2	0	0.0	96	0.1
Obesity	Yes	1,413	2.6	1,019	1.3	2,432	1.9
Dementia, Charlson	Yes	116	0.2	1,764	2.3	1,880	1.4
Drug abuse	Yes	397	0.7	126	0.2	523	0.4
Transient ischemic attack	Yes	188	0.3	1,545	2.0	1,733	1.3
Cerebrovascular disease, Charlson	Yes	1,561	2.9	8,083	10.6	9,644	7.4
Paraplegia and hemiplegia, Charlson	Yes	928	1.7	738	1.0	1,666	1.3
Heart failure	Yes	390	0.7	4,460	5.8	4,850	3.7
Coronary heart disease	Yes	1,892	3.5	10,807	14.2	12,699	9.7
Acute myocardial infarction	Yes	780	1.4	5,087	6.7	5,867	4.5
Congestive heart failure, Charlson	Yes	424	0.8	4,605	6.0	5,029	3.8

Table A1. Characteristics of Those Exposed to Any OAB Medication at FIRST Study Cohort Entry (N = 130,944)

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Stroke	Yes	1,106	2.0	6,339	8.3	7,445	5.7
Peripheral vascular disease, Charlson	Yes	391	0.7	2,632	3.5	3,023	2.3
Chronic pulmonary disease, Charlson	Yes	2,022	3.7	4,892	6.4	6,914	5.3
Peptic ulcer disease, Charlson	Yes	487	0.9	1,579	2.1	2,066	1.6
Moderate or severe liver disease, Charlson	Yes	73	0.1	95	0.1	168	0.1
Connective tissue disease-rheumatic disease, Charlson	Yes	817	1.5	2,917	3.8	3,734	2.9
Arthritis	Yes	723	1.3	1,939	2.5	2,662	2.0
Gout	Yes	131	0.2	713	0.9	844	0.6
Fractures	Yes	2,446	4.5	7,521	9.9	9,967	7.6
Renal impairment	Yes	2,230	4.1	3,400	4.5	5,630	4.3
Renal disease, Charlson	Yes	238	0.4	1,072	1.4	1,310	1.0
Endometrial polyps or other benign growths of the uterus	Yes	415	0.8	39	0.1	454	0.3
Overactive bladder	Yes	10,375	19.0	12,835	16.8	23,210	17.7
Dialysis	Yes	16	0.0	65	0.1	81	0.1
Diabetes	Yes	3,653	6.7	11,079	14.5	14,732	11.3
Diabetes - diagnosis	Yes	2,406	4.4	8,280	10.9	10,686	8.2
Diabetes - drugs	Yes	3,279	6.0	9,706	12.7	12,985	9.9
Dyslipidemia	Yes	7,646	14.0	24,254	31.8	31,900	24.4
Dyslipidemia - diagnosis	Yes	1,394	2.5	5,027	6.6	6,421	4.9
Dyslipidemia - drugs	Yes	7,491	13.7	23,736	31.1	31,227	23.8
Hypertension	Yes	14,988	27.4	47,504	62.3	62,492	47.7
Hypertension - diagnosis	Yes	4,773	8.7	19,934	26.1	24,707	18.9
Hypertension - drugs	Yes	14,610	26.7	46,134	60.5	60,744	46.4
Peripheral artery disease	Yes	428	0.8	2,874	3.8	3,302	2.5
Peripheral artery disease - diagnosis	Yes	401	0.7	2,667	3.5	3,068	2.3
Peripheral artery disease - procedures	Yes	107	0.2	748	1.0	855	0.7
Organ transplantation	Yes	100	0.2	144	0.2	244	0.2
Organ transplantation - diagnosis	Yes	95	0.2	143	0.2	238	0.2
Organ transplantation - procedures	Yes	33	0.1	17	0.0	50	0.0
Smoking	Yes	889	1.6	687	0.9	1,576	1.2
Smoking - diagnosis	Yes	225	0.4	301	0.4	526	0.4

Table A1. Characteristics of Those Exposed to Any OAB Medication at FIRST Study Cohort Entry (N = 130,944)

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Smoking - drugs	Yes	682	1.2	404	0.5	1,086	0.8
Antiplatelets (including aspirin in low doses)	Yes	6,455	11.8	34,662	45.4	41,117	31.4
Low-dose aspirin	Yes	4,693	8.6	27,263	35.7	31,956	24.4
Digoxin	Yes	124	0.2	2,347	3.1	2,471	1.9
Nitrates	Yes	1,501	2.7	10,060	13.2	11,561	8.8
Statins	Yes	7,168	13.1	23,122	30.3	30,290	23.1
Hormone-replacement therapy	Yes	13,990	25.6	25,371	33.3	39,361	30.1
Thyroid hormone replacement	Yes	3,893	7.1	8,888	11.7	12,781	9.8
Tamoxifen	No	54,668	100.0	76,276	100.0	130,944	100.0
Immunosuppressive agents	Yes	920	1.7	1,435	1.9	2,355	1.8
Non-aspirin NSAIDs	Yes	19,131	35.0	23,040	30.2	42,171	32.2
Mammograms	Yes	46	0.1	48	0.1	94	0.1
Sigmoidoscopies	Yes	546	1.0	1,127	1.5	1,673	1.3

HIV = human immunodeficiency virus; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder; SD = standard deviation.

Table A2. Descriptive Summary of OAB Medication Exposure at FIRST Study Cohort Entry (N = 130,944)

Variable	n	%
Single exposure[a]		
Darifenacin	7,720	6.23
Fesoterodine	12,470	10.07
Oxybutynin	4,736	3.82
Solifenacin	44,086	35.60
Tolterodine	54,825	44.27
New exposure[b]		
Darifenacin	9,093	6.95
Fesoterodine	13,536	10.34
Oxybutynin	5,420	4.14
Solifenacin	47,313	36.15
Tolterodine	55,510	42.42
More than one study OAB medication at cohort entry[c]	72	100

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.

c. These are NOT included in the rows elsewhere in this table.

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

		Darifenacin		Fesoterodine		Oxybutynin		Solifenacin		Tolterodine		Multiple	
		(n=9,093)		(n=13,536)		(n=5,420)		(n=47,313)		(n=55,510)		(n=72)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Age at cohort entry (years)													
	Mean (SD)	*67*	*(14.2)*	*65*	*(14.5)*	*55*	*(20.2)*	*65*	*(14.8)*	*68*	*(15.1)*	*64*	*(14.5)*
	18-24	91	1.0	205	1.5	559	10.3	618	1.3	697	1.3	0	0.0
	25-34	198	2.2	358	2.6	636	11.7	1,282	2.7	1,335	2.4	4	5.6
	35-44	420	4.6	731	5.4	572	10.6	2,815	5.9	2,806	5.1	5	6.9
	45-54	943	10.4	1,535	11.3	692	12.8	5,588	11.8	5,595	10.1	8	11.1
	55-64	1,954	21.5	2,964	21.9	878	16.2	10,266	21.7	10,895	19.6	18	25.0
	65-74	2,544	28.0	4,124	30.5	1,061	19.6	13,414	28.4	14,762	26.6	19	26.4
	75-84	2,194	24.1	2,872	21.2	782	14.4	9,956	21.0	13,620	24.5	14	19.4
	85+	749	8.2	747	5.5	240	4.4	3,374	7.1	5,800	10.4	4	5.6
Sex													
	Female	5,748	63.2	8,075	59.7	3,409	62.9	30,457	64.4	30,259	54.5	44	61.1
	Male	3,345	36.8	5,461	40.3	2,011	37.1	16,856	35.6	25,251	45.5	28	38.9
Calendar year at cohort entry													
	2006	1,441	15.8	0	0.0	761	14.0	2,996	6.3	8,010	14.4	15	20.8
	2007	2,763	30.4	0	0.0	908	16.8	6,615	14.0	13,872	25.0	15	20.8
	2008	1,766	19.4	841	6.2	501	9.2	7,440	15.7	11,303	20.4	9	12.5
	2009	710	7.8	3,140	23.2	486	9.0	6,656	14.1	7,942	14.3	8	11.1
	2010	937	10.3	3,155	23.3	740	13.7	7,423	15.7	6,028	10.9	6	8.3
	2011	856	9.4	3,314	24.5	858	15.8	7,989	16.9	4,814	8.7	8	11.1
	2012	620	6.8	3,086	22.8	1,166	21.5	8,194	17.3	3,541	6.4	11	15.3
Duration of enrollment prior to cohort entry													
	Mean (SD)	*1,182*	*(657.7)*	*1,959*	*(446.5)*	*1,566*	*(783.1)*	*1,612*	*(682.9)*	*1,230*	*(632.4)*	*1,343*	*(782.3)*
	1 to < 2 years	3,134	34.5	0	0.0	1,329	24.5	6,253	13.2	15,245	27.5	25	34.7
	2 to < 4 years	3,266	35.9	2,501	18.5	1,086	20.0	14,176	30.0	22,229	40.0	19	26.4
	4 to < 8 years	2,693	29.6	11,035	81.5	3,005	55.4	26,884	56.8	18,036	32.5	28	38.9

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

		Darifenacin		Fesoterodine		Oxybutynin		Solifenacin		Tolterodine		Multiple	
		(n=9,093)		(n=13,536)		(n=5,420)		(n=47,313)		(n=55,510)		(n=72)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of follow-up													
	Mean (SD)	*1,413*	*(701.9)*	*747*	*(447.1)*	*1,090*	*(764.2)*	*1,043*	*(674.9)*	*1,339*	*(679.4)*	*1,258*	*(800.7)*
	< 1 year	958	10.5	3,423	25.3	1,291	23.8	9,692	20.5	6,221	11.2	15	20.8
	1 to < 2 years	1,102	12.1	3,413	25.2	926	17.1	8,718	18.4	6,645	12.0	8	11.1
	2 to < 4 years	1,930	21.2	5,961	44.0	1,298	23.9	14,219	30.1	15,484	27.9	17	23.6
	4 to < 8 years	5,103	56.1	739	5.5	1,905	35.1	14,684	31.0	27,160	48.9	32	44.4
Menopause	Yes	5,004	55.0	6,747	49.8	2,244	41.4	25,275	53.4	25,917	46.7	37	51.4
Number of study drugs during follow-up													
	1	6,224	68.4	11,443	84.5	4,020	74.2	40,000	84.5	44,455	80.1	0	0.0
	2	2,082	22.9	1,826	13.5	998	18.4	5,926	12.5	9,172	16.5	56	77.8
	3	644	7.1	235	1.7	308	5.7	1,173	2.5	1,580	2.8	9	12.5
	4	126	1.4	28	0.2	76	1.4	188	0.4	267	0.5	7	9.7
	5	17	0.2	4	0.0	18	0.3	26	0.1	36	0.1	0	0.0
Number of different study drugs to which patient was exposed in the 12 months before this study													
	1	7,022	77.2	11,562	85.4	4,299	79.3	41,342	87.4	50,234	90.5	47	65.3
	2	1,714	18.8	1,729	12.8	938	17.3	5,446	11.5	4,877	8.8	21	29.2
	3	324	3.6	220	1.6	170	3.1	482	1.0	366	0.7	3	4.2
	4	32	0.4	24	0.2	12	0.2	38	0.1	31	0.1	1	1.4
	5	1	0.0	1	0.0	1	0.0	5	0.0	2	0.0	0	0.0
Education													
	Missing	1,725	19.0	1,434	10.6	830	15.3	7,067	14.9	10,132	18.3	9	12.5
	≤ 9 years	2,003	22.0	3,834	28.3	1,308	24.1	12,055	25.5	12,974	23.4	18	25.0
	< 9 to ≤ 12 years	3,155	34.7	4,843	35.8	2,008	37.0	16,839	35.6	19,427	35.0	31	43.1
	> 12 years	2,210	24.3	3,425	25.3	1,274	23.5	11,352	24.0	12,977	23.4	14	19.4

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

		Darifenacin		Fesoterodine		Oxybutynin		Solifenacin		Tolterodine		Multiple	
		(n=9,093)		(n=13,536)		(n=5,420)		(n=47,313)		(n=55,510)		(n=72)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Income													
	Missing	195	2.1	284	2.1	114	2.1	1,024	2.2	1,289	2.3	1	1.4
	Low	1,435	15.8	1,815	13.4	810	14.9	6,866	14.5	8,621	15.5	12	16.7
	Midlow	1,967	21.6	2,819	20.8	1,178	21.7	10,145	21.4	12,099	21.8	15	20.8
	Midhigh	2,098	23.1	3,048	22.5	1,220	22.5	10,691	22.6	12,963	23.4	14	19.4
	High	3,398	37.4	5,570	41.1	2,098	38.7	18,587	39.3	20,538	37.0	30	41.7
Hospitalizations													
	None	4,666	51.3	7,183	53.1	3,318	61.2	25,570	54.0	28,417	51.2	35	48.6
	< 5	3,746	41.2	5,466	40.4	1,815	33.5	18,734	39.6	22,886	41.2	27	37.5
	5-10	576	6.3	728	5.4	243	4.5	2,542	5.4	3,535	6.4	9	12.5
	11-25	100	1.1	150	1.1	42	0.8	426	0.9	626	1.1	1	1.4
	26-50	5	0.1	8	0.1	2	0.0	39	0.1	44	0.1	0	0.0
	> 50	0	0.0	1	0.0	0	0.0	2	0.0	2	0.0	0	0.0
Outpatient visits													
	None	1,648	18.1	1,926	14.2	1,253	23.1	8,335	17.6	12,025	21.7	13	18.1
	< 5	4,094	45.0	5,900	43.6	2,286	42.2	21,041	44.5	24,884	44.8	32	44.4
	5-10	2,222	24.4	3,584	26.5	1,164	21.5	11,472	24.2	12,449	22.4	14	19.4
	11-25	945	10.4	1,765	13.0	597	11.0	5,396	11.4	5,207	9.4	8	11.1
	26-50	152	1.7	314	2.3	104	1.9	904	1.9	810	1.5	5	6.9
	> 50	32	0.4	47	0.3	16	0.3	165	0.3	135	0.2	0	0.0
Comorbidities													
Mild liver disease, Charlson	Yes	63	0.7	98	0.7	35	0.6	337	0.7	374	0.7	0	0.0
AIDS/HIV, Charlson	No	9,093	100.0	13,536	100.0	5,420	100.0	47,313	100.0	55,510	100.0	72	100.0
Cancer, Charlson	No	9,093	100.0	13,536	100.0	5,420	100.0	47,313	100.0	55,510	100.0	72	100.0
Metastatic carcinoma, Charlson	No	9,093	100.0	13,536	100.0	5,420	100.0	47,313	100.0	55,510	100.0	72	100.0
Diabetes without complications, Charlson	Yes	715	7.9	1,079	8.0	288	5.3	3,488	7.4	4,323	7.8	3	4.2
Diabetes with complications, Charlson	Yes	248	2.7	348	2.6	101	1.9	1,178	2.5	1,556	2.8	1	1.4
Alcohol abuse and related conditions	Yes	132	1.5	188	1.4	102	1.9	747	1.6	947	1.7	2	2.8
Polycystic ovary syndrome	Yes	1	0.0	9	0.1	14	0.3	41	0.1	31	0.1	0	0.0
Obesity	Yes	134	1.5	300	2.2	108	2.0	970	2.1	918	1.7	2	2.8
Dementia, Charlson	Yes	179	2.0	138	1.0	48	0.9	582	1.2	933	1.7	0	0.0

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

		Darifenacin		Fesoterodine		Oxybutynin		Solifenacin		Tolterodine		Multiple	
		(n=9,093)		(n=13,536)		(n=5,420)		(n=47,313)		(n=55,510)		(n=72)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Drug abuse	Yes	34	0.4	48	0.4	44	0.8	188	0.4	209	0.4	0	0.0
Transient ischemic attack	Yes	153	1.7	217	1.6	31	0.6	602	1.3	729	1.3	1	1.4
Cerebrovascular disease, Charlson	Yes	749	8.2	966	7.1	213	3.9	3,044	6.4	4,668	8.4	4	5.6
Paraplegia and hemiplegia, Charlson	Yes	87	1.0	249	1.8	69	1.3	475	1.0	784	1.4	2	2.8
Heart failure	Yes	366	4.0	480	3.5	109	2.0	1,576	3.3	2,315	4.2	4	5.6
Coronary heart disease	Yes	995	10.9	1,326	9.8	367	6.8	4,270	9.0	5,734	10.3	7	9.7
Acute myocardial infarction	Yes	448	4.9	617	4.6	163	3.0	1,949	4.1	2,689	4.8	1	1.4
Congestive heart failure, Charlson	Yes	380	4.2	499	3.7	115	2.1	1,630	3.4	2,401	4.3	4	5.6
Stroke	Yes	563	6.2	724	5.3	159	2.9	2,322	4.9	3,673	6.6	4	5.6
Peripheral vascular disease, Charlson	Yes	224	2.5	306	2.3	88	1.6	1,056	2.2	1,349	2.4	0	0.0
Chronic pulmonary disease, Charlson	Yes	478	5.3	775	5.7	238	4.4	2,581	5.5	2,839	5.1	3	4.2
Peptic ulcer disease, Charlson	Yes	152	1.7	207	1.5	54	1.0	682	1.4	969	1.7	2	2.8
Moderate or severe liver disease, Charlson	Yes	8	0.1	23	0.2	10	0.2	64	0.1	63	0.1	0	0.0
Connective tissue disease-rheumatic disease, Charlson	Yes	284	3.1	405	3.0	137	2.5	1,298	2.7	1,608	2.9	2	2.8
Arthritis	Yes	203	2.2	324	2.4	109	2.0	921	1.9	1,105	2.0	0	0.0
Gout	Yes	67	0.7	100	0.7	17	0.3	262	0.6	398	0.7	0	0.0
Fractures	Yes	658	7.2	948	7.0	352	6.5	3,521	7.4	4,481	8.1	7	9.7
Renal impairment	Yes	340	3.7	630	4.7	140	2.6	2,096	4.4	2,421	4.4	3	4.2
Renal disease, Charlson	Yes	111	1.2	143	1.1	23	0.4	439	0.9	594	1.1	0	0.0
Endometrial polyps or other benign growths of the uterus	Yes	40	0.4	61	0.5	17	0.3	188	0.4	148	0.3	0	0.0
Overactive bladder	Yes	2,105	23.1	3,214	23.7	816	15.1	10,870	23.0	6,190	11.2	15	20.8
Dialysis	Yes	6	0.1	8	0.1	0	0.0	27	0.1	40	0.1	0	0.0
Diabetes	Yes	1,010	11.1	1,532	11.3	455	8.4	5,185	11.0	6,545	11.8	5	6.9
Diabetes - diagnosis	Yes	758	8.3	1,150	8.5	310	5.7	3,747	7.9	4,717	8.5	4	5.6

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

		Darifenacin		Fesoterodine		Oxybutynin		Solifenacin		Tolterodine		Multiple	
		(n=9,093)		(n=13,536)		(n=5,420)		(n=47,313)		(n=55,510)		(n=72)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Diabetes - drugs	Yes	907	10.0	1,365	10.1	407	7.5	4,555	9.6	5,748	10.4	3	4.2
Dyslipidemia	Yes	2,228	24.5	3,647	26.9	937	17.3	11,691	24.7	13,380	24.1	17	23.6
Dyslipidemia - diagnosis	Yes	465	5.1	805	5.9	181	3.3	2,399	5.1	2,570	4.6	1	1.4
Dyslipidemia - drugs	Yes	2,187	24.1	3,553	26.2	918	16.9	11,442	24.2	13,110	23.6	17	23.6
Hypertension	Yes	4,331	47.6	6,448	47.6	1,905	35.1	22,385	47.3	27,391	49.3	32	44.4
Hypertension - diagnosis	Yes	1,731	19.0	2,890	21.4	681	12.6	8,999	19.0	10,392	18.7	14	19.4
Hypertension - drugs	Yes	4,212	46.3	6,243	46.1	1,867	34.4	21,751	46.0	26,641	48.0	30	41.7
Peripheral artery disease	Yes	241	2.7	355	2.6	98	1.8	1,130	2.4	1,478	2.7	0	0.0
Peripheral artery disease - diagnosis	Yes	224	2.5	317	2.3	93	1.7	1,051	2.2	1,383	2.5	0	0.0
Peripheral artery disease - procedures	Yes	71	0.8	123	0.9	23	0.4	280	0.6	358	0.6	0	0.0
Organ transplantation	Yes	24	0.3	29	0.2	7	0.1	67	0.1	117	0.2	0	0.0
Organ transplantation - diagnosis	Yes	24	0.3	28	0.2	7	0.1	67	0.1	112	0.2	0	0.0
Organ transplantation - procedures	Yes	7	0.1	6	0.0	1	0.0	7	0.0	29	0.1	0	0.0
Smoking	Yes	109	1.2	220	1.6	54	1.0	575	1.2	617	1.1	1	1.4
Smoking - diagnosis	Yes	37	0.4	112	0.8	11	0.2	180	0.4	185	0.3	1	1.4
Smoking - drugs	Yes	74	0.8	117	0.9	43	0.8	402	0.8	450	0.8	0	0.0
Antiplatelets (including aspirin in low doses)	Yes	2,909	32.0	4,131	30.5	1,111	20.5	14,135	29.9	18,810	33.9	21	29.2
Low-dose aspirin	Yes	2,240	24.6	3,115	23.0	846	15.6	10,892	23.0	14,845	26.7	18	25.0
Digoxin	Yes	182	2.0	204	1.5	69	1.3	734	1.6	1,280	2.3	2	2.8
Nitrates	Yes	914	10.1	1,017	7.5	335	6.2	3,861	8.2	5,426	9.8	8	11.1
Statins	Yes	2,113	23.2	3,459	25.6	877	16.2	11,079	23.4	12,746	23.0	16	22.2
Hormone-replacement therapy	Yes	3,628	39.9	4,634	34.2	1,429	26.4	16,894	35.7	12,755	23.0	21	29.2
Thyroid hormone replacement	Yes	984	10.8	1,358	10.0	494	9.1	4,838	10.2	5,102	9.2	5	6.9
Tamoxifen	No	9,093	100.0	13,536	100.0	5,420	100.0	47,313	100.0	55,510	100.0	72	100.0
Immunosuppressive agents	Yes	156	1.7	270	2.0	92	1.7	832	1.8	1,003	1.8	2	2.8
Non-aspirin NSAIDs	Yes	3,100	34.1	4,315	31.9	1,671	30.8	15,459	32.7	17,604	31.7	22	30.6
Mammograms	Yes	5	0.1	6	0.0	6	0.1	54	0.1	23	0.0	0	0.0
Sigmoidoscopies	Yes	94	1.0	179	1.3	53	1.0	624	1.3	721	1.3	2	2.8

HIV = human immunodeficiency virus; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder; SD = standard deviation.

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

Study Antimuscarinic Drug	Patients	Person-years	Person-years per Exposed Individual				
			Mean	SD	Median	P25	P75
Current exposure							
Darifenacin	12,335	9,654	0.78	1.09	0.33	0.1	0.91
Fesoterodine	21,922	14,511	0.66	0.81	0.3	0.1	0.86
Oxybutynin	8,142	4,991	0.61	0.81	0.29	0.25	0.64
Solifenacin	57,112	44,946	0.79	1.05	0.33	0.1	0.95
Tolterodine	59,805	47,527	0.79	1.09	0.3	0.17	0.92
	159,316						
Recent exposure							
Darifenacin	11,847	2,841	0.24	0.16	0.16	0.16	0.3
Fesoterodine	20,122	4,270	0.21	0.13	0.16	0.16	0.24
Oxybutynin	7,251	1,631	0.22	0.17	0.16	0.16	0.21
Solifenacin	53,179	12,852	0.24	0.17	0.16	0.16	0.32
Tolterodine	57,264	14,512	0.25	0.18	0.16	0.16	0.33
	149,663						
Ever exposure							
Darifenacin	12,335	45,153	3.66	1.91	4.05	1.97	5.35
Fesoterodine	21,922	45,193	2.06	1.23	1.99	1.01	3.1
Oxybutynin	8,142	23,686	2.91	1.97	2.6	1.14	4.65
Solifenacin	57,112	159,879	2.8	1.82	2.61	1.19	4.29
Tolterodine	59,805	215,270	3.6	1.86	3.83	2.06	5.2
	159,316						
Single exposure							
Darifenacin	9,093	31,073	3.42	2.07	3.72	1.43	5.34
Fesoterodine	13,536	25,887	1.91	1.24	1.8	0.82	2.94
Oxybutynin	5,420	13,984	2.58	2.07	2.03	0.7	4.4
Solifenacin	47,313	125,376	2.65	1.85	2.35	1.02	4.17
Tolterodine	55,510	187,779	3.38	1.95	3.57	1.66	5.12
	130,872						
Multiple study OAB medications	23,317	105,082	4.51	3.8	3.48	1.61	6.55
Cumulative dose (mg)							
Darifenacin	12,335	37,973,041	3,078	5,169	945	210	3,150
Fesoterodine	21,922	30,986,809	1,414	2,100	448	212	1,680
Oxybutynin	8,142	16,080,777	1,975	3,276	864	500	2,000
Solifenacin	57,112	112237474	1,965	3,131	600	150	2,250
Tolterodine	59,805	60,462,703	1,011	1,649	360	120	1,060
	159,316						

OAB = overactive bladder; P25 = 25th percentile; P75 = 75th percentile; SD = standard deviation.
Current exposure = dispensing + duration + 7 days.
Recent exposure = up to 60 days gap after end of supply.
Ever exposure = starts at first dispensing of the drug and ends at minimum of mortality, emigration or end of study.
Single exposure starts at cohort entry on single drug and ends when another drug starts.
Multiple drug exposure starts when another drug is added to single exposure.
Cumulative dose = sum of dispensed amount (mg).
Cumulative duration = sum of duration.

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

	Episodes of Current or Recent Exposure to a Single OAB Medication										Episodes of Exposure to Multiple OAB Medications	
	Darifenacin (n = 9,093)		Fesoterodine (n = 13,536)		Oxybutynin (n = 5,420)		Solifenacin (n = 47,313)		Tolterodine (n = 55,510)		Multiple (n = 72)	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of therapy episode[b]												
Completed episodes												
Mean (SD) months	*8*	*(9.15)*	*6*	*(6.06)*	*7*	*(6.67)*	*8*	*(8.15)*	*8*	*(8.34)*	*3*	*(1.3)*
< 1 month	145	1.71	179	1.64	92	2.06	482	1.21	738	1.42	13	18.84
1-3 months	3,599	42.41	5,021	45.87	1,000	22.43	17,511	43.83	17,616	33.96	46	66.67
4-6 months	2,068	24.37	3,038	27.75	2,361	52.96	10,440	26.13	19,122	36.86	10	14.49
7-9 months	594	7.00	770	7.03	301	6.75	2,760	6.91	3,386	6.53	0	0.00
> 9 months	2,081	24.52	1,938	17.71	704	15.79	8,758	21.92	11,010	21.23	0	0.00
Ongoing episodes												
Mean (SD) months	*20*	*(20.96)*	*13*	*(13.1)*	*10*	*(11.64)*	*15*	*(17.44)*	*21*	*(21.96)*	*1*	*(0.99)*
< 1 month	44	7.26	215	8.30	60	6.24	622	8.45	236	6.49	1	33.33
1-3 months	140	23.10	696	26.87	313	32.54	2,151	29.22	923	25.37	2	66.67
4-6 months	60	9.90	259	10.00	182	18.92	719	9.77	319	8.77	0	0.00
7-9 months	24	3.96	184	7.10	91	9.46	437	5.94	139	3.82	0	0.00
> 9 months	338	55.78	1,236	47.72	316	32.85	3,433	46.63	2,021	55.55	0	0.00
Number of prescriptions during episode[b]												
1	4,338	47.71	6,800	50.24	3,371	62.20	23,143	48.91	30,460	54.87	58	80.56
2	1,527	16.79	1,975	14.59	747	13.78	7,268	15.36	7,746	13.95	12	16.67
3	799	8.79	1,077	7.96	380	7.01	3,705	7.83	3,810	6.86	2	2.78
4	511	5.62	751	5.55	239	4.41	2,749	5.81	2,713	4.89	0	0.00
5+	1,918	21.09	2,933	21.67	683	12.60	10,448	22.08	10,781	19.42	0	0.00

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

	Episodes of Current or Recent Exposure to a Single OAB Medication										Episodes of Exposure to Multiple OAB Medications	
	Darifenacin (n = 9,093)		Fesoterodine (n = 13,536)		Oxybutynin (n = 5,420)		Solifenacin (n = 47,313)		Tolterodine (n = 55,510)		Multiple (n = 72)	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Prior exposure to study drugs[c]												
Darifenacin	.	.	72	0.53	80	1.48	240	0.51	148	0.27	1	1.39
Fesoterodine	0	0.00	.	.	0	0.00	3	0.01	1	0.00	0	0.00
Oxybutynin	288	3.17	163	1.20	.	.	573	1.21	433	0.78	5	6.94
Solifenacin	598	6.58	482	3.56	318	5.87	.	.	803	1.45	6	8.33
Tolterodine	1,501	16.51	1,528	11.29	708	13.06	4,950	10.46	.	.	18	25.00
Multiple study drugs	2,071	22.78	1,974	14.58	1,121	20.68	5,971	12.62	5,276	9.50	.	.
No prior exposure	7,022	77.22	11,562	85.42	4,299	79.32	41,342	87.38	50,234	90.50	47	65.28
Reason therapy episode ended												
Discontinued OAB medication	6,330	69.61	9,411	69.53	3,371	62.20	34,605	73.14	43,543	78.44	38	52.78
Added another OAB medication	266	2.93	190	1.40	177	3.27	626	1.32	1,134	2.04	19	26.39
Switched to another OAB medication	1,891	20.80	1,345	9.94	910	16.79	4,720	9.98	7,195	12.96	12	16.67
Did not end[d]	606	6.66	2,590	19.13	962	17.75	7,362	15.56	3,638	6.55	3	4.17
Duration of episode, days; mean (SD)	269	(327.6)	235	(253.6)	224	(238.9)	264	(320.1)	258	(316)	78	(39.81)

OAB = overactive bladder; SD = standard deviation.

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

a. Therapy episodes are created by concatenating consecutive drug episodes into a single therapy episode as long as the gap between consecutive drug episodes is no more than 60 days. A drug episode refers to the period covered by the prescription date through the full days' supply plus 7 days. A switch or add on of another OAB medication also defines the end of a therapy episode.

b. Categories may be changed following review of data.

c. If multiple exposures preceded a therapy segment, then it is counted in each individual drug and in "Multiple study drugs."

d. Either continued through end of study period or patient mortality/emigration.

Table A9. Characteristics of Therapy Episodes,[a] by OAB Medication

	Therapy Episode Drug											
	Darifenacin		Fesoterodine		Oxybutynin		Solifenacin		Tolterodine		Multiple Study OAB Medications	
Variable	n	%	n	%	n	%	n	%	n	%	n	%
Total therapy episodes	17,989	7.5	30,570	12.7	11,813	4.9	83,222	34.7	88,844	37.0	7,703	3.2
Total therapy episodes that ended because of a switch to another OAB medication or an add-on of another OAB medication	4,449	24.7	4,575	15.0	2,789	23.6	10,611	12.8	14,262	16.1	3,208	41.7
Add-on OAB medication												
Any OAB medication	695	15.6	693	15.2	537	19.3	1,638	15.4	2,396	16.8	1,368	42.6
Darifenacin	.	.	72	9.31	81	10.48	272	35.19	286	37	62	8.0
Fesoterodine	179	10.66	.	.	115	6.85	606	36.09	669	39.85	110	6.6
Oxybutynin	97	12.08	133	16.56	.	.	225	28.02	231	28.77	117	14.6
Solifenacin	230	11.23	296	14.45	180	8.79	.	.	1189	58.06	153	7.5
Tolterodine	182	15.28	179	15.03	156	13.1	517	43.41	.	.	157	13.2
Multiple	7	0.8	13	1.6	5	0.6	18	2.2	21	2.5	769	92.3
Switch to another OAB medication												
Any OAB medication	3,754	84.4	3,882	84.9	2,252	80.8	8,973	84.6	11,866	83.2	1,840	57.4
Darifenacin	.	.	382	11.0	333	9.6	1,225	35.3	1,326	38.2	205	5.9
Fesoterodine	964	11.7	.	.	452	5.5	3,373	40.8	3,174	38.4	301	3.6
Oxybutynin	356	12.6	429	15.2	.	.	1,010	35.7	823	29.1	210	7.4
Solifenacin	1,430	12.7	1,992	17.7	844	7.5	.	.	6,436	57.1	567	5.0
Tolterodine	981	15.1	1,063	16.4	607	9.3	3,290	50.6	.	.	557	8.6
Multiple	23	9.7	16	6.8	16	6.8	75	31.7	107	45.2	.	.
Drug was not renewed or refilled[b]	13,540	75.3	25,995	85.0	9,024	76.4	72,611	87.3	74,582	84.0	4,495	58.4
Episode not preceded by exposure to any OAB medication in prior 12 months (naive episode)	7,858	43.7	14,162	46.3	4,856	41.1	46,470	55.8	54,809	61.7	60	0.8

OAB = overactive bladder.

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

a. Therapy episodes are created by concatenating consecutive drug episodes into a single therapy episode as long as the gap between consecutive drug episodes is no more than 60 days. A drug episode refers to the period covered by the prescription date through the full days supply plus 7 days. A switch or add-on of another OAB medication also defines the end of a therapy episode.

b. That is, a gap longer than 60 days occurred.

Table A10. Prescribed Strengths of Overactive Bladder Drugs

Formulation	Number Exposed n	Total Dispensings n	Dispensings per Exposed Mean	Dispensings per Exposed SD
Darifenacin				
15 mg (tablet)	917	3,482	3.80	4.71
15 mg (tablet) + 7.5 mg (tablet)	1,655	15,502	9.37	7.20
7.5 mg (tablet)	9,763	36,123	3.70	4.81
Fesoterodine				
4 mg (tablet)	16,592	63,854	3.85	5.54
4 mg (tablet) + 8 mg (tablet)	2,882	27,177	9.43	7.67
8 mg (tablet)	2,448	10,056	4.11	5.59
Oxybutynin				
0.5 mg/ml (solution)	180	980	5.44	7.31
0.5 mg/ml (solution) + 1 mg/ml (solution)	1	14	14.00	.
0.5 mg/ml (solution) + 3.9 mg/24 h (patch)	37	254	6.86	6.17
0.5 mg/ml (solution) + 3.9 mg/24 h (patch) + 5 mg (tablet)	4	88	22.00	3.37
0.5 mg/ml (solution) + 5 mg (tablet)	6	36	6.00	3.74
1 mg/ml (solution)	2	5	2.50	2.12
3.9 mg/24 h (patch)	3,443	11,316	3.29	4.52
3.9 mg/24 h (patch) + 5 mg (tablet)	118	1,324	11.22	14.20
5 mg (tablet)	4,351	15,463	3.55	7.02
Solifenacin				
10 mg (tablet)	4,163	19,804	4.76	8.28
10 mg (tablet) + 5 mg (tablet)	6,356	77,704	12.23	14.20
5 mg (tablet)	46,593	235,323	5.05	10.03
Tolterodine				
1 mg (tablet)	3,870	21,346	5.52	13.32
1 mg (tablet) + 2 mg (tablet)	945	13,169	13.94	18.91
1 mg (tablet) + 2 mg (tablet) + 4 mg (tablet)	208	4,250	20.43	20.57
1 mg (tablet) + 4 mg (tablet)	384	5,373	13.99	25.38
2 mg (tablet)	21,965	130,688	5.95	14.08
2 mg (tablet) + 4 mg (tablet)	4,685	62,201	13.28	18.45
4 mg (tablet)	27,748	151,895	5.47	12.12

SD = standard deviation.

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

						FIRST Neoplasm Event Type							
		Patients Without Cancer Endpoint*		Composite Event		Colon and Rectum		Pancreas		Lung and Bronchus		Female Breast	
		(n=122,049)		(n=5,653)		(n=888)		(n=140)		(n=427)		(n=961)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Age at cohort entry (years)													
	Mean (SD)	*66*	*(15.5)*	*71*	*(10.2)*	*73*	*(9.7)*	*72*	*(7.8)*	*71*	*(9.1)*	*68*	*(11.4)*
	18-24	2,153	1.8	2	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	25-34	3,778	3.1	9	0.2	3	0.3	0	0.0	0	0.0	1	0.1
	35-44	7,234	5.9	65	1.1	8	0.9	0	0.0	4	0.9	27	2.8
	45-54	13,976	11.5	254	4.5	35	3.9	3	2.1	10	2.3	90	9.4
	55-64	25,343	20.8	1,203	21.3	122	13.7	23	16.4	106	24.8	270	28.1
	65-74	33,003	27.0	2,002	35.4	318	35.8	66	47.1	150	35.1	292	30.4
	75-84	26,540	21.7	1,685	29.8	333	37.5	43	30.7	132	30.9	208	21.6
	85+	10,022	8.2	433	7.7	69	7.8	5	3.6	25	5.9	73	7.6
		122,049	100	5,653	100	888	100	140	100	427	100	961	100
Sex													
	Female	73,566	60.3	2,532	44.8	459	51.7	73	52.1	219	51.3	961	100.0
	Male	48,483	39.7	3,121	55.2	429	48.3	67	47.9	208	48.7	0	0.0
		122,049	100	5,653	100	888	100	140	100	427	100	961	100
Calendar year at cohort entry													
	2006	11,752	9.6	912	16.1	163	18.4	26	18.6	72	16.9	178	18.5
	2007	21,672	17.8	1,606	28.4	256	28.8	43	30.7	130	30.4	302	31.4
	2008	20,045	16.4	1,134	20.1	192	21.6	33	23.6	87	20.4	175	18.2
	2009	17,630	14.4	823	14.6	123	13.9	13	9.3	53	12.4	138	14.4
	2010	17,336	14.2	594	10.5	90	10.1	14	10.0	41	9.6	91	9.5
	2011	17,214	14.1	423	7.5	45	5.1	10	7.1	33	7.7	59	6.1
	2012	16,400	13.4	161	2.8	19	2.1	1	0.7	11	2.6	18	1.9
		122,049	100	5,653	100	888	100	140	100	427	100	961	100
Duration of enrollment prior to cohort													
	Mean (SD)	*1,478*	*(692.7)*	*1,138*	*(573.2)*	*1,082*	*(536.8)*	*1,063*	*(549.1)*	*1,098*	*(570.6)*	*1,075*	*(551.7)*
	1 to < 2 years	23,180	19.0	1,775	31.4	292	32.9	48	34.3	153	35.8	349	36.3
	2 to < 4 years	39,561	32.4	2,337	41.3	383	43.1	60	42.9	170	39.8	384	40.0
	4 to < 8 years	59,308	48.6	1,541	27.3	213	24.0	32	22.9	104	24.4	228	23.7

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

						FIRST Neoplasm Event Type							
		Patients Without Cancer Endpoint*		Composite Event		Colon and Rectum		Pancreas		Lung and Bronchus		Female Breast	
		(n=122,049)		(n=5,653)		(n=888)		(n=140)		(n=427)		(n=961)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of follow-up													
	Mean (SD)	*1,187*	*(691.2)*	*714*	*(571)*	*812*	*(571.2)*	*788*	*(552.5)*	*783*	*(569)*	*826*	*(569.5)*
	< 1 year	18,983	15.6	2,042	36.1	249	28.0	36	25.7	130	30.4	255	26.5
	1 to < 2 years	19,088	15.6	1,189	21.0	194	21.8	37	26.4	90	21.1	212	22.1
	2 to < 4 years	36,243	29.7	1,666	29.5	297	33.4	46	32.9	145	34.0	337	35.1
	4 to < 8 years	47,735	39.1	756	13.4	148	16.7	21	15.0	62	14.5	157	16.3
Menopause	Yes	61,031	50.0	2,411	42.6	444	50.0	73	52.1	216	50.6	894	93.0
Number of study drugs during follow-up													
	1	98,857	81.0	4,718	83.5	742	83.6	103	73.6	351	82.2	791	82.3
	2	18,722	15.3	791	14.0	121	13.6	30	21.4	64	15.0	133	13.8
	3	3,718	3.0	122	2.2	23	2.6	7	5.0	10	2.3	31	3.2
	4	656	0.5	20	0.4	2	0.2	0	0.0	2	0.5	6	0.6
	5	96	0.1	2	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		122,049	100	5,653	100	888	100	140	100	427	100	961	100
Number of different study drugs to which patient was exposed in the 12 months before this study													
	0	106,949	87.6	4,882	86.4	752	84.7	115	82.1	360	84.3	793	82.5
	1	13,525	11.1	690	12.2	124	14.0	23	16.4	63	14.8	149	15.5
	2	1,438	1.2	77	1.4	11	1.2	2	1.4	4	0.9	17	1.8
	3	128	0.1	4	0.1	1	0.1	0	0.0	0	0.0	2	0.2
	4	9	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		122,049	100	5,653	100	888	100	140	100	427	100	961	100

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

						FIRST Neoplasm Event Type							
		Patients Without Cancer Endpoint*		Composite Event		Colon and Rectum		Pancreas		Lung and Bronchus		Female Breast	
		(n=122,049)		(n=5,653)		(n=888)		(n=140)		(n=427)		(n=961)	
Variable	Category	n	%	n	%	n	%	n	%	n	%	n	%
Education (years)													
	Missing	19,479	16.0	1,083	19.2	165	18.6	34	24.3	78	18.3	182	18.9
	≤ 9	30,138	24.7	1,286	22.7	207	23.3	29	20.7	88	20.6	224	23.3
	< 9 to ≤ 12	43,227	35.4	1,984	35.1	307	34.6	44	31.4	158	37.0	348	36.2
	> 12	29,205	23.9	1,300	23.0	209	23.5	33	23.6	103	24.1	207	21.5
Income													
	Missing	2,706	2.2	126	2.2	14	1.6	4	2.9	10	2.3	27	2.8
	Low	18,138	14.9	904	16.0	140	15.8	19	13.6	62	14.5	156	16.2
	Midlow	26,272	21.5	1,237	21.9	201	22.6	30	21.4	88	20.6	215	22.4
	Midhigh	27,968	22.9	1,294	22.9	197	22.2	37	26.4	102	23.9	220	22.9
	High	46,965	38.5	2,092	37.0	336	37.8	50	35.7	165	38.6	343	35.7
Hospitalizations													
	None	64,720	53.0	2,962	52.4	445	50.1	66	47.1	187	43.8	524	54.5
	< 5	48,871	40.0	2,352	41.6	393	44.3	63	45.0	194	45.4	385	40.1
	5-10	7,098	5.8	297	5.3	44	5.0	8	5.7	42	9.8	46	4.8
	11-25	1,260	1.0	41	0.7	6	0.7	3	2.1	4	0.9	6	0.6
	26-50	95	0.1	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	> 50	5	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Outpatient visits													
	None	23,500	19.3	1,195	21.1	181	20.4	18	12.9	80	18.7	207	21.5
	< 5	54,323	44.5	2,534	44.8	386	43.5	59	42.1	178	41.7	429	44.6
	5-10	28,760	23.6	1,293	22.9	221	24.9	40	28.6	102	23.9	217	22.6
	11-25	12,973	10.6	529	9.4	77	8.7	20	14.3	54	12.6	91	9.5
	26-50	2,133	1.7	83	1.5	17	1.9	3	2.1	10	2.3	12	1.2
	> 50	360	0.3	19	0.3	6	0.7	0	0.0	3	0.7	5	0.5
Comorbidities													
Mild liver disease, Charlson	Yes	849	0.7	30	0.5	11	1.2	0	0.0	4	0.9	7	0.7
AIDS/HIV, Charlson	No	122,049	100.0	5,653	100.0	888	100.0	140	100.0	427	100.0	961	100.0
Cancer, Charlson	No	122,049	100.0	5,653	100.0	888	100.0	140	100.0	427	100.0	961	100.0
Metastatic carcinoma, Charlson	No	122,049	100.0	5,653	100.0	888	100.0	140	100.0	427	100.0	961	100.0

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

						FIRST Neoplasm Event Type							
		Patients Without Cancer Endpoint*		Composite Event		Colon and Rectum		Pancreas		Lung and Bronchus		Female Breast	
		(n=122,049)		(n=5,653)		(n=888)		(n=140)		(n=427)		(n=961)	
Variable	Category	n	%	n	%	n	%	n	%	n	%	n	%
Diabetes without complications, Charlson	Yes	9,172	7.5	449	7.9	86	9.7	20	14.3	41	9.6	57	5.9
Diabetes with complications, Charlson	Yes	3,181	2.6	153	2.7	34	3.8	6	4.3	18	4.2	17	1.8
Alcohol abuse and related conditions	Yes	1,979	1.6	89	1.6	11	1.2	3	2.1	15	3.5	14	1.5
Polycystic ovary syndrome	Yes	96	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Obesity	Yes	2,317	1.9	80	1.4	19	2.1	2	1.4	10	2.3	13	1.4
Dementia, Charlson	Yes	1,792	1.5	50	0.9	8	0.9	1	0.7	4	0.9	8	0.8
Drug abuse	Yes	508	0.4	8	0.1	1	0.1	0	0.0	3	0.7	3	0.3
Transient ischemic attack	Yes	1,614	1.3	65	1.1	9	1.0	1	0.7	5	1.2	13	1.4
Cerebrovascular disease, Charlson	Yes	8,948	7.3	415	7.3	77	8.7	11	7.9	44	10.3	63	6.6
Paraplegia and hemiplegia, Charlson	Yes	1,601	1.3	46	0.8	7	0.8	0	0.0	6	1.4	7	0.7
Heart failure	Yes	4,478	3.7	205	3.6	42	4.7	3	2.1	20	4.7	23	2.4
Coronary heart disease	Yes	11,639	9.5	662	11.7	104	11.7	15	10.7	59	13.8	71	7.4
Acute myocardial infarction	Yes	5,354	4.4	339	6.0	59	6.6	8	5.7	34	8.0	22	2.3
Congestive heart failure, Charlson	Yes	4,639	3.8	215	3.8	44	5.0	3	2.1	20	4.7	25	2.6
Stroke	Yes	6,897	5.7	334	5.9	66	7.4	8	5.7	35	8.2	43	4.5
Peripheral vascular disease, Charlson	Yes	2,740	2.2	175	3.1	26	2.9	9	6.4	40	9.4	18	1.9
Chronic pulmonary disease, Charlson	Yes	6,443	5.3	297	5.3	44	5.0	6	4.3	58	13.6	50	5.2
Peptic ulcer disease, Charlson	Yes	1,899	1.6	93	1.6	19	2.1	6	4.3	4	0.9	14	1.5
Moderate or severe liver disease, Charlson	Yes	156	0.1	7	0.1	3	0.3	2	1.4	0	0.0	1	0.1
Connective tissue disease-rheumatic disease, Charlson	Yes	3,451	2.8	145	2.6	23	2.6	3	2.1	20	4.7	30	3.1
Arthritis	Yes	2,450	2.0	115	2.0	21	2.4	3	2.1	17	4.0	23	2.4

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

						FIRST Neoplasm Event Type							
		Patients Without Cancer Endpoint*		Composite Event		Colon and Rectum		Pancreas		Lung and Bronchus		Female Breast	
		(n=122,049)		(n=5,653)		(n=888)		(n=140)		(n=427)		(n=961)	
Variable	Category	n	%	n	%	n	%	n	%	n	%	n	%
Gout	Yes	779	0.6	32	0.6	7	0.8	0	0.0	1	0.2	1	0.1
Fractures	Yes	9,319	7.6	363	6.4	73	8.2	10	7.1	42	9.8	64	6.7
Renal impairment	Yes	5,219	4.3	226	4.0	25	2.8	8	5.7	29	6.8	19	2.0
Renal disease, Charlson	Yes	1,191	1.0	59	1.0	10	1.1	1	0.7	8	1.9	4	0.4
Endometrial polyps or other benign growths of the uterus	Yes	441	0.4	9	0.2	0	0.0	0	0.0	0	0.0	5	0.5
Overactive bladder	Yes	21,907	17.9	765	13.5	155	17.5	25	17.9	78	18.3	235	24.5
Dialysis	Yes	73	0.1	5	0.1	1	0.1	0	0.0	0	0.0	2	0.2
Diabetes	Yes	13,676	11.2	661	11.7	130	14.6	27	19.3	58	13.6	87	9.1
Diabetes - diagnosis	Yes	9,897	8.1	488	8.6	95	10.7	20	14.3	47	11.0	61	6.3
Diabetes - drugs	Yes	12,073	9.9	585	10.3	112	12.6	25	17.9	52	12.2	69	7.2
Dyslipidemia	Yes	29,399	24.1	1,604	28.4	256	28.8	56	40.0	139	32.6	218	22.7
Dyslipidemia - diagnosis	Yes	5,919	4.8	302	5.3	43	4.8	10	7.1	29	6.8	28	2.9
Dyslipidemia - drugs	Yes	28,777	23.6	1,573	27.8	253	28.5	54	38.6	134	31.4	213	22.2
Hypertension	Yes	57,531	47.1	3,069	54.3	494	55.6	77	55.0	243	56.9	453	47.1
Hypertension - diagnosis	Yes	22,829	18.7	1,115	19.7	202	22.7	26	18.6	94	22.0	164	17.1
Hypertension - drugs	Yes	55,906	45.8	3,006	53.2	478	53.8	77	55.0	237	55.5	438	45.6
Peripheral artery disease	Yes	3,004	2.5	186	3.3	27	3.0	10	7.1	40	9.4	17	1.8
Peripheral artery disease - diagnosis	Yes	2,786	2.3	176	3.1	25	2.8	10	7.1	39	9.1	17	1.8
Peripheral artery disease - procedures	Yes	787	0.6	43	0.8	5	0.6	2	1.4	11	2.6	3	0.3
Organ transplantation	Yes	207	0.2	10	0.2	0	0.0	0	0.0	0	0.0	2	0.2
Organ transplantation - diagnosis	Yes	202	0.2	10	0.2	0	0.0	0	0.0	0	0.0	2	0.2
Organ transplantation - procedures	Yes	40	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Smoking	Yes	1,470	1.2	73	1.3	7	0.8	2	1.4	20	4.7	13	1.4
Smoking - diagnosis	Yes	484	0.4	25	0.4	3	0.3	1	0.7	5	1.2	3	0.3
Smoking - drugs	Yes	1,021	0.8	49	0.9	4	0.5	1	0.7	15	3.5	10	1.0

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

						FIRST Neoplasm Event Type							
		Patients Without Cancer Endpoint*		Composite Event		Colon and Rectum		Pancreas		Lung and Bronchus		Female Breast	
		(n=122,049)		(n=5,653)		(n=888)		(n=140)		(n=427)		(n=961)	
Variable	Category	n	%	n	%	n	%	n	%	n	%	n	%
Antiplatelets (including aspirin in low doses)	Yes	37,693	30.9	2,091	37.0	342	38.5	53	37.9	181	42.4	258	26.8
Low-dose aspirin	Yes	29,261	24.0	1,636	28.9	248	27.9	47	33.6	148	34.7	200	20.8
Digoxin	Yes	2,251	1.8	126	2.2	24	2.7	3	2.1	9	2.1	16	1.7
Nitrates	Yes	10,615	8.7	576	10.2	97	10.9	16	11.4	50	11.7	80	8.3
Statins	Yes	27,913	22.9	1,528	27.0	250	28.2	51	36.4	129	30.2	206	21.4
Hormone-replacement therapy	Yes	36,807	30.2	1,487	26.3	258	29.1	52	37.1	122	28.6	551	57.3
Thyroid hormone replacement	Yes	11,935	9.8	493	8.7	88	9.9	19	13.6	29	6.8	142	14.8
Tamoxifen	No	122,049	100.0	5,653	100.0	888	100.0	140	100.0	427	100.0	961	100.0
Immunosuppressive agents	Yes	2,137	1.8	111	2.0	21	2.4	4	2.9	14	3.3	15	1.6
Non-aspirin NSAIDs	Yes	39,365	32.3	1,725	30.5	256	28.8	46	32.9	139	32.6	349	36.3
Mammograms	Yes	93	0.1	1	0.0	0	0.0	0	0.0	0	0.0	1	0.1
Sigmoidoscopies	Yes	1,569	1.3	63	1.1	13	1.5	2	1.4	7	1.6	10	1.0

HIV = human immunodeficiency virus; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation.

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

	FIRST Neoplasm Event Type											
	Corpus Uteri		Prostate		Urinary Bladder		Kidney & Renal Pelvis		Melanoma of the Skin		Non-Hodgkin Lymphoma	
	(n=245)		(n=1,530)		(n=695)		(n=144)		(n=425)		(n=198)	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Age at cohort entry (years)												
	71	*(10.4)*	*71*	*(8.9)*	*73*	*(10.4)*	*69*	*(11)*	*71*	*(11.7)*	*73*	*(10.1)*
	0	0.0	0	0.0	0	0.0	1	0.7	1	0.2	0	0.0
	0	0.0	0	0.0	0	0.0	2	1.4	3	0.7	0	0.0
	2	0.8	0	0.0	7	1.0	1	0.7	14	3.3	2	1.0
	17	6.9	44	2.9	28	4.0	8	5.6	14	3.3	5	2.5
	48	19.6	363	23.7	118	17.0	30	20.8	82	19.3	41	20.7
	76	31.0	613	40.1	241	34.7	57	39.6	139	32.7	50	25.3
	84	34.3	417	27.3	216	31.1	37	25.7	135	31.8	80	40.4
	18	7.3	93	6.1	85	12.2	8	5.6	37	8.7	20	10.1
	245	100	1,530	100	695	100	144	100	425	100	198	100
Sex												
	245	100.0	0	0.0	201	28.9	70	48.6	218	51.3	86	43.4
	0	0.0	1,530	100.0	494	71.1	74	51.4	207	48.7	112	56.6
	245	100	1,530	100	695	100	144	100	425	100	198	100
Calendar year at cohort entry												
	42	17.1	234	15.3	84	12.1	14	9.7	61	14.4	38	19.2
	80	32.7	418	27.3	159	22.9	43	29.9	121	28.5	54	27.3
	57	23.3	285	18.6	140	20.1	33	22.9	92	21.6	40	20.2
	36	14.7	239	15.6	112	16.1	18	12.5	66	15.5	25	12.6
	11	4.5	164	10.7	90	12.9	17	11.8	54	12.7	22	11.1
	15	6.1	128	8.4	82	11.8	13	9.0	23	5.4	15	7.6
	4	1.6	62	4.1	28	4.0	6	4.2	8	1.9	4	2.0
	245	100	1,530	100	695	100	144	100	425	100	198	100
Duration of enrollment prior to cohort												
	1,037	*(513.6)*	*1,179*	*(592.5)*	*1,278*	*(607)*	*1,199*	*(600.7)*	*1,135*	*(543.2)*	*1,104*	*(585)*
	82	33.5	457	29.9	159	22.9	38	26.4	124	29.2	73	36.9
	119	48.6	619	40.5	283	40.7	65	45.1	183	43.1	71	35.9
	44	18.0	454	29.7	253	36.4	41	28.5	118	27.8	54	27.3

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

	FIRST Neoplasm Event Type											
	Corpus Uteri		Prostate		Urinary Bladder		Kidney & Renal Pelvis		Melanoma of the Skin		Non-Hodgkin Lymphoma	
	(n=245)		(n=1,530)		(n=695)		(n=144)		(n=425)		(n=198)	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of follow-up												
	790	*(587.6)*	*621*	*(557.5)*	*492*	*(516.8)*	*673*	*(550.6)*	*807*	*(556.7)*	*764*	*(576.3)*
	75	30.6	683	44.6	387	55.7	50	34.7	115	27.1	62	31.3
	49	20.0	282	18.4	133	19.1	41	28.5	99	23.3	52	26.3
	85	34.7	406	26.5	122	17.6	39	27.1	139	32.7	50	25.3
	36	14.7	159	10.4	53	7.6	14	9.7	72	16.9	34	17.2
Menopause	239	97.6	0	0.0	196	28.2	64	44.4	200	47.1	85	42.9
Number of study drugs during follow-up												
	198	80.8	1,316	86.0	561	80.7	126	87.5	365	85.9	165	83.3
	41	16.7	190	12.4	117	16.8	16	11.1	53	12.5	26	13.1
	4	1.6	20	1.3	16	2.3	1	0.7	6	1.4	4	2.0
	2	0.8	2	0.1	1	0.1	1	0.7	1	0.2	3	1.5
	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	245	100	1,530	100	695	100	144	100	425	100	198	100
Number of different study drugs to which patient was exposed in the 12 months before this study												
	193	78.8	1,396	91.2	639	91.9	124	86.1	359	84.5	151	76.3
	43	17.6	120	7.8	48	6.9	19	13.2	59	13.9	42	21.2
	8	3.3	14	0.9	8	1.2	1	0.7	7	1.6	5	2.5
	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	245	100	1,530	100	695	100	144	100	425	100	198	100

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

	FIRST Neoplasm Event Type											
	Corpus Uteri		Prostate		Urinary Bladder		Kidney & Renal Pelvis		Melanoma of the Skin		Non-Hodgkin Lymphoma	
	(n=245)		(n=1,530)		(n=695)		(n=144)		(n=425)		(n=198)	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Education (years)												
	39	15.9	311	20.3	121	17.4	28	19.4	97	22.8	28	14.1
	45	18.4	337	22.0	172	24.7	39	27.1	93	21.9	52	26.3
	99	40.4	533	34.8	233	33.5	35	24.3	152	35.8	75	37.9
	62	25.3	349	22.8	169	24.3	42	29.2	83	19.5	43	21.7
Income												
	2	0.8	34	2.2	15	2.2	5	3.5	9	2.1	6	3.0
	34	13.9	242	15.8	120	17.3	18	12.5	81	19.1	32	16.2
	41	16.7	333	21.8	156	22.4	32	22.2	102	24.0	39	19.7
	71	29.0	368	24.1	141	20.3	36	25.0	78	18.4	44	22.2
	97	39.6	553	36.1	263	37.8	53	36.8	155	36.5	77	38.9
Hospitalizations												
	127	51.8	863	56.4	365	52.5	64	44.4	221	52.0	100	50.5
	106	43.3	575	37.6	295	42.4	75	52.1	184	43.3	82	41.4
	11	4.5	80	5.2	32	4.6	3	2.1	17	4.0	14	7.1
	1	0.4	11	0.7	3	0.4	2	1.4	3	0.7	2	1.0
	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Outpatient visits												
	47	19.2	368	24.1	154	22.2	22	15.3	67	15.8	51	25.8
	118	48.2	704	46.0	324	46.6	59	41.0	210	49.4	67	33.8
	62	25.3	303	19.8	152	21.9	50	34.7	98	23.1	48	24.2
	18	7.3	136	8.9	55	7.9	11	7.6	42	9.9	25	12.6
	0	0.0	17	1.1	10	1.4	2	1.4	6	1.4	6	3.0
	0	0.0	2	0.1	0	0.0	0	0.0	2	0.5	1	0.5
Comorbidities												
Mild liver disease, Charlson	0	0.0	6	0.4	0	0.0	0	0.0	0	0.0	2	1.0
AIDS/HIV, Charlson	245	100.0	1,530	100.0	695	100.0	144	100.0	425	100.0	198	100.0
Cancer, Charlson	245	100.0	1,530	100.0	695	100.0	144	100.0	425	100.0	198	100.0
Metastatic carcinoma, Charlson	245	100.0	1,530	100.0	695	100.0	144	100.0	425	100.0	198	100.0

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

	FIRST Neoplasm Event Type											
	Corpus Uteri		Prostate		Urinary Bladder		Kidney & Renal Pelvis		Melanoma of the Skin		Non-Hodgkin Lymphoma	
	(n=245)		(n=1,530)		(n=695)		(n=144)		(n=425)		(n=198)	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Diabetes without complications, Charlson	21	8.6	100	6.5	62	8.9	13	9.0	32	7.5	17	8.6
Diabetes with complications, Charlson	6	2.4	36	2.4	19	2.7	2	1.4	6	1.4	9	4.5
Alcohol abuse and related conditions	1	0.4	32	2.1	5	0.7	3	2.1	4	0.9	1	0.5
Polycystic ovary syndrome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Obesity	8	3.3	13	0.8	9	1.3	1	0.7	3	0.7	2	1.0
Dementia, Charlson	1	0.4	10	0.7	9	1.3	1	0.7	4	0.9	4	2.0
Drug abuse	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5
Transient ischemic attack	2	0.8	20	1.3	10	1.4	1	0.7	3	0.7	1	0.5
Cerebrovascular disease, Charlson	14	5.7	102	6.7	50	7.2	9	6.3	32	7.5	13	6.6
Paraplegia and hemiplegia, Charlson	4	1.6	12	0.8	3	0.4	4	2.8	3	0.7	0	0.0
Heart failure	9	3.7	53	3.5	32	4.6	9	6.3	8	1.9	6	3.0
Coronary heart disease	26	10.6	203	13.3	96	13.8	11	7.6	53	12.5	24	12.1
Acute myocardial infarction	8	3.3	110	7.2	58	8.3	5	3.5	22	5.2	13	6.6
Congestive heart failure, Charlson	9	3.7	58	3.8	32	4.6	9	6.3	9	2.1	6	3.0
Stroke	12	4.9	81	5.3	41	5.9	8	5.6	30	7.1	10	5.1
Peripheral vascular disease, Charlson	3	1.2	33	2.2	22	3.2	2	1.4	15	3.5	7	3.5
Chronic pulmonary disease, Charlson	8	3.3	64	4.2	40	5.8	7	4.9	17	4.0	3	1.5
Peptic ulcer disease, Charlson	3	1.2	28	1.8	9	1.3	3	2.1	5	1.2	2	1.0
Moderate or severe liver disease, Charlson	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5
Connective tissue disease-rheumatic disease, Charlson	4	1.6	22	1.4	19	2.7	1	0.7	15	3.5	8	4.0
Arthritis	2	0.8	17	1.1	16	2.3	1	0.7	10	2.4	5	2.5

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

	FIRST Neoplasm Event Type											
	Corpus Uteri		Prostate		Urinary Bladder		Kidney & Renal Pelvis		Melanoma of the Skin		Non-Hodgkin Lymphoma	
	(n=245)		(n=1,530)		(n=695)		(n=144)		(n=425)		(n=198)	
Variable	n	%	n	%	n	%	n	%	n	%	n	%
Gout	0	0.0	13	0.8	7	1.0	0	0.0	2	0.5	1	0.5
Fractures	17	6.9	69	4.5	37	5.3	10	6.9	29	6.8	12	6.1
Renal impairment	7	2.9	73	4.8	38	5.5	9	6.3	10	2.4	8	4.0
Renal disease, Charlson	2	0.8	22	1.4	10	1.4	0	0.0	0	0.0	2	1.0
Endometrial polyps or other benign growths of the uterus	0	0.0	0	0.0	2	0.3	0	0.0	2	0.5	0	0.0
Overactive bladder	62	25.3	45	2.9	48	6.9	23	16.0	65	15.3	29	14.6
Dialysis	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.5
Diabetes	31	12.7	146	9.5	98	14.1	16	11.1	47	11.1	21	10.6
Diabetes - diagnosis	24	9.8	107	7.0	69	9.9	13	9.0	33	7.8	19	9.6
Diabetes - drugs	28	11.4	132	8.6	92	13.2	14	9.7	44	10.4	17	8.6
Dyslipidemia	59	24.1	442	28.9	220	31.7	39	27.1	126	29.6	49	24.7
Dyslipidemia - diagnosis	16	6.5	96	6.3	36	5.2	7	4.9	27	6.4	10	5.1
Dyslipidemia - drugs	57	23.3	434	28.4	217	31.2	38	26.4	125	29.4	48	24.2
Hypertension	139	56.7	834	54.5	380	54.7	95	66.0	250	58.8	104	52.5
Hypertension - diagnosis	52	21.2	273	17.8	138	19.9	37	25.7	91	21.4	38	19.2
Hypertension - drugs	137	55.9	817	53.4	378	54.4	94	65.3	247	58.1	103	52.0
Peripheral artery disease	3	1.2	39	2.5	23	3.3	3	2.1	16	3.8	8	4.0
Peripheral artery disease - diagnosis	3	1.2	36	2.4	20	2.9	3	2.1	16	3.8	7	3.5
Peripheral artery disease - procedures	0	0.0	7	0.5	9	1.3	2	1.4	3	0.7	1	0.5
Organ transplantation	0	0.0	3	0.2	5	0.7	0	0.0	0	0.0	0	0.0
Organ transplantation - diagnosis	0	0.0	3	0.2	5	0.7	0	0.0	0	0.0	0	0.0
Organ transplantation - procedures	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Smoking	0	0.0	14	0.9	8	1.2	6	4.2	2	0.5	1	0.5
Smoking - diagnosis	0	0.0	7	0.5	5	0.7	1	0.7	0	0.0	0	0.0
Smoking - drugs	0	0.0	8	0.5	3	0.4	5	3.5	2	0.5	1	0.5

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

	FIRST Neoplasm Event Type											
	Corpus Uteri		Prostate		Urinary Bladder		Kidney & Renal Pelvis		Melanoma of the Skin		Non-Hodgkin Lymphoma	
	(n=245)		(n=1,530)		(n=695)		(n=144)		(n=425)		(n=198)	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Antiplatelets (including aspirin in low doses)	82	33.5	596	39.0	291	41.9	57	39.6	162	38.1	69	34.8
Low-dose aspirin	70	28.6	477	31.2	224	32.2	42	29.2	123	28.9	57	28.8
Digoxin	4	1.6	35	2.3	18	2.6	4	2.8	8	1.9	5	2.5
Nitrates	25	10.2	156	10.2	74	10.6	8	5.6	45	10.6	25	12.6
Statins	56	22.9	422	27.6	208	29.9	37	25.7	124	29.2	45	22.7
Hormone-replacement therapy	162	66.1	0	0.0	129	18.6	37	25.7	132	31.1	44	22.2
Thyroid hormone replacement	43	17.6	56	3.7	49	7.1	12	8.3	35	8.2	20	10.1
Tamoxifen	245	100.0	1,530	100.0	695	100.0	144	100.0	425	100.0	198	100.0
Immunosuppressive agents	0	0.0	22	1.4	14	2.0	1	0.7	11	2.6	9	4.5
Non-aspirin NSAIDs	92	37.6	403	26.3	200	28.8	49	34.0	138	32.5	53	26.8
Mammograms	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sigmoidoscopies	4	1.6	12	0.8	10	1.4	0	0.0	1	0.2	4	2.0

HIV = human immunodeficiency virus; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation.

Table N3. 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	
Composite	Overall ever treated with:									
	Any OAB medication	5,653	130,944	417,795	13.53	13.18	13.89	13.52	13.17	13.88
	Darifenacin	606	12,335	45,153	13.42	12.37	14.53	13.57	12.48	14.66
	Fesoterodine	598	21,922	45,193	13.23	12.19	14.34	13.26	12.19	14.33
	Oxybutynin	273	8,142	23,686	11.53	10.20	12.98	14.14	12.41	15.88
	Solifenacin	2,177	57,112	159,876	13.62	13.05	14.20	14.08	13.49	14.68
	Tolterodine	2,996	59,805	215,270	13.92	13.42	14.42	13.37	12.89	13.85
	Female ever treated with:									
	Any OAB medication	2,532	77,992	256,053	9.89	9.51	10.28	9.96	9.57	10.35
	Darifenacin	323	7,894	30,547	10.57	9.45	11.79	10.43	9.29	11.57
	Fesoterodine	277	13,674	29,187	9.49	8.41	10.68	9.42	8.30	10.53
	Oxybutynin	154	5,327	16,330	9.43	8.00	11.04	10.27	8.63	11.91
	Solifenacin	1,078	36,948	105,737	10.20	9.60	10.82	10.30	9.68	10.92
	Tolterodine	1,225	33,076	122,874	9.97	9.42	10.54	9.90	9.35	10.46
	Male ever treated with:									
	Any OAB medication	3,121	52,952	161,742	19.30	18.63	19.99	19.41	18.72	20.09
	Darifenacin	283	4,441	14,606	19.38	17.18	21.77	18.75	16.56	20.94
	Fesoterodine	321	8,248	16,005	20.06	17.92	22.37	19.61	17.45	21.77
	Oxybutynin	119	2,815	7,356	16.18	13.40	19.36	20.55	16.82	24.27
	Solifenacin	1,099	20,164	54,139	20.30	19.12	21.54	20.33	19.13	21.53
	Tolterodine	1,771	26,729	92,396	19.17	18.29	20.08	19.10	18.21	19.99

Table N3. 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	
Colorectal	Overall ever treated with:									
	Any OAB medication	888	130,944	417,795	2.13	1.99	2.27	2.14	2.00	2.28
	Darifenacin	107	12,335	45,153	2.37	1.94	2.86	2.34	1.89	2.78
	Fesoterodine	73	21,922	45,193	1.62	1.27	2.03	1.61	1.24	1.99
	Oxybutynin	47	8,142	23,686	1.98	1.46	2.64	2.39	1.69	3.09
	Solifenacin	322	57,112	159,876	2.01	1.80	2.25	2.08	1.85	2.31
	Tolterodine	487	59,805	215,270	2.26	2.07	2.47	2.20	2.00	2.39
	Female ever treated with:									
	Any OAB medication	459	77,992	256,053	1.79	1.63	1.96	1.81	1.65	1.98
	Darifenacin	66	7,894	30,547	2.16	1.67	2.75	2.13	1.61	2.64
	Fesoterodine	39	13,674	29,187	1.34	0.95	1.83	1.33	0.91	1.75
	Oxybutynin	30	5,327	16,330	1.84	1.24	2.62	2.06	1.32	2.81
	Solifenacin	176	36,948	105,737	1.66	1.43	1.93	1.70	1.45	1.95
	Tolterodine	240	33,076	122,874	1.95	1.71	2.22	1.91	1.67	2.16
	Male ever treated with:									
	Any OAB medication	429	52952	161742	2.65	2.41	2.92	2.67	2.42	2.93
	Darifenacin	41	4441	14606	2.81	2.01	3.81	2.68	1.86	3.51
	Fesoterodine	34	8248	16005	2.12	1.47	2.97	2.07	1.37	2.78
	Oxybutynin	17	2815	7356	2.31	1.35	3.70	2.93	1.53	4.34
	Solifenacin	146	20164	54139	2.70	2.28	3.17	2.72	2.27	3.16
	Tolterodine	247	26729	92396	2.67	2.35	3.03	2.66	2.33	2.99

Table N3. 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	
Pancreas	Overall ever treated with:									
	Any OAB medication	140	130,944	417,795	0.34	0.28	0.40	0.34	0.28	0.39
	Darifenacin	13	12,335	45,153	0.29	0.15	0.49	0.28	0.13	0.43
	Fesoterodine	19	21,922	45,193	0.42	0.25	0.66	0.40	0.22	0.58
	Oxybutynin	15	8,142	23,686	0.63	0.35	1.04	0.75	0.36	1.14
	Solifenacin	55	57,112	159,876	0.34	0.26	0.45	0.36	0.26	0.46
	Tolterodine	77	59,805	215,270	0.36	0.28	0.45	0.35	0.27	0.43
	Female ever treated with:									
	Any OAB medication	73	77,992	256,053	0.29	0.22	0.36	0.29	0.22	0.36
	Darifenacin	10	7,894	30,547	0.33	0.16	0.60	0.32	0.12	0.52
	Fesoterodine	11	13,674	29,187	0.38	0.19	0.67	0.34	0.14	0.55
	Oxybutynin	10	5,327	16,330	0.61	0.29	1.12	0.70	0.26	1.14
	Solifenacin	27	36,948	105,737	0.26	0.17	0.37	0.26	0.16	0.36
	Tolterodine	36	33,076	122,874	0.29	0.21	0.41	0.30	0.20	0.39
	Male ever treated with:									
	Any OAB medication	67	52,952	161,742	0.41	0.32	0.53	0.42	0.32	0.52
	Darifenacin	3	4,441	14,606	0.21	0.04	0.59	0.21	0.00	0.44
	Fesoterodine	8	8,248	16,005	0.50	0.22	0.98	0.49	0.15	0.83
	Oxybutynin	5	2,815	7,356	0.68	0.22	1.57	0.84	0.10	1.58
	Solifenacin	28	20,164	54,139	0.52	0.34	0.75	0.52	0.33	0.72
	Tolterodine	41	26,729	92,396	0.44	0.32	0.60	0.45	0.31	0.58

Table N3. 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	
Lung & bronchus	Overall ever treated with:									
	Any OAB medication	427	130,944	417,795	1.02	0.93	1.12	1.03	0.93	1.12
	Darifenacin	48	12,335	45,153	1.06	0.78	1.41	1.06	0.76	1.36
	Fesoterodine	45	21,922	45,193	1.00	0.73	1.33	0.97	0.69	1.26
	Oxybutynin	22	8,142	23,686	0.93	0.58	1.41	1.20	0.68	1.73
	Solifenacin	165	57,112	159,876	1.03	0.88	1.20	1.05	0.89	1.21
	Tolterodine	230	59,805	215,270	1.07	0.93	1.22	1.04	0.91	1.18
	Female ever treated with:									
	Any OAB medication	219	77,992	256,053	0.86	0.75	0.98	0.86	0.75	0.98
	Darifenacin	27	7,894	30,547	0.88	0.58	1.29	0.86	0.53	1.18
	Fesoterodine	23	13,674	29,187	0.79	0.50	1.18	0.78	0.46	1.10
	Oxybutynin	12	5,327	16,330	0.73	0.38	1.28	0.79	0.34	1.24
	Solifenacin	99	36,948	105,737	0.94	0.76	1.14	0.94	0.76	1.13
	Tolterodine	105	33,076	122,874	0.85	0.70	1.03	0.86	0.69	1.02
	Male ever treated with:									
	Any OAB medication	208	52,952	161,742	1.29	1.12	1.47	1.29	1.12	1.47
	Darifenacin	21	4,441	14,606	1.44	0.89	2.20	1.39	0.80	1.99
	Fesoterodine	22	8,248	16,005	1.37	0.86	2.08	1.29	0.75	1.83
	Oxybutynin	10	2,815	7,356	1.36	0.65	2.49	1.88	0.70	3.06
	Solifenacin	66	20,164	54,139	1.22	0.94	1.55	1.22	0.92	1.51
	Tolterodine	125	26,729	92,396	1.35	1.13	1.61	1.34	1.11	1.58

Table N3. 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	
Breast	Overall ever treated with:									
	Any OAB medication	961	130,944	417,795	2.30	2.16	2.45	2.35	2.20	2.50
	Darifenacin	125	12,335	45,153	2.77	2.30	3.30	2.50	2.06	2.94
	Fesoterodine	99	21,922	45,193	2.19	1.78	2.67	2.12	1.70	2.54
	Oxybutynin	55	8,142	23,686	2.32	1.75	3.02	2.25	1.65	2.85
	Solifenacin	424	57,112	159,876	2.65	2.41	2.92	2.50	2.26	2.74
	Tolterodine	455	59,805	215,270	2.11	1.92	2.32	2.32	2.10	2.53
	Female ever treated with:									
	Any OAB medication	961	77,992	256,053	3.75	3.52	4.00	3.77	3.53	4.01
	Darifenacin	125	7,894	30,547	4.09	3.41	4.88	4.01	3.30	4.71
	Fesoterodine	99	13,674	29,187	3.39	2.76	4.13	3.40	2.72	4.07
	Oxybutynin	55	5,327	16,330	3.37	2.54	4.38	3.61	2.65	4.57
	Solifenacin	424	36,948	105,737	4.01	3.64	4.41	4.01	3.63	4.39
	Tolterodine	455	33,076	122,874	3.70	3.37	4.06	3.72	3.38	4.06
	Male ever treated with:									
	Any OAB medication	.	52,952	161,742	.	.	.	0.00	.	.
	Darifenacin	.	4,441	14,606	.	.	.	0.00	.	.
	Fesoterodine	.	8,248	16,005	.	.	.	0.00	.	.
	Oxybutynin	.	2,815	7,356	.	.	.	0.00	.	.
	Solifenacin	.	20,164	54,139	.	.	.	0.00	.	.
	Tolterodine	.	26,729	92,396	.	.	.	0.00	.	.

Table N3. 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	
Corpus uteri	Overall ever treated with:									
	Any OAB medication	245	130,944	417,795	0.59	0.52	0.66	0.60	0.53	0.68
	Darifenacin	23	12,335	45,153	0.51	0.32	0.76	0.47	0.28	0.66
	Fesoterodine	26	21,922	45,193	0.58	0.38	0.84	0.53	0.33	0.74
	Oxybutynin	14	8,142	23,686	0.59	0.32	0.99	0.58	0.27	0.89
	Solifenacin	107	57,112	159,876	0.67	0.55	0.81	0.64	0.51	0.76
	Tolterodine	123	59,805	215,270	0.57	0.47	0.68	0.61	0.51	0.72
		.	.	.	.	.	.	.	.	.
	Female ever treated with:									
	Any OAB medication	245	77,992	256,053	0.96	0.84	1.08	0.97	0.84	1.09
	Darifenacin	23	7,894	30,547	0.75	0.48	1.13	0.75	0.44	1.05
	Fesoterodine	26	13,674	29,187	0.89	0.58	1.30	0.86	0.53	1.19
	Oxybutynin	14	5,327	16,330	0.86	0.47	1.44	0.93	0.44	1.43
	Solifenacin	107	36,948	105,737	1.01	0.83	1.22	1.02	0.83	1.21
	Tolterodine	123	33,076	122,874	1.00	0.83	1.19	0.99	0.81	1.16
		.	.	.	.	.	.	.	.	.
	Male ever treated with:									
	Any OAB medication	.	52,952	161,742	.	.	.	0.00	.	.
	Darifenacin	.	4,441	14,606	.	.	.	0.00	.	.
	Fesoterodine	.	8,248	16,005	.	.	.	0.00	.	.
	Oxybutynin	.	2,815	7,356	.	.	.	0.00	.	.
	Solifenacin	.	20,164	54,139	.	.	.	0.00	.	.
	Tolterodine	.	26,729	92,396	.	.	.	0.00	.	.
		.	.	.	.	.	.	.	.	.

Table N3. 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	
Prostate	Overall ever treated with:									
	Any OAB medication	1,530	130,944	417,795	3.66	3.48	3.85	3.58	3.41	3.76
	Darifenacin	140	12,335	45,153	3.10	2.61	3.66	3.51	2.93	4.09
	Fesoterodine	160	21,922	45,193	3.54	3.01	4.13	3.67	3.10	4.25
	Oxybutynin	50	8,142	23,686	2.11	1.57	2.78	3.23	2.33	4.14
	Solifenacin	557	57,112	159,876	3.48	3.20	3.79	3.86	3.54	4.18
	Tolterodine	850	59,805	215,270	3.95	3.69	4.22	3.46	3.23	3.70
	Female ever treated with:									
	Any OAB medication	.	77,992	256,053	.	.	.	0.00	.	.
	Darifenacin	.	7,894	30,547	.	.	.	0.00	.	.
	Fesoterodine	.	13,674	29,187	.	.	.	0.00	.	.
	Oxybutynin	.	5,327	16,330	.	.	.	0.00	.	.
	Solifenacin	.	36,948	105,737	.	.	.	0.00	.	.
	Tolterodine	.	33,076	122,874	.	.	.	0.00	.	.
		.	.	.	.	.	.	.	.	.
	Male ever treated with:									
	Any OAB medication	1,530	52,952	161,742	9.46	8.99	9.95	9.50	9.03	9.98
	Darifenacin	140	4,441	14,606	9.59	8.06	11.31	9.31	7.77	10.86
	Fesoterodine	160	8,248	16,005	10.00	8.51	11.67	9.74	8.22	11.26
	Oxybutynin	50	2,815	7,356	6.80	5.04	8.96	8.57	6.17	10.97
	Solifenacin	557	20,164	54,139	10.29	9.45	11.18	10.24	9.39	11.09
	Tolterodine	850	26,729	92,396	9.20	8.59	9.84	9.18	8.56	9.80
		.	.	.	.	.	.	.	.	.

Table N3. 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	
Bladder	Overall ever treated with:									
	Any OAB medication	695	130,944	417,795	1.66	1.54	1.79	1.65	1.53	1.77
	Darifenacin	51	12,335	45,153	1.13	0.84	1.48	1.22	0.88	1.55
	Fesoterodine	101	21,922	45,193	2.23	1.82	2.72	2.30	1.84	2.75
	Oxybutynin	29	8,142	23,686	1.22	0.82	1.76	1.72	1.08	2.36
	Solifenacin	272	57,112	159,876	1.70	1.51	1.92	1.82	1.60	2.04
	Tolterodine	379	59,805	215,270	1.76	1.59	1.95	1.62	1.46	1.79
		.	.	.	.	.	.	.	.	.
	Female ever treated with:									
	Any OAB medication	201	77,992	256,053	0.78	0.68	0.90	0.79	0.68	0.90
	Darifenacin	15	7,894	30,547	0.49	0.27	0.81	0.50	0.25	0.76
	Fesoterodine	39	13,674	29,187	1.34	0.95	1.83	1.35	0.92	1.78
	Oxybutynin	7	5,327	16,330	0.43	0.17	0.88	0.49	0.12	0.85
	Solifenacin	95	36,948	105,737	0.90	0.73	1.10	0.92	0.74	1.11
	Tolterodine	98	33,076	122,874	0.80	0.65	0.97	0.78	0.62	0.93
		.	.	.	.	.	.	.	.	.
	Male ever treated with:									
	Any OAB medication	494	52,952	161,742	3.05	2.79	3.34	3.07	2.80	3.34
	Darifenacin	36	4,441	14,606	2.46	1.73	3.41	2.40	1.61	3.18
	Fesoterodine	62	8,248	16,005	3.87	2.97	4.97	3.85	2.89	4.82
	Oxybutynin	22	2,815	7,356	2.99	1.87	4.53	3.75	2.16	5.35
	Solifenacin	177	20,164	54,139	3.27	2.81	3.79	3.30	2.82	3.79
	Tolterodine	281	26,729	92,396	3.04	2.70	3.42	3.02	2.66	3.37
		.	.	.	.	.	.	.	.	.

Table N3. 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	
Kidney & renal pelvis	Overall ever treated with:									
	Any OAB medication	144	130,944	417,795	0.34	0.29	0.41	0.34	0.29	0.40
	Darifenacin	19	12,335	45,153	0.42	0.25	0.66	0.42	0.23	0.62
	Fesoterodine	14	21,922	45,193	0.31	0.17	0.52	0.31	0.15	0.47
	Oxybutynin	4	8,142	23,686	0.17	0.05	0.43	0.18	0.00	0.35
	Solifenacin	61	57,112	159,876	0.38	0.29	0.49	0.39	0.29	0.49
	Tolterodine	66	59,805	215,270	0.31	0.24	0.39	0.30	0.22	0.37
		.	.	.	.	.	.	.	.	.
	Female ever treated with:									
	Any OAB medication	70	77,992	256,053	0.27	0.21	0.35	0.28	0.21	0.34
	Darifenacin	10	7,894	30,547	0.33	0.16	0.60	0.33	0.12	0.53
	Fesoterodine	7	13,674	29,187	0.24	0.10	0.49	0.22	0.06	0.39
	Oxybutynin	3	5,327	16,330	0.18	0.04	0.53	0.18	0.00	0.39
	Solifenacin	33	36,948	105,737	0.31	0.21	0.44	0.31	0.20	0.42
	Tolterodine	28	33,076	122,874	0.23	0.15	0.33	0.23	0.14	0.31
		.	.	.	.	.	.	.	.	.
	Male ever treated with:									
	Any OAB medication	74	52,952	161,742	0.46	0.36	0.57	0.46	0.36	0.56
	Darifenacin	9	4,441	14,606	0.62	0.28	1.17	0.58	0.20	0.97
	Fesoterodine	7	8,248	16,005	0.44	0.18	0.90	0.45	0.11	0.79
	Oxybutynin	1	2,815	7,356	0.14	0.00	0.69	0.16	0.00	0.48
	Solifenacin	28	20,164	54,139	0.52	0.34	0.75	0.52	0.33	0.71
	Tolterodine	38	26,729	92,396	0.41	0.29	0.56	0.41	0.28	0.54
		.	.	.	.	.	.	.	.	.

Table N3. 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	
Melanoma	Overall ever treated with:									
	Any OAB medication	425	130,944	417,795	1.02	0.92	1.12	1.02	0.92	1.12
	Darifenacin	49	12,335	45,153	1.09	0.80	1.43	1.09	0.79	1.40
	Fesoterodine	36	21,922	45,193	0.80	0.56	1.10	0.79	0.53	1.05
	Oxybutynin	22	8,142	23,686	0.93	0.58	1.41	1.07	0.60	1.54
	Solifenacin	156	57,112	159,876	0.98	0.83	1.14	1.00	0.84	1.16
	Tolterodine	221	59,805	215,270	1.03	0.90	1.17	0.99	0.86	1.12
		.	.	.	.	.	.	.	.	.
	Female ever treated with:									
	Any OAB medication	218	77,992	256,053	0.85	0.74	0.97	0.86	0.74	0.97
	Darifenacin	30	7,894	30,547	0.98	0.66	1.40	0.99	0.64	1.35
	Fesoterodine	20	13,674	29,187	0.69	0.42	1.06	0.67	0.38	0.97
	Oxybutynin	14	5,327	16,330	0.86	0.47	1.44	0.87	0.40	1.33
	Solifenacin	90	36,948	105,737	0.85	0.68	1.05	0.86	0.69	1.04
	Tolterodine	99	33,076	122,874	0.81	0.65	0.98	0.80	0.64	0.95
		.	.	.	.	.	.	.	.	.
	Male ever treated with:									
	Any OAB medication	207	52,952	161,742	1.28	1.11	1.47	1.29	1.11	1.46
	Darifenacin	19	4,441	14,606	1.30	0.78	2.03	1.26	0.69	1.83
	Fesoterodine	16	8,248	16,005	1.00	0.57	1.62	0.98	0.50	1.46
	Oxybutynin	8	2,815	7,356	1.09	0.47	2.14	1.40	0.42	2.37
	Solifenacin	66	20,164	54,139	1.22	0.94	1.55	1.23	0.93	1.53
	Tolterodine	122	26,729	92,396	1.32	1.10	1.58	1.31	1.08	1.55
		.	.	.	.	.	.	.	.	.

Table N3. 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	
Non-Hodgkin lymphoma	Overall ever treated with:									
	Any OAB medication	198	130,944	417,795	0.47	0.41	0.54	0.47	0.41	0.54
	Darifenacin	31	12,335	45,153	0.69	0.47	0.97	0.69	0.44	0.93
	Fesoterodine	25	21,922	45,193	0.55	0.36	0.82	0.56	0.34	0.79
	Oxybutynin	15	8,142	23,686	0.63	0.35	1.04	0.77	0.37	1.17
	Solifenacin	58	57,112	159,876	0.36	0.28	0.47	0.38	0.28	0.48
	Tolterodine	108	59,805	215,270	0.50	0.41	0.61	0.47	0.38	0.56
		.	.	.	.	.	.	.	.	.
	Female ever treated with:									
	Any OAB medication	86	77,992	256,053	0.34	0.27	0.41	0.34	0.27	0.41
	Darifenacin	17	7,894	30,547	0.56	0.32	0.89	0.54	0.29	0.80
	Fesoterodine	13	13,674	29,187	0.45	0.24	0.76	0.46	0.21	0.71
	Oxybutynin	9	5,327	16,330	0.55	0.25	1.04	0.63	0.22	1.05
	Solifenacin	27	36,948	105,737	0.26	0.17	0.37	0.27	0.17	0.37
	Tolterodine	41	33,076	122,874	0.33	0.24	0.45	0.32	0.22	0.42
		.	.	.	.	.	.	.	.	.
	Male ever treated with:									
	Any OAB medication	112	52,952	161,742	0.69	0.57	0.83	0.70	0.57	0.82
	Darifenacin	14	4,441	14,606	0.96	0.52	1.61	0.92	0.44	1.40
	Fesoterodine	12	8,248	16,005	0.75	0.39	1.31	0.74	0.32	1.15
	Oxybutynin	6	2,815	7,356	0.82	0.30	1.77	1.01	0.20	1.81
	Solifenacin	31	20,164	54,139	0.57	0.39	0.81	0.58	0.37	0.78
	Tolterodine	67	26,729	92,396	0.73	0.56	0.92	0.72	0.55	0.90

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

a. Standardized to sex and age distribution of the study population person-years.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Composite	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	5,190	130,872	384,096	13.51	13.15	13.88	13.51	13.14	13.88
	Darifenacin	414	9,093	31,073	13.32	12.07	14.67	13.51	12.20	14.83
	Fesoterodine	328	13,536	25,887	12.67	11.34	14.12	12.85	11.44	14.25
	Oxybutynin	147	5,420	13,984	10.51	8.88	12.36	13.63	11.35	15.92
	Solifenacin	1,713	47,313	125,373	13.66	13.02	14.33	14.24	13.56	14.91
	Tolterodine	2,588	55,510	187,779	13.78	13.26	14.32	13.20	12.69	13.72
		5,190	130,872	384,096	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	2,297	77,948	233,368	9.84	9.44	10.25	9.84	9.44	10.25
	Darifenacin	219	5,748	20,844	10.51	9.16	11.99	10.38	9.00	11.76
	Fesoterodine	131	8,075	15,913	8.23	6.88	9.77	8.50	7.02	9.98
	Oxybutynin	82	3,409	9,259	8.86	7.04	10.99	10.05	7.85	12.25
	Solifenacin	836	30,457	82,155	10.18	9.50	10.89	10.28	9.58	10.98
	Tolterodine	1,029	30,259	105,197	9.78	9.19	10.40	9.65	9.06	10.25
		2,297	77,948	233,368	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	2,893	52,924	150,728	19.19	18.50	19.91	19.19	18.49	19.89
	Darifenacin	195	3,345	10,229	19.06	16.48	21.93	18.36	15.78	20.94
	Fesoterodine	197	5,461	9,974	19.75	17.09	22.71	19.57	16.81	22.32
	Oxybutynin	65	2,011	4,725	13.76	10.62	17.53	19.18	14.45	23.91
	Solifenacin	877	16,856	43,219	20.29	18.97	21.68	20.36	19.01	21.71
	Tolterodine	1,559	25,251	82,581	18.88	17.95	19.84	18.70	17.77	19.63
		2,893	52,924	150,728	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Colorectal	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	.	130,872	384,096	2.15	2.00	2.30	2.15	2.00	2.29
	Darifenacin	75	9,093	31,073	2.41	1.90	3.03	2.42	1.87	2.97
	Fesoterodine	46	13,536	25,887	1.78	1.30	2.37	1.77	1.25	2.29
	Oxybutynin	33	5,420	13,984	2.36	1.62	3.31	2.99	1.94	4.03
	Solifenacin	254	47,313	125,373	2.03	1.78	2.29	2.11	1.85	2.37
	Tolterodine	417	55,510	187,779	2.22	2.01	2.44	2.14	1.93	2.35
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	417	77,948	233,368	1.79	1.62	1.97	1.79	1.62	1.96
	Darifenacin	42	5,748	20,844	2.01	1.45	2.72	2.00	1.39	2.60
	Fesoterodine	19	8,075	15,913	1.19	0.72	1.86	1.21	0.66	1.77
	Oxybutynin	21	3,409	9,259	2.27	1.40	3.47	2.69	1.52	3.86
	Solifenacin	137	30,457	82,155	1.67	1.40	1.97	1.71	1.42	2.00
	Tolterodine	198	30,259	105,197	1.88	1.63	2.16	1.83	1.58	2.09
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	408	52,924	150,728	2.71	2.45	2.98	2.71	2.44	2.97
	Darifenacin	33	3,345	10,229	3.23	2.22	4.53	3.07	2.03	4.12
	Fesoterodine	27	5,461	9,974	2.71	1.78	3.94	2.65	1.64	3.65
	Oxybutynin	12	2,011	4,725	2.54	1.31	4.43	3.45	1.50	5.40
	Solifenacin	117	16,856	43,219	2.71	2.24	3.24	2.73	2.23	3.23
	Tolterodine	219	25,251	82,581	2.65	2.31	3.03	2.62	2.27	2.97
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Pancreas	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	124	130,872	384,096	0.32	0.27	0.38	0.32	0.27	0.38
	Darifenacin	4	9,093	31,073	0.13	0.03	0.33	0.12	0.00	0.24
	Fesoterodine	7	13,536	25,887	0.27	0.11	0.55	0.25	0.06	0.43
	Oxybutynin	9	5,420	13,984	0.64	0.29	1.22	0.82	0.27	1.37
	Solifenacin	41	47,313	125,373	0.33	0.23	0.44	0.34	0.24	0.45
	Tolterodine	63	55,510	187,779	0.34	0.26	0.43	0.33	0.25	0.42
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	68	77,948	233,368	0.29	0.23	0.37	0.29	0.22	0.36
	Darifenacin	3	5,748	20,844	0.14	0.03	0.41	0.13	0.00	0.29
	Fesoterodine	5	8,075	15,913	0.31	0.10	0.73	0.28	0.03	0.53
	Oxybutynin	6	3,409	9,259	0.65	0.24	1.40	0.78	0.15	1.41
	Solifenacin	22	30,457	82,155	0.27	0.17	0.41	0.28	0.16	0.39
	Tolterodine	32	30,259	105,197	0.30	0.21	0.43	0.30	0.20	0.41
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	56	52,924	150,728	0.37	0.28	0.48	0.37	0.27	0.47
	Darifenacin	1	3,345	10,229	0.10	0.00	0.49	0.10	0.00	0.29
	Fesoterodine	2	5,461	9,974	0.20	0.02	0.70	0.20	0.00	0.47
	Oxybutynin	3	2,011	4,725	0.63	0.13	1.82	0.89	0.00	1.90
	Solifenacin	19	16,856	43,219	0.44	0.26	0.69	0.44	0.24	0.64
	Tolterodine	31	25,251	82,581	0.38	0.26	0.53	0.38	0.24	0.51
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Lung & bronchus	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	389	130,872	384,096	1.01	0.91	1.12	1.01	0.91	1.11
	Darifenacin	34	9,093	31,073	1.09	0.76	1.53	1.09	0.72	1.46
	Fesoterodine	26	13,536	25,887	1.00	0.66	1.47	0.99	0.60	1.37
	Oxybutynin	11	5,420	13,984	0.79	0.39	1.40	1.02	0.38	1.67
	Solifenacin	124	47,313	125,373	0.99	0.82	1.18	1.00	0.82	1.18
	Tolterodine	194	55,510	187,779	1.03	0.89	1.19	1.00	0.86	1.15
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	200	77,948	233,368	0.86	0.74	0.98	0.86	0.74	0.98
	Darifenacin	19	5,748	20,844	0.91	0.55	1.42	0.87	0.48	1.27
	Fesoterodine	12	8,075	15,913	0.75	0.39	1.32	0.77	0.33	1.20
	Oxybutynin	8	3,409	9,259	0.86	0.37	1.70	0.96	0.29	1.63
	Solifenacin	77	30,457	82,155	0.94	0.74	1.17	0.94	0.73	1.15
	Tolterodine	84	30,259	105,197	0.80	0.64	0.99	0.80	0.63	0.97
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	189	52,924	150,728	1.25	1.08	1.45	1.25	1.08	1.43
	Darifenacin	15	3,345	10,229	1.47	0.82	2.42	1.42	0.70	2.14
	Fesoterodine	14	5,461	9,974	1.40	0.77	2.35	1.33	0.63	2.03
	Oxybutynin	3	2,011	4,725	0.63	0.13	1.82	1.12	0.00	2.40
	Solifenacin	47	16,856	43,219	1.09	0.80	1.45	1.09	0.78	1.40
	Tolterodine	110	25,251	82,581	1.33	1.09	1.61	1.32	1.07	1.56
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Breast	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	870	130,872	384,096	2.27	2.12	2.42	2.27	2.11	2.42
	Darifenacin	89	9,093	31,073	2.86	2.30	3.52	2.53	2.00	3.06
	Fesoterodine	48	13,536	25,887	1.85	1.37	2.46	1.91	1.36	2.45
	Oxybutynin	24	5,420	13,984	1.72	1.10	2.55	1.69	1.01	2.37
	Solifenacin	327	47,313	125,373	2.61	2.33	2.91	2.41	2.15	2.67
	Tolterodine	382	55,510	187,779	2.03	1.84	2.25	2.21	1.98	2.43
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	870	77,948	233,368	3.73	3.48	3.98	3.73	3.48	3.98
	Darifenacin	89	5,748	20,844	4.27	3.43	5.25	4.17	3.30	5.04
	Fesoterodine	48	8,075	15,913	3.02	2.22	4.00	3.14	2.24	4.04
	Oxybutynin	24	3,409	9,259	2.59	1.66	3.86	2.78	1.65	3.90
	Solifenacin	327	30,457	82,155	3.98	3.56	4.44	3.96	3.53	4.40
	Tolterodine	382	30,259	105,197	3.63	3.28	4.01	3.63	3.27	4.00
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	.	52,924	150,728	.	.	.	0.00	.	.
	Darifenacin	.	3,345	10,229	.	.	.	0.00	.	.
	Fesoterodine	.	5,461	9,974	.	.	.	0.00	.	.
	Oxybutynin	.	2,011	4,725	.	.	.	0.00	.	.
	Solifenacin	.	16,856	43,219	.	.	.	0.00	.	.
	Tolterodine	.	25,251	82,581	.	.	.	0.00	.	.
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Corpos uteri	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	223	130,872	384,096	0.58	0.51	0.66	0.58	0.50	0.66
	Darifenacin	17	9,093	31,073	0.55	0.32	0.88	0.49	0.26	0.73
	Fesoterodine	12	13,536	25,887	0.46	0.24	0.81	0.47	0.20	0.74
	Oxybutynin	7	5,420	13,984	0.50	0.20	1.03	0.54	0.14	0.95
	Solifenacin	83	47,313	125,373	0.66	0.53	0.82	0.62	0.48	0.75
	Tolterodine	104	55,510	187,779	0.55	0.45	0.67	0.59	0.47	0.70
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	223	77,948	233,368	0.96	0.83	1.09	0.96	0.83	1.08
	Darifenacin	17	5,748	20,844	0.82	0.47	1.30	0.81	0.42	1.20
	Fesoterodine	12	8,075	15,913	0.75	0.39	1.32	0.78	0.33	1.22
	Oxybutynin	7	3,409	9,259	0.76	0.30	1.55	0.89	0.23	1.56
	Solifenacin	83	30,457	82,155	1.01	0.80	1.25	1.02	0.80	1.24
	Tolterodine	104	30,259	105,197	0.99	0.81	1.20	0.97	0.78	1.16
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	.	52,924	150,728	.	.	.	0.00	.	.
	Darifenacin	.	3,345	10,229	.	.	.	0.00	.	.
	Fesoterodine	.	5,461	9,974	.	.	.	0.00	.	.
	Oxybutynin	.	2,011	4,725	.	.	.	0.00	.	.
	Solifenacin	.	16,856	43,219	.	.	.	0.00	.	.
	Tolterodine	.	25,251	82,581	.	.	.	0.00	.	.
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Prostate	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	1,419	130,872	384,096	3.69	3.50	3.89	3.69	3.50	3.89
	Darifenacin	96	9,093	31,073	3.09	2.50	3.77	3.55	2.84	4.26
	Fesoterodine	92	13,536	25,887	3.55	2.86	4.36	3.58	2.84	4.32
	Oxybutynin	27	5,420	13,984	1.93	1.27	2.81	3.14	1.94	4.35
	Solifenacin	449	47,313	125,373	3.58	3.26	3.93	4.07	3.69	4.45
	Tolterodine	755	55,510	187,779	4.02	3.74	4.32	3.56	3.30	3.81
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	.	77,948	233,368	.	.	.	0.00	.	.
	Darifenacin	.	5,748	20,844	.	.	.	0.00	.	.
	Fesoterodine	.	8,075	15,913	.	.	.	0.00	.	.
	Oxybutynin	.	3,409	9,259	.	.	.	0.00	.	.
	Solifenacin	.	30,457	82,155	.	.	.	0.00	.	.
	Tolterodine	.	30,259	105,197	.	.	.	0.00	.	.
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	1,419	52,924	150,728	9.41	8.93	9.92	9.41	8.92	9.90
	Darifenacin	96	3,345	10,229	9.38	7.60	11.46	9.05	7.24	10.86
	Fesoterodine	92	5,461	9,974	9.22	7.44	11.31	9.13	7.25	11.01
	Oxybutynin	27	2,011	4,725	5.71	3.77	8.31	8.01	4.94	11.08
	Solifenacin	449	16,856	43,219	10.39	9.45	11.40	10.37	9.41	11.33
	Tolterodine	755	25,251	82,581	9.14	8.50	9.82	9.07	8.42	9.72
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Bladder	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	623	130,872	384,096	1.62	1.50	1.75	1.62	1.49	1.75
	Darifenacin	28	9,093	31,073	0.90	0.60	1.30	1.00	0.63	1.37
	Fesoterodine	54	13,536	25,887	2.09	1.57	2.72	2.16	1.57	2.74
	Oxybutynin	14	5,420	13,984	1.00	0.55	1.68	1.44	0.66	2.22
	Solifenacin	209	47,313	125,373	1.67	1.45	1.91	1.82	1.57	2.07
	Tolterodine	318	55,510	187,779	1.69	1.51	1.89	1.56	1.39	1.74
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	175	77,948	233,368	0.75	0.64	0.87	0.75	0.64	0.86
	Darifenacin	7	5,748	20,844	0.34	0.13	0.69	0.36	0.09	0.62
	Fesoterodine	18	8,075	15,913	1.13	0.67	1.79	1.20	0.64	1.77
	Oxybutynin	3	3,409	9,259	0.32	0.07	0.93	0.38	0.00	0.81
	Solifenacin	67	30,457	82,155	0.82	0.63	1.04	0.84	0.64	1.05
	Tolterodine	80	30,259	105,197	0.76	0.60	0.95	0.74	0.58	0.90
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	448	52,924	150,728	2.97	2.70	3.26	2.97	2.70	3.25
	Darifenacin	21	3,345	10,229	2.05	1.27	3.14	1.98	1.13	2.83
	Fesoterodine	36	5,461	9,974	3.61	2.53	5.00	3.63	2.43	4.83
	Oxybutynin	11	2,011	4,725	2.33	1.16	4.16	3.09	1.21	4.96
	Solifenacin	142	16,856	43,219	3.29	2.77	3.87	3.33	2.78	3.88
	Tolterodine	238	25,251	82,581	2.88	2.53	3.27	2.84	2.48	3.20
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Kidney & renal pelvis		.	.	.	.	.	.	.	.	.
	Overall with single exposure:									
	Any OAB medication	**132**	130,872	384,096	0.34	0.29	0.41	0.34	0.29	0.40
	Darifenacin	13	9,093	31,073	0.42	0.22	0.71	0.42	0.19	0.65
	Fesoterodine	9	13,536	25,887	0.35	0.16	0.66	0.35	0.12	0.58
	Oxybutynin	1	5,420	13,984	0.07	0.00	0.36	0.11	0.00	0.33
	Solifenacin	52	47,313	125,373	0.41	0.31	0.54	0.42	0.31	0.54
	Tolterodine	57	55,510	187,779	0.30	0.23	0.39	0.29	0.22	0.37
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	63	77,948	233,368	0.27	0.21	0.35	0.27	0.20	0.34
	Darifenacin	8	5,748	20,844	0.38	0.17	0.75	0.39	0.12	0.67
	Fesoterodine	3	8,075	15,913	0.19	0.04	0.54	0.19	0.00	0.40
	Oxybutynin	.	3,409	9,259	.	.	.	0.00	.	.
	Solifenacin	28	30,457	82,155	0.34	0.23	0.49	0.34	0.21	0.47
	Tolterodine	24	30,259	105,197	0.23	0.15	0.34	0.22	0.13	0.31
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	69	52,924	150,728	0.46	0.36	0.58	0.46	0.35	0.57
	Darifenacin	5	3,345	10,229	0.49	0.16	1.13	0.47	0.06	0.88
	Fesoterodine	6	5,461	9,974	0.60	0.22	1.30	0.60	0.12	1.08
	Oxybutynin	1	2,011	4,725	0.21	0.00	1.07	0.29	0.00	0.85
	Solifenacin	24	16,856	43,219	0.56	0.36	0.83	0.56	0.33	0.78
	Tolterodine	33	25,251	82,581	0.40	0.28	0.56	0.40	0.26	0.53
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Melanoma	Overall with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	403	130,872	384,096	1.05	0.95	1.16	1.05	0.95	1.15
	Darifenacin	39	9,093	31,073	1.26	0.89	1.72	1.28	0.87	1.68
	Fesoterodine	22	13,536	25,887	0.85	0.53	1.29	0.86	0.50	1.23
	Oxybutynin	13	5,420	13,984	0.93	0.49	1.59	1.12	0.49	1.76
	Solifenacin	127	47,313	125,373	1.01	0.84	1.21	1.04	0.86	1.22
	Tolterodine	202	55,510	187,779	1.08	0.93	1.23	1.04	0.89	1.18
		.	.	.	.	.	.	.	.	.
	Females with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	203	77,948	233,368	0.87	0.75	1.00	0.87	0.75	0.99
	Darifenacin	23	5,748	20,844	1.10	0.70	1.66	1.12	0.66	1.58
	Fesoterodine	9	8,075	15,913	0.57	0.26	1.07	0.58	0.20	0.95
	Oxybutynin	8	3,409	9,259	0.86	0.37	1.70	0.91	0.27	1.55
	Solifenacin	73	30,457	82,155	0.89	0.70	1.12	0.90	0.69	1.11
	Tolterodine	90	30,259	105,197	0.86	0.69	1.05	0.84	0.67	1.02
		.	.	.	.	.	.	.	.	.
	Male with single exposure:	.	.	.	.	.	.	.	.	.
	Any OAB medication	200	52,924	150,728	1.33	1.15	1.52	1.33	1.14	1.51
	Darifenacin	16	3,345	10,229	1.56	0.89	2.54	1.52	0.77	2.26
	Fesoterodine	13	5,461	9,974	1.30	0.69	2.23	1.31	0.59	2.03
	Oxybutynin	5	2,011	4,725	1.06	0.34	2.45	1.45	0.18	2.73
	Solifenacin	54	16,856	43,219	1.25	0.94	1.63	1.26	0.92	1.60
	Tolterodine	112	25,251	82,581	1.36	1.12	1.63	1.34	1.09	1.59
		.	.	.	.	.	.	.	.	.

Table N4. Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition 1 for Single Exposure 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	
Non-Hodgkin lymphoma	Overall with single exposure:									
	Any OAB medication	182	130,872	384,096	0.47	0.41	0.55	0.47	0.40	0.54
	Darifenacin	19	9,093	31,073	0.61	0.37	0.95	0.61	0.33	0.88
	Fesoterodine	12	13,536	25,887	0.46	0.24	0.81	0.51	0.22	0.80
	Oxybutynin	8	5,420	13,984	0.57	0.25	1.12	0.75	0.22	1.28
	Solifenacin	47	47,313	125,373	0.37	0.28	0.50	0.40	0.29	0.52
	Tolterodine	96	55,510	187,779	0.51	0.41	0.62	0.48	0.38	0.57
	Females with single exposure:									
	Any OAB medication	78	77,948	233,368	0.33	0.26	0.42	0.33	0.26	0.41
	Darifenacin	11	5,748	20,844	0.53	0.26	0.94	0.52	0.21	0.84
	Fesoterodine	5	8,075	15,913	0.31	0.10	0.73	0.37	0.04	0.69
	Oxybutynin	5	3,409	9,259	0.54	0.17	1.25	0.67	0.08	1.25
	Solifenacin	22	30,457	82,155	0.27	0.17	0.41	0.28	0.17	0.40
	Tolterodine	35	30,259	105,197	0.33	0.23	0.46	0.31	0.21	0.42
	Male with single exposure:									
	Any OAB medication	104	52,924	150,728	0.69	0.56	0.84	0.69	0.56	0.82
	Darifenacin	8	3,345	10,229	0.78	0.34	1.54	0.74	0.23	1.25
	Fesoterodine	7	5,461	9,974	0.70	0.28	1.44	0.73	0.18	1.27
	Oxybutynin	3	2,011	4,725	0.63	0.13	1.82	0.88	0.00	1.89
	Solifenacin	25	16,856	43,219	0.58	0.37	0.85	0.59	0.36	0.81
	Tolterodine	61	25,251	82,581	0.74	0.56	0.95	0.73	0.55	0.92

CI = confidence interval; OAB = overactive bladder.

a. Standardized to sex and age distribution of the study population person-years.

Table N4(2). Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition for Dose and Duration, by OAB Medication

Specific OAB Medication	Exposure at End of Follow-up	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Darifenacin	Cumulative dose	.	.	.	.	.	.	.	.	.
	Q1	217	12,335	17,021	12.75	11.11	14.56	13.50	11.68	15.32
	Q2	206	8,026	13,827	14.90	12.93	17.08	15.05	12.97	17.13
	Q3	117	4,417	8,307	14.08	11.65	16.88	13.58	11.10	16.06
	Q4	66	2,167	5,997	11.01	8.51	14.00	10.43	7.86	13.00
	Duration of exposure	.	.	.	.	.	.	.	.	.
	Q1	219	12,335	15,869	13.80	12.03	15.75	14.58	12.63	16.53
	Q2	189	8,300	13,692	13.80	11.91	15.92	13.96	11.95	15.97
	Q3	130	4,796	9,645	13.48	11.26	16.00	13.14	10.86	15.41
	Q4	68	2,205	5,946	11.44	8.88	14.50	10.75	8.15	13.36
	Time since first exposure	.	.	.	.	.	.	.	.	.
	Q1	65	12,335	3,485	18.65	14.39	23.77	18.41	13.90	22.93
	Q2	111	11,892	7,188	15.44	12.70	18.60	15.12	12.29	17.94
	Q3	169	11,006	14,239	11.87	10.15	13.80	11.77	9.99	13.56
	Q4	261	8,514	20,241	12.89	11.38	14.56	13.33	11.68	14.99
Fesoterodine	Cumulative dose	.	.	.	.	.	.	.	.	.
	Q1	235	21,922	17,099	13.74	12.04	15.62	14.47	12.61	16.34
	Q2	158	14,616	13,191	11.98	10.18	14.00	11.65	9.82	13.48
	Q3	126	8,513	8,490	14.84	12.36	17.67	14.50	11.93	17.07
	Q4	79	4,416	6,412	12.32	9.75	15.35	11.93	9.22	14.63
	Duration of exposure	.	.	.	.	.	.	.	.	.
	Q1	245	21,922	16,693	14.68	12.90	16.63	15.22	13.31	17.14
	Q2	157	14,711	12,959	12.12	10.29	14.17	12.04	10.14	13.94
	Q3	118	8,792	9,182	12.85	10.64	15.39	12.46	10.17	14.75
	Q4	78	4,414	6,358	12.27	9.70	15.31	12.09	9.36	14.82

Table N4(2). Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition for Dose and Duration, by OAB Medication

Specific OAB Medication	Exposure at End of Follow-up	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Fesoterodine (continued)	Time since first exposure	.	.	.	.	.	.	.	.	.
	Q1	101	21,922	5,521	18.29	14.90	22.23	17.65	14.20	21.11
	Q2	147	20,461	9,497	15.48	13.08	18.19	15.38	12.88	17.88
	Q3	173	17,975	14,196	12.19	10.44	14.14	12.16	10.33	13.98
	Q4	177	12,743	15,979	11.08	9.50	12.83	11.23	9.55	12.91
Oxybutynin	Cumulative dose	.	.	.	.	.	.	.	.	.
	Q1	131	8,142	10,545	12.42	10.39	14.74	15.04	12.43	17.65
	Q2	59	4,667	6,086	9.70	7.38	12.51	11.69	8.37	15.01
	Q3	40	2,786	4,368	9.16	6.54	12.47	11.06	7.51	14.61
	Q4	43	1,197	2,686	16.01	11.58	21.56	18.88	12.51	25.24
	Duration of exposure	.	.	.	.	.	.	.	.	.
	Q1	125	8,142	9,848	12.69	10.56	15.12	15.79	12.79	18.78
	Q2	63	5,576	6,232	10.11	7.77	12.93	12.68	9.53	15.83
	Q3	45	3,075	4,818	9.34	6.81	12.50	11.71	8.18	15.24
	Q4	40	1,269	2,787	14.35	10.25	19.54	16.71	11.04	22.38
	Time since first exposure	.	.	.	.	.	.	.	.	.
	Q1	33	8,142	2,314	14.26	9.81	20.02	20.32	13.27	27.36
	Q2	38	7,628	3,460	10.98	7.77	15.07	13.50	9.14	17.85
	Q3	69	6,717	7,317	9.43	7.34	11.93	12.26	9.28	15.25
	Q4	133	4,831	10,594	12.55	10.51	14.88	14.30	11.75	16.86
Solifenacin	Cumulative dose	.	.	.	.	.	.	.	.	.
	Q1	1,069	57,112	76,442	13.98	13.16	14.85	15.09	14.18	16.00
	Q2	495	31,797	36,749	13.47	12.31	14.71	13.55	12.35	14.75
	Q3	329	19,182	26,601	12.37	11.07	13.78	12.04	10.73	13.35
	Q4	284	9,708	20,084	14.14	12.54	15.88	13.85	12.22	15.48

Table N4(2). Person-time, Frequency, and Incidence Rates of Composite Cancer Endpoint Definition for Dose and Duration, by OAB Medication

Specific OAB Medication	Exposure at End of Follow-up	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Solifenacin (continued)	Duration of exposure	.	.	.	.	.	.	.	.	.
	Q1	935	57,112	63,918	14.63	13.71	15.60	15.83	14.80	16.85
	Q2	600	36,006	46,445	12.92	11.91	13.99	13.14	12.09	14.20
	Q3	382	20,076	29,997	12.73	11.49	14.08	12.50	11.24	13.76
	Q4	260	9,385	19,516	13.32	11.75	15.04	13.12	11.50	14.73
	Time since first exposure	.	.	.	.	.	.	.	.	.
	Q1	413	57,112	18,908	21.84	19.79	24.05	22.25	20.10	24.40
	Q2	462	52,419	32,699	14.13	12.87	15.48	14.33	13.02	15.64
	Q3	583	45,079	49,206	11.85	10.91	12.85	12.14	11.15	13.13
	Q4	719	30,966	59,064	12.17	11.30	13.10	12.61	11.67	13.54
Tolterodine	Cumulative dose	.	.	.	.	.	.	.	.	.
	Q1	1,466	59,805	106,828	13.72	13.03	14.44	13.36	12.67	14.06
	Q2	737	32,267	49,822	14.79	13.74	15.90	14.13	13.11	15.16
	Q3	486	19,053	35,564	13.67	12.48	14.94	12.87	11.72	14.03
	Q4	307	9,095	23,056	13.32	11.87	14.89	12.58	11.17	14.00
	Duration of exposure	.	.	.	.	.	.	.	.	.
	Q1	1,384	59,805	94,711	14.61	13.85	15.40	14.28	13.51	15.04
	Q2	857	35,693	63,505	13.50	12.61	14.43	12.96	12.08	13.83
	Q3	487	18,874	35,810	13.60	12.42	14.86	12.77	11.62	13.92
	Q4	268	8,934	21,245	12.61	11.15	14.22	11.92	10.48	13.36
	Time since first exposure	.	.	.	.	.	.	.	.	.
	Q1	518	59,805	22,500	23.02	21.08	25.09	20.71	18.88	22.53
	Q2	619	56,751	42,473	14.57	13.45	15.77	13.53	12.45	14.61
	Q3	860	51,389	67,344	12.77	11.93	13.65	12.23	11.40	13.05
	Q4	999	40,226	82,953	12.04	11.31	12.81	11.96	11.21	12.70

CI = confidence interval; OAB = overactive bladder.

a. Standardized to sex and age distribution of the study population person-years.

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

		Patients Without a Cardiovascular Endpoint Event		Cardiovascular Event Type								All-Cause Death	
				Acute Myocardial Infarction		Stroke		Cardiovascular Mortality		Composite Endpoint			
		(n=114,910)		(n=5,089)		(n=6,177)		(n=3,471)		(n=10,567)		(n=10,097)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Age at cohort entry (years)													
	Mean (SD)	*64*	*(15.2)*	*78*	*(9.8)*	*76*	*(10.1)*	*81*	*(8.2)*	*77*	*(10.1)*	*80*	*(9.5)*
	18-24	2,159	1.9	0	0.0	5	0.1	0	0.0	5	0.0	6	0.1
	25-34	3,795	3.3	1	0.0	7	0.1	0	0.0	8	0.1	10	0.1
	35-44	7,254	6.3	21	0.4	40	0.6	2	0.1	61	0.6	37	0.4
	45-54	14,026	12.2	105	2.1	148	2.4	25	0.7	247	2.3	120	1.2
	55-64	25,563	22.2	439	8.6	651	10.5	106	3.1	1,057	10.0	508	5.0
	65-74	32,322	28.1	1,140	22.4	1,662	26.9	579	16.7	2,666	25.2	1,716	17.0
	75-84	22,995	20.0	2,083	40.9	2,488	40.3	1,494	43.0	4,252	40.2	4,229	41.9
	85+	6,796	5.9	1,300	25.5	1,176	19.0	1,265	36.4	2,271	21.5	3,471	34.4
Sex													
	Female	69,985	60.9	2,424	47.6	3,114	50.4	1,691	48.7	5,207	49.3	5,102	50.5
	Male	44,925	39.1	2,665	52.4	3,063	49.6	1,780	51.3	5,360	50.7	4,995	49.5
	2006	10,365	9.0	966	19.0	1,064	17.2	759	21.9	1,886	17.8	2,009	19.9
	2007	19,637	17.1	1,449	28.5	1,687	27.3	1,016	29.3	2,911	27.5	3,000	29.7
	2008	18,429	16.0	1,111	21.8	1,310	21.2	731	21.1	2,259	21.4	2,151	21.3
	2009	16,559	14.4	732	14.4	924	15.0	462	13.3	1,580	15.0	1,431	14.2
	2010	16,674	14.5	498	9.8	645	10.4	287	8.3	1,086	10.3	881	8.7
	2011	16,906	14.7	270	5.3	414	6.7	172	5.0	653	6.2	487	4.8
	2012	16,340	14.2	63	1.2	133	2.2	44	1.3	192	1.8	138	1.4
Duration of enrollment prior to cohort entry													
	Mean (SD)	*1,505*	*(693.6)*	*1,065*	*(529.5)*	*1,117*	*(556.4)*	*1,026*	*(523.6)*	*1,100*	*(548)*	*1,041*	*(522.8)*
	1 to < 2 years	20,699	18.0	1,747	34.3	1,935	31.3	1,284	37.0	3,422	32.4	3,619	35.8
	2 to < 4 years	36,393	31.7	2,195	43.1	2,637	42.7	1,483	42.7	4,516	42.7	4,368	43.3
	4 to < 8 years	57,818	50.3	1,147	22.5	1,605	26.0	704	20.3	2,629	24.9	2,110	20.9

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

		Patients Without a Cardiovascular Endpoint Event		Cardiovascular Event Type								All-Cause Death	
				Acute Myocardial Infarction		Stroke		Cardiovascular Mortality		Composite Endpoint			
		(n=114,910)		(n=5,089)		(n=6,177)		(n=3,471)		(n=10,567)		(n=10,097)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Duration of follow-up													
	Mean (SD)	*1,169*	*)'(699.3*	*1,226*	*(646.6)*	*1,307*	*(643.1)*	*903*	*(566.6)*	*1,271*	*(646.8)*	*914*	*(571.3)*
	< 1 year	19,311	16.8	571	11.2	574	9.3	714	20.6	1,078	10.2	2,101	20.8
	1 to < 2 years	18,099	15.8	778	15.3	828	13.4	814	23.5	1,508	14.3	2,226	22.0
	2 to < 4 years	33,374	29.0	1,746	34.3	2,004	32.4	1,273	36.7	3,504	33.2	3,784	37.5
	4 to < 8 years	44,126	38.4	1,994	39.2	2,771	44.9	670	19.3	4,477	42.4	1,986	19.7
Menopause	Yes	57,350	49.9	2,398	47.1	3,047	49.3	1,687	48.6	5,115	48.4	5,055	50.1
Number of study drugs during follow-up													
	1	93,030	81.0	4,149	81.5	4,872	78.9	2,989	86.1	8,453	80.0	8,632	85.5
	2	17,624	15.3	790	15.5	1,053	17.0	429	12.4	1,728	16.4	1,286	12.7
	3	3,527	3.1	132	2.6	216	3.5	47	1.4	334	3.2	157	1.6
	4	634	0.6	17	0.3	33	0.5	5	0.1	48	0.5	19	0.2
	5	95	0.1	1	0.0	3	0.0	1	0.0	4	0.0	3	0.0
Number of different study drugs to which patient was exposed in the 12 months before this study													
	1	100,873	87.8	4,350	85.5	5,180	83.9	2,960	85.3	8,945	84.7	8,631	85.5
	2	12,553	10.9	671	13.2	883	14.3	457	13.2	1,448	13.7	1,332	13.2
	3	1,352	1.2	62	1.2	106	1.7	51	1.5	160	1.5	128	1.3
	4	122	0.1	6	0.1	8	0.1	3	0.1	14	0.1	6	0.1
	5	10	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Education (years)													
	Missing	18,069	15.7	1,000	19.7	1,166	18.9	681	19.6	2,041	19.3	2,041	20.2
	≤ 9	28,594	24.9	1,111	21.8	1,430	23.2	754	21.7	2,394	22.7	2,198	21.8
	< 9 to ≤ 12	40,758	35.5	1,798	35.3	2,157	34.9	1,208	34.8	3,688	34.9	3,460	34.3
	> 12	27,489	23.9	1,180	23.2	1,424	23.1	828	23.9	2,444	23.1	2,398	23.7

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

		Patients Without a Cardiovascular Endpoint Event		Cardiovascular Event Type								All-Cause Death	
				Acute Myocardial Infarction		Stroke		Cardiovascular Mortality		Composite Endpoint			
		(n=114,910)		(n=5,089)		(n=6,177)		(n=3,471)		(n=10,567)		(n=10,097)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Income (in quartiles)													
	Missing	2,522	2.2	132	2.6	152	2.5	91	2.6	265	2.5	243	2.4
	Low	16,987	14.8	837	16.4	941	15.2	564	16.2	1,667	15.8	1,667	16.5
	Midlow	24,635	21.4	1,148	22.6	1,392	22.5	781	22.5	2,388	22.6	2,246	22.2
	Midhigh	26,349	22.9	1,153	22.7	1,423	23.0	761	21.9	2,419	22.9	2,286	22.6
	High	44,417	38.7	1,819	35.7	2,269	36.7	1,274	36.7	3,828	36.2	3,655	36.2
Hospitalizations													
	None	64,425	56.1	1,582	31.1	1,864	30.2	833	24.0	3,287	31.1	2,599	25.7
	< 5	44,239	38.5	2,578	50.7	3,347	54.2	1,926	55.5	5,535	52.4	5,433	53.8
	5-10	5,330	4.6	740	14.5	813	13.2	580	16.7	1,432	13.6	1,662	16.5
	11-25	855	0.7	175	3.4	148	2.4	125	3.6	295	2.8	369	3.7
	26-50	60	0.1	13	0.3	4	0.1	7	0.2	16	0.2	31	0.3
	> 50	1	0.0	1	0.0	1	0.0	0	0.0	2	0.0	3	0.0
Outpatient visits													
	None	22,842	19.9	732	14.4	920	14.9	529	15.2	1,572	14.9	1,483	14.7
	< 5	51,385	44.7	2,197	43.2	2,645	42.8	1,549	44.6	4,548	43.0	4,337	43.0
	5-10	26,677	23.2	1,350	26.5	1,667	27.0	914	26.3	2,808	26.6	2,634	26.1
	11-25	11,773	10.2	665	13.1	781	12.6	398	11.5	1,351	12.8	1,359	13.5
	26-50	1,906	1.7	129	2.5	138	2.2	70	2.0	248	2.3	239	2.4
	> 50	327	0.3	16	0.3	26	0.4	11	0.3	40	0.4	45	0.4
Comorbidities													
Mild liver disease, Charlson	Yes	736	0.6	33	0.6	55	0.9	21	0.6	82	0.8	124	1.2
AIDS/HIV, Charlson	No	114,910	100.0	5,089	100.0	6,177	100.0	3,471	100.0	10,567	100.0	10,097	100.0
Cancer, Charlson	No	114,910	100.0	5,089	100.0	6,177	100.0	3,471	100.0	10,567	100.0	10,097	100.0
Metastatic carcinoma, Charlson	No	114,910	100.0	5,089	100.0	6,177	100.0	3,471	100.0	10,567	100.0	10,097	100.0
Diabetes without complications, Charlson	Yes	7,428	6.5	865	17.0	937	15.2	547	15.8	1,656	15.7	1,596	15.8
Diabetes with complications, Charlson	Yes	2,412	2.1	372	7.3	382	6.2	237	6.8	694	6.6	673	6.7

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

		Patients Without a Cardiovascular Endpoint Event		Cardiovascular Event Type								All-Cause Death	
				Acute Myocardial Infarction		Stroke		Cardiovascular Mortality		Composite Endpoint			
		(n=114,910)		(n=5,089)		(n=6,177)		(n=3,471)		(n=10,567)		(n=10,097)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Alcohol abuse and related conditions	Yes	1,738	1.5	99	1.9	121	2.0	67	1.9	203	1.9	269	2.7
Polycystic ovary syndrome	Yes	95	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0
Obesity	Yes	2,162	1.9	81	1.6	107	1.7	40	1.2	183	1.7	141	1.4
Dementia, Charlson	Yes	1,117	1.0	156	3.1	190	3.1	182	5.2	323	3.1	681	6.7
Drug abuse	Yes	440	0.4	11	0.2	27	0.4	10	0.3	37	0.4	60	0.6
Transient ischemic attack	Yes	1,223	1.1	134	2.6	278	4.5	120	3.5	382	3.6	305	3.0
Cerebrovascular disease, Charlson	Yes	6,265	5.5	824	16.2	1,970	31.9	932	26.9	2,562	24.2	2,035	20.2
Paraplegia and hemiplegia, Charlson	Yes	1,327	1.2	75	1.5	194	3.1	74	2.1	260	2.5	175	1.7
Heart failure	Yes	2,990	2.6	722	14.2	493	8.0	592	17.1	1,104	10.4	1,522	15.1
Coronary heart disease	Yes	9,293	8.1	1,533	30.1	1,159	18.8	999	28.8	2,465	23.3	2,223	22.0
Acute myocardial infarction	Yes	4,063	3.5	915	18.0	580	9.4	593	17.1	1,358	12.9	1,196	11.8
Congestive heart failure, Charlson	Yes	3,128	2.7	742	14.6	511	8.3	607	17.5	1,137	10.8	1,552	15.4
Stroke	Yes	4,646	4.0	715	14.0	1,636	26.5	811	23.4	2,139	20.2	1,702	16.9
Peripheral vascular disease, Charlson	Yes	2,032	1.8	400	7.9	307	5.0	275	7.9	657	6.2	706	7.0
Chronic pulmonary disease, Charlson	Yes	5,372	4.7	474	9.3	452	7.3	320	9.2	859	8.1	1,139	11.3
Peptic ulcer disease, Charlson	Yes	1,575	1.4	155	3.0	158	2.6	131	3.8	291	2.8	367	3.6
Moderate or severe liver disease, Charlson	Yes	116	0.1	6	0.1	11	0.2	4	0.1	15	0.1	45	0.4
Connective tissue disease-rheumatic disease, Charlson	Yes	2,894	2.5	283	5.6	286	4.6	188	5.4	527	5.0	579	5.7
Arthritis	Yes	2,108	1.8	181	3.6	178	2.9	120	3.5	332	3.1	381	3.8
Gout	Yes	576	0.5	95	1.9	89	1.4	84	2.4	169	1.6	208	2.1
Fractures	Yes	7,754	6.7	641	12.6	636	10.3	518	14.9	1,208	11.4	1,715	17.0

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

		Patients Without a Cardiovascular Endpoint Event		Cardiovascular Event Type								All-Cause Death	
				Acute Myocardial Infarction		Stroke		Cardiovascular Mortality		Composite Endpoint			
		(n=114,910)		(n=5,089)		(n=6,177)		(n=3,471)		(n=10,567)		(n=10,097)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Renal impairment	Yes	4,470	3.9	393	7.7	358	5.8	272	7.8	697	6.6	845	8.4
Renal disease, Charlson	Yes	789	0.7	183	3.6	123	2.0	117	3.4	282	2.7	414	4.1
Endometrial polyps or other benign growths of the uterus	Yes	436	0.4	1	0.0	11	0.2	1	0.0	12	0.1	7	0.1
Overactive bladder	Yes	20,958	18.2	741	14.6	949	15.4	442	12.7	1,581	15.0	1,282	12.7
Dialysis	Yes	65	0.1	6	0.1	7	0.1	9	0.3	12	0.1	14	0.1
Diabetes	Yes	11,546	10.0	1,131	22.2	1,229	19.9	717	20.7	2,173	20.6	2,024	20.0
Diabetes - diagnosis	Yes	8,037	7.0	926	18.2	1,005	16.3	593	17.1	1,776	16.8	1,722	17.1
Diabetes - drugs	Yes	10,215	8.9	1,003	19.7	1,083	17.5	625	18.0	1,922	18.2	1,729	17.1
Dyslipidemia	Yes	26,813	23.3	1,876	36.9	2,279	36.9	1,179	34.0	3,870	36.6	2,777	27.5
Dyslipidemia - diagnosis	Yes	5,176	4.5	460	9.0	594	9.6	271	7.8	966	9.1	653	6.5
Dyslipidemia - drugs	Yes	26,298	22.9	1,820	35.8	2,214	35.8	1,133	32.6	3,757	35.6	2,669	26.4
Hypertension	Yes	51,303	44.6	3,802	74.7	4,462	72.2	2,686	77.4	7,693	72.8	7,071	70.0
Hypertension - diagnosis	Yes	19,310	16.8	1,757	34.5	2,310	37.4	1,310	37.7	3,770	35.7	3,394	33.6
Hypertension - drugs	Yes	49,988	43.5	3,686	72.4	4,297	69.6	2,580	74.3	7,429	70.3	6,767	67.0
Peripheral artery disease	Yes	2,226	1.9	426	8.4	356	5.8	299	8.6	724	6.9	760	7.5
Peripheral artery disease - diagnosis	Yes	2,064	1.8	407	8.0	312	5.1	284	8.2	666	6.3	724	7.2
Peripheral artery disease - procedures	Yes	566	0.5	119	2.3	112	1.8	75	2.2	213	2.0	185	1.8
Organ transplantation	Yes	202	0.2	13	0.3	12	0.2	8	0.2	23	0.2	31	0.3
Organ transplantation - diagnosis	Yes	197	0.2	12	0.2	12	0.2	8	0.2	22	0.2	31	0.3
Organ transplantation - procedures	Yes	44	0.0	1	0.0	3	0.0	0	0.0	4	0.0	3	0.0
Smoking	Yes	1,349	1.2	68	1.3	87	1.4	37	1.1	146	1.4	135	1.3
Smoking - diagnosis	Yes	424	0.4	31	0.6	42	0.7	16	0.5	70	0.7	53	0.5
Smoking - drugs	Yes	948	0.8	40	0.8	52	0.8	24	0.7	86	0.8	88	0.9

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

		Patients Without a Cardiovascular Endpoint Event		Cardiovascular Event Type								All-Cause Death	
				Acute Myocardial Infarction		Stroke		Cardiovascular Mortality		Composite Endpoint			
		(n=114,910)		(n=5,089)		(n=6,177)		(n=3,471)		(n=10,567)		(n=10,097)	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Antiplatelets (including aspirin in low doses)	Yes	31,655	27.5	3,175	62.4	3,874	62.7	2,412	69.5	6,522	61.7	6,126	60.7
Low-dose aspirin	Yes	24,418	21.2	2,613	51.3	3,060	49.5	1,921	55.3	5,257	49.7	4,825	47.8
Digoxin	Yes	1,518	1.3	290	5.7	334	5.4	299	8.6	585	5.5	773	7.7
Nitrates	Yes	8,443	7.3	1,457	28.6	1,011	16.4	905	26.1	2,238	21.2	2,060	20.4
Statins	Yes	25,491	22.2	1,780	35.0	2,162	35.0	1,117	32.2	3,668	34.7	2,601	25.8
Hormone-replacement therapy	Yes	35,724	31.1	1,126	22.1	1,513	24.5	695	20.0	2,481	23.5	2,100	20.8
Thyroid hormone replacement	Yes	11,060	9.6	535	10.5	656	10.6	354	10.2	1,105	10.5	1,106	11.0
Tamoxifen	No	114,910	100.0	5,089	100.0	6,177	100.0	3,471	100.0	10,567	100.0	10,097	100.0
Immunosuppressive agents	Yes	1,984	1.7	120	2.4	130	2.1	76	2.2	238	2.3	240	2.4
Non-aspirin NSAIDs	Yes	37,879	33.0	1,400	27.5	1,732	28.0	733	21.1	2,964	28.0	2,334	23.1
Mammograms	Yes	88	0.1	2	0.0	0	0.0	0	0.0	2	0.0	4	0.0
Sigmoidoscopies	Yes	1,423	1.2	84	1.7	82	1.3	56	1.6	150	1.4	173	1.7

HIV = human immunodeficiency virus; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder; SD = standard deviation.

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Acute myocardial infarction									
Overall with current exposure to				.	.	.	.	.	.
Any OAB medication	1,358	130,944	118,923	11.42	10.82	12.04	11.40	10.80	12.01
Darifenacin	112	12,335	9,586	11.68	9.62	14.06	11.60	9.43	13.76
Fesoterodine	108	21,922	14,457	7.47	6.13	9.02	8.17	6.59	9.75
Oxybutynin	33	8,142	4,980	6.63	4.56	9.30	9.12	5.87	12.38
Solifenacin	421	57,112	44,711	9.42	8.54	10.36	10.24	9.26	11.22
Tolterodine	706	59,805	47,094	14.99	13.91	16.14	13.32	12.32	14.31
Overall aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,222	76,276	71,679	17.05	16.11	18.03	17.03	16.07	17.98
Darifenacin	103	7,519	6,145	16.76	13.68	20.33	17.53	14.13	20.93
Fesoterodine	94	12,510	8,446	11.13	8.99	13.62	12.02	9.53	14.52
Oxybutynin	26	3,540	2,126	12.23	7.99	17.92	13.15	7.98	18.32
Solifenacin	376	32,611	26,455	14.21	12.81	15.72	15.27	13.72	16.82
Tolterodine	643	36,824	29,640	21.69	20.05	23.44	19.85	18.30	21.40
Overall with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	859	41,749	40,176	21.38	19.97	22.86	21.34	19.92	22.77
Darifenacin	66	3,919	3,367	19.60	15.16	24.94	30.53	21.24	39.82
Fesoterodine	66	6,709	4,572	14.44	11.16	18.37	15.72	11.82	19.61
Oxybutynin	24	2,001	1,287	18.65	11.94	27.74	21.19	12.33	30.06
Solifenacin	261	17,650	14,675	17.79	15.69	20.08	19.11	16.78	21.44
Tolterodine	454	19,924	16,934	26.81	24.40	29.39	24.66	22.37	26.95

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Acute myocardial infarction									
Female with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	626	77,992	74,702	8.38	7.74	9.06	8.37	7.71	9.02
Darifenacin	54	7,894	6,151	8.78	6.59	11.45	8.89	6.50	11.28
Fesoterodine	48	13,674	9,236	5.20	3.83	6.89	5.94	4.21	7.67
Oxybutynin	22	5,327	3,214	6.85	4.29	10.36	9.13	5.19	13.06
Solifenacin	183	36,948	29,998	6.10	5.25	7.05	6.60	5.64	7.56
Tolterodine	331	33,076	27,330	12.11	10.84	13.49	10.51	9.36	11.66
Female aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	569	44,352	44,146	12.89	11.85	13.99	12.87	11.81	13.93
Darifenacin	49	4,651	3,810	12.86	9.51	17.00	13.64	9.78	17.50
Fesoterodine	41	7,500	5,203	7.88	5.65	10.69	8.85	6.06	11.64
Oxybutynin	18	2,395	1,462	12.31	7.29	19.45	13.57	7.18	19.97
Solifenacin	167	20,518	17,247	9.68	8.27	11.27	10.31	8.74	11.87
Tolterodine	306	20,246	17,151	17.84	15.90	19.96	16.08	14.25	17.90
Female with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	375	21,854	22,116	16.96	15.28	18.76	16.92	15.21	18.64
Darifenacin	32	2,199	1,893	16.90	11.56	23.85	17.50	11.38	23.62
Fesoterodine	28	3,620	2,503	11.19	7.43	16.16	12.81	7.92	17.70
Oxybutynin	15	1,223	793	18.93	10.59	31.19	21.35	10.17	32.52
Solifenacin	101	9,971	8,611	11.73	9.55	14.25	12.58	10.11	15.05
Tolterodine	205	9,814	8,678	23.62	20.50	27.09	21.05	18.12	23.98

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Acute myocardial infarction									
Male with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	732	52,952	44,221	16.55	15.38	17.80	16.53	15.34	17.73
Darifenacin	58	4,441	3,435	16.88	12.82	21.82	16.17	11.99	20.34
Fesoterodine	60	8,248	5,221	11.49	8.77	14.79	11.95	8.87	15.04
Oxybutynin	11	2,815	1,767	6.23	3.10	11.12	9.12	3.41	14.83
Solifenacin	238	20,164	14,713	16.18	14.19	18.37	16.40	14.31	18.48
Tolterodine	375	26,729	19,764	18.97	17.10	20.99	18.07	16.23	19.90
Male aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	653	31,924	27,533	23.72	21.93	25.61	23.70	21.88	25.52
Darifenacin	54	2,868	2,335	23.12	17.37	30.17	23.78	17.43	30.12
Fesoterodine	53	5,010	3,243	16.34	12.24	21.37	17.11	12.40	21.83
Oxybutynin	8	1,145	664	12.05	5.19	23.67	12.47	3.75	21.19
Solifenacin	209	12,093	9,208	22.70	19.72	25.99	23.24	20.09	26.40
Tolterodine	337	16,578	12,488	26.99	24.18	30.03	25.91	23.13	28.69
Male with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	484	19,895	18,060	26.80	24.46	29.30	26.76	24.37	29.14
Darifenacin	34	1,720	1,474	23.07	15.97	32.23	36.67	21.67	51.67
Fesoterodine	38	3,089	2,069	18.37	13.00	25.21	19.28	13.02	25.55
Oxybutynin	9	778	494	18.20	8.31	34.46	21.00	6.81	35.20
Solifenacin	160	7,679	6,064	26.39	22.46	30.81	27.10	22.89	31.31
Tolterodine	249	10,110	8,255	30.16	26.53	34.15	29.08	25.45	32.71

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Stroke									
Overall with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	2,204	130,944	117,794	18.71	17.94	19.51	18.70	17.92	19.48
Darifenacin	171	12,335	9,524	17.95	15.36	20.86	17.58	14.93	20.23
Fesoterodine	233	21,922	14,355	16.23	14.21	18.46	17.37	15.08	19.66
Oxybutynin	57	8,142	4,955	11.50	8.71	14.90	16.00	11.67	20.33
Solifenacin	712	57,112	44,368	16.05	14.89	17.27	16.85	15.60	18.09
Tolterodine	1,062	59,805	46,669	22.76	21.41	24.17	20.98	19.70	22.25
Overall aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,841	76,276	70,923	25.96	24.79	27.17	25.94	24.75	27.12
Darifenacin	150	7,519	6,099	24.59	20.81	28.86	25.16	21.12	29.21
Fesoterodine	185	12,510	8,378	22.08	19.01	25.50	23.54	20.05	27.03
Oxybutynin	44	3,540	2,113	20.82	15.13	27.95	22.71	15.90	29.53
Solifenacin	588	32,611	26,227	22.42	20.64	24.31	23.42	21.52	25.33
Tolterodine	896	36,824	29,359	30.52	28.55	32.58	28.86	26.95	30.78
Overall with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,442	41,749	39,359	36.64	34.77	38.58	36.62	34.73	38.51
Darifenacin	115	3,919	3,314	34.70	28.65	41.65	46.29	35.23	57.35
Fesoterodine	149	6,709	4,503	33.09	27.99	38.84	34.73	29.00	40.46
Oxybutynin	38	2,001	1,265	30.04	21.25	41.22	34.23	22.77	45.69
Solifenacin	447	17,650	14,450	30.93	28.13	33.94	31.91	28.93	34.88
Tolterodine	714	19,924	16,591	43.03	39.94	46.31	41.38	38.31	44.45

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Stroke									
Female with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,074	77,992	74,149	14.48	13.63	15.38	14.48	13.61	15.34
Darifenacin	82	7,894	6,131	13.37	10.64	16.60	13.30	10.40	16.20
Fesoterodine	116	13,674	9,170	12.65	10.45	15.17	13.72	11.15	16.29
Oxybutynin	29	5,327	3,204	9.05	6.06	13.00	11.40	7.17	15.63
Solifenacin	377	36,948	29,790	12.66	11.41	14.00	13.16	11.83	14.49
Tolterodine	483	33,076	27,159	17.78	16.23	19.44	16.36	14.88	17.84
Female aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	907	44,352	43,753	20.73	19.40	22.12	20.71	19.36	22.06
Darifenacin	73	4,651	3,793	19.24	15.08	24.20	19.88	15.28	24.47
Fesoterodine	92	7,500	5,152	17.86	14.39	21.90	19.19	15.15	23.23
Oxybutynin	21	2,395	1,461	14.37	8.89	21.95	15.15	8.59	21.71
Solifenacin	311	20,518	17,102	18.19	16.22	20.32	18.72	16.64	20.81
Tolterodine	421	20,246	17,024	24.73	22.42	27.21	23.48	21.20	25.76
Female with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	631	21,854	21,793	28.95	26.74	31.30	28.93	26.68	31.19
Darifenacin	53	2,199	1,879	28.21	21.13	36.90	28.75	20.94	36.56
Fesoterodine	58	3,620	2,471	23.48	17.82	30.35	24.96	18.32	31.60
Oxybutynin	16	1,223	784	20.40	11.65	33.10	20.58	10.26	30.90
Solifenacin	217	9,971	8,487	25.57	22.28	29.21	26.11	22.61	29.60
Tolterodine	295	9,814	8,573	34.41	30.59	38.57	33.27	29.42	37.13

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Stroke									
Male with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,130	52,952	43,645	25.89	24.40	27.45	25.87	24.36	27.38
Darifenacin	89	4,441	3,393	26.23	21.06	32.28	24.84	19.66	30.03
Fesoterodine	117	8,248	5,185	22.57	18.66	27.05	23.57	19.20	27.94
Oxybutynin	28	2,815	1,751	15.99	10.62	23.10	23.81	14.61	33.02
Solifenacin	335	20,164	14,578	22.98	20.59	25.58	23.11	20.63	25.59
Tolterodine	579	26,729	19,510	29.68	27.31	32.20	28.81	26.46	31.17
Male aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	934	31,924	27,170	34.38	32.21	36.65	34.35	32.15	36.56
Darifenacin	77	2,868	2,306	33.39	26.35	41.73	33.68	26.15	41.21
Fesoterodine	93	5,010	3,225	28.83	23.27	35.32	30.55	24.17	36.93
Oxybutynin	23	1,145	652	35.28	22.36	52.91	34.90	20.58	49.22
Solifenacin	277	12,093	9,125	30.36	26.89	34.15	30.99	27.34	34.65
Tolterodine	475	16,578	12,335	38.51	35.12	42.13	37.54	34.15	40.93
Male with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	811	19,895	17,567	46.17	43.04	49.46	46.13	42.95	49.30
Darifenacin	62	1,720	1,436	43.18	33.11	55.36	58.35	39.76	76.94
Fesoterodine	91	3,089	2,033	44.77	36.04	54.96	46.82	36.97	56.66
Oxybutynin	22	778	481	45.76	28.67	69.26	51.13	28.90	73.36
Solifenacin	230	7,679	5,962	38.58	33.75	43.90	39.09	34.03	44.15
Tolterodine	419	10,110	8,018	52.26	47.37	57.51	51.41	46.46	56.35

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Cardiovascular mortality									
Overall with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	762	130,944	119,768	6.36	5.92	6.83	6.35	5.90	6.80
Darifenacin	62	12,335	9,654	6.42	4.92	8.23	6.52	4.89	8.15
Fesoterodine	54	21,922	14,511	3.72	2.80	4.86	4.20	3.04	5.35
Oxybutynin	14	8,142	4,991	2.80	1.53	4.70	4.43	2.06	6.80
Solifenacin	216	57,112	44,946	4.81	4.19	5.49	5.26	4.56	5.97
Tolterodine	425	59,805	47,527	8.94	8.11	9.83	7.75	7.01	8.50
Overall aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	714	76,276	72,411	9.86	9.15	10.61	9.84	9.12	10.56
Darifenacin	59	7,519	6,206	9.51	7.24	12.26	10.23	7.60	12.86
Fesoterodine	48	12,510	8,490	5.65	4.17	7.50	6.31	4.47	8.16
Oxybutynin	13	3,540	2,134	6.09	3.24	10.40	7.11	3.22	11.00
Solifenacin	201	32,611	26,662	7.54	6.53	8.66	8.16	7.03	9.29
Tolterodine	402	36,824	30,015	13.39	12.12	14.77	11.99	10.80	13.17
Overall with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	524	41,749	40,678	12.88	11.80	14.03	12.85	11.75	13.95
Darifenacin	40	3,919	3,407	11.74	8.39	15.98	25.29	16.13	34.46
Fesoterodine	40	6,709	4,601	8.69	6.21	11.84	9.84	6.68	13.00
Oxybutynin	11	2,001	1,292	8.51	4.24	15.21	10.74	4.18	17.30
Solifenacin	146	17,650	14,825	9.85	8.32	11.58	10.72	8.97	12.47
Tolterodine	291	19,924	17,179	16.94	15.05	19.00	15.30	13.52	17.08

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Cardiovascular mortality									
Female with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	349	77,992	75,100	4.65	4.17	5.16	4.64	4.15	5.12
Darifenacin	27	7,894	6,182	4.37	2.88	6.35	4.72	2.92	6.51
Fesoterodine	21	13,674	9,258	2.27	1.40	3.47	2.76	1.53	4.00
Oxybutynin	6	5,327	3,222	1.86	0.68	4.03	3.00	0.57	5.44
Solifenacin	105	36,948	30,091	3.49	2.85	4.22	3.80	3.07	4.53
Tolterodine	193	33,076	27,552	7.00	6.05	8.07	5.93	5.08	6.78
Female aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	325	44,352	44,492	7.30	6.53	8.14	7.29	6.50	8.08
Darifenacin	26	4,651	3,838	6.77	4.42	9.92	7.67	4.69	10.65
Fesoterodine	17	7,500	5,218	3.26	1.90	5.21	4.01	2.03	5.98
Oxybutynin	6	2,395	1,470	4.08	1.49	8.84	5.07	0.96	9.18
Solifenacin	98	20,518	17,329	5.66	4.59	6.89	6.04	4.84	7.24
Tolterodine	181	20,246	17,345	10.44	8.97	12.07	9.20	7.84	10.56
Female with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	219	21,854	22,340	9.80	8.55	11.19	9.78	8.48	11.07
Darifenacin	18	2,199	1,912	9.41	5.58	14.87	10.31	5.49	15.13
Fesoterodine	13	3,620	2,510	5.18	2.75	8.84	6.69	2.92	10.47
Oxybutynin	4	1,223	797	5.02	1.35	12.71	6.77	0.04	13.51
Solifenacin	63	9,971	8,667	7.27	5.59	9.30	7.93	5.96	9.90
Tolterodine	122	9,814	8,799	13.86	11.51	16.55	12.21	10.01	14.42

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Cardiovascular mortality									
Male with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	413	52,952	44,669	9.25	8.38	10.18	9.23	8.34	10.12
Darifenacin	35	4,441	3,472	10.08	7.02	14.02	9.56	6.39	12.73
Fesoterodine	33	8,248	5,253	6.28	4.32	8.82	6.61	4.31	8.92
Oxybutynin	8	2,815	1,769	4.52	1.95	8.88	6.84	1.98	11.69
Solifenacin	111	20,164	14,855	7.47	6.15	9.00	7.72	6.29	9.16
Tolterodine	232	26,729	19,975	11.61	10.17	13.21	10.82	9.42	12.22
Male aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	389	31,924	27,919	13.93	12.58	15.39	13.92	12.53	15.30
Darifenacin	33	2,868	2,368	13.93	9.59	19.56	14.33	9.44	19.22
Fesoterodine	31	5,010	3,271	9.48	6.44	13.45	10.00	6.40	13.60
Oxybutynin	7	1,145	665	10.53	4.22	21.61	10.37	2.68	18.05
Solifenacin	103	12,093	9,333	11.04	9.01	13.38	11.53	9.30	13.77
Tolterodine	221	16,578	12,670	17.44	15.22	19.90	16.43	14.26	18.61
Male with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	305	19,895	18,338	16.63	14.82	18.61	16.59	14.73	18.46
Darifenacin	22	1,720	1,495	14.71	9.22	22.27	31.50	16.42	46.57
Fesoterodine	27	3,089	2,091	12.91	8.51	18.78	13.67	8.38	18.96
Oxybutynin	7	778	495	14.13	5.66	29.00	15.57	3.55	27.59
Solifenacin	83	7,679	6,157	13.48	10.74	16.71	14.13	11.08	17.17
Tolterodine	169	10,110	8,380	20.17	17.24	23.45	19.06	16.18	21.95

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Composite cardiovascular endpoint									
Overall with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	3,413	130,944	117,022	29.17	28.20	30.16	29.15	28.17	30.13
Darifenacin	271	12,335	9,469	28.62	25.31	32.24	28.19	24.82	31.57
Fesoterodine	332	21,922	14,303	23.21	20.78	25.85	24.95	22.20	27.70
Oxybutynin	88	8,142	4,944	17.80	14.27	21.93	24.50	19.16	29.84
Solifenacin	1,094	57,112	44,148	24.78	23.33	26.29	26.34	24.77	27.91
Tolterodine	1,678	59,805	46,277	36.26	34.55	38.04	33.00	31.40	34.60
Overall aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	2,921	76,276	70,260	41.57	40.08	43.11	41.54	40.03	43.04
Darifenacin	241	7,519	6,050	39.84	34.96	45.20	41.16	35.94	46.38
Fesoterodine	270	12,510	8,336	32.39	28.64	36.49	34.63	30.39	38.88
Oxybutynin	68	3,540	2,105	32.31	25.09	40.96	34.88	26.45	43.32
Solifenacin	927	32,611	26,033	35.61	33.35	37.98	37.61	35.17	40.04
Tolterodine	1,454	36,824	29,023	50.10	47.56	52.74	46.82	44.38	49.25
Overall with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	2,196	41,749	38,911	56.44	54.10	58.85	56.38	54.03	58.74
Darifenacin	170	3,919	3,286	51.73	44.25	60.12	73.24	59.07	87.40
Fesoterodine	209	6,709	4,475	46.70	40.59	53.48	49.47	42.58	56.36
Oxybutynin	60	2,001	1,260	47.61	36.33	61.28	53.52	39.29	67.74
Solifenacin	681	17,650	14,312	47.58	44.07	51.29	49.76	46.00	53.52
Tolterodine	1,106	19,924	16,369	67.57	63.64	71.67	63.95	60.14	67.77

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Composite cardiovascular endpoint									
Female with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,638	77,992	73,782	22.20	21.14	23.30	22.19	21.11	23.26
Darifenacin	131	7,894	6,104	21.46	17.94	25.46	21.48	17.77	25.19
Fesoterodine	158	13,674	9,148	17.27	14.68	20.18	18.92	15.88	21.95
Oxybutynin	51	5,327	3,195	15.96	11.88	20.99	20.57	14.79	26.36
Solifenacin	541	36,948	29,706	18.21	16.71	19.81	19.15	17.53	20.77
Tolterodine	781	33,076	26,950	28.98	26.98	31.08	26.12	24.26	27.98
Female aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,417	44,352	43,437	32.62	30.95	34.37	32.59	30.89	34.28
Darifenacin	117	4,651	3,769	31.04	25.67	37.20	32.38	26.46	38.30
Fesoterodine	127	7,500	5,137	24.72	20.61	29.41	26.83	22.03	31.63
Oxybutynin	39	2,395	1,453	26.83	19.08	36.68	28.84	19.65	38.03
Solifenacin	459	20,518	17,028	26.96	24.55	29.54	28.05	25.48	30.63
Tolterodine	697	20,246	16,844	41.38	38.36	44.57	38.56	35.65	41.46
Female with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	967	21,854	21,591	44.79	42.01	47.70	44.74	41.92	47.56
Darifenacin	81	2,199	1,864	43.46	34.51	54.01	44.50	34.72	54.27
Fesoterodine	82	3,620	2,464	33.28	26.47	41.31	35.95	27.92	43.99
Oxybutynin	31	1,223	780	39.73	26.99	56.38	42.15	26.87	57.43
Solifenacin	306	9,971	8,439	36.26	32.31	40.56	37.51	33.28	41.74
Tolterodine	480	9,814	8,459	56.74	51.78	62.06	53.23	48.39	58.07

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Composite cardiovascular endpoint									
Male with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,775	52,952	43,240	41.05	39.16	43.01	41.02	39.11	42.93
Darifenacin	140	4,441	3,364	41.61	35.01	49.11	39.64	33.05	46.23
Fesoterodine	174	8,248	5,154	33.76	28.93	39.17	35.24	29.88	40.59
Oxybutynin	37	2,815	1,749	21.15	14.89	29.15	31.19	20.63	41.75
Solifenacin	553	20,164	14,442	38.29	35.17	41.62	38.61	35.39	41.84
Tolterodine	897	26,729	19,326	46.41	43.42	49.55	44.73	41.79	47.67
Male aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,504	31,924	26,823	56.07	53.27	58.98	56.03	53.20	58.86
Darifenacin	124	2,868	2,281	54.37	45.22	64.82	55.37	45.62	65.13
Fesoterodine	143	5,010	3,198	44.71	37.68	52.67	47.27	39.31	55.22
Oxybutynin	29	1,145	651	44.53	29.82	63.94	44.67	28.33	61.01
Solifenacin	468	12,093	9,005	51.97	47.37	56.90	53.08	48.26	57.89
Tolterodine	757	16,578	12,179	62.16	57.81	66.75	60.20	55.89	64.50
Male with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,229	19,895	17,320	70.96	67.05	75.04	70.87	66.90	74.83
Darifenacin	89	1,720	1,422	62.58	50.26	77.01	90.48	67.00	114.00
Fesoterodine	127	3,089	2,011	63.14	52.63	75.12	66.28	54.47	78.08
Oxybutynin	29	778	480	60.42	40.46	86.75	67.65	42.00	93.29
Solifenacin	375	7,679	5,874	63.85	57.55	70.65	64.99	58.40	71.58
Tolterodine	626	10,110	7,910	79.14	73.06	85.59	77.28	71.20	83.36

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
All-cause mortality									
Overall with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	2,148	130,944	119,768	17.93	17.18	18.71	17.90	17.14	18.65
Darifenacin	172	12,335	9,654	17.82	15.25	20.69	18.11	15.39	20.83
Fesoterodine	153	21,922	14,511	10.54	8.94	12.35	12.39	10.36	14.43
Oxybutynin	53	8,142	4,991	10.62	7.95	13.89	15.54	11.18	19.91
Solifenacin	642	57,112	44,946	14.28	13.20	15.43	15.65	14.43	16.86
Tolterodine	1,155	59,805	47,527	24.30	22.92	25.75	21.35	20.10	22.60
Overall aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,964	76,276	72,411	27.12	25.94	28.35	27.07	25.87	28.27
Darifenacin	161	7,519	6,206	25.94	22.09	30.27	27.94	23.59	32.28
Fesoterodine	136	12,510	8,490	16.02	13.44	18.95	18.72	15.46	21.98
Oxybutynin	46	3,540	2,134	21.55	15.78	28.74	23.69	16.68	30.70
Solifenacin	591	32,611	26,662	22.17	20.41	24.03	23.99	22.05	25.94
Tolterodine	1,052	36,824	30,015	35.05	32.96	37.23	31.56	29.63	33.49
Overall with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,283	41,749	40,678	31.54	29.84	33.31	31.47	29.74	33.19
Darifenacin	94	3,919	3,407	27.59	22.29	33.76	55.58	42.43	68.73
Fesoterodine	98	6,709	4,601	21.30	17.29	25.95	24.50	19.46	29.53
Oxybutynin	30	2,001	1,292	23.22	15.67	33.14	28.01	17.55	38.46
Solifenacin	381	17,650	14,825	25.70	23.18	28.42	27.87	25.06	30.69
Tolterodine	697	19,924	17,179	40.57	37.62	43.70	36.97	34.19	39.75

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
All-cause mortality									
Female with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,032	77,992	75,100	13.74	12.92	14.61	13.71	12.88	14.55
Darifenacin	74	7,894	6,182	11.97	9.40	15.03	12.89	9.92	15.86
Fesoterodine	63	13,674	9,258	6.80	5.23	8.71	8.17	6.07	10.27
Oxybutynin	33	5,327	3,222	10.24	7.05	14.38	14.56	9.50	19.62
Solifenacin	312	36,948	30,091	10.37	9.25	11.59	11.34	10.08	12.61
Tolterodine	564	33,076	27,552	20.47	18.82	22.23	17.63	16.15	19.11
Female aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	942	44,352	44,492	21.17	19.84	22.57	21.13	19.78	22.48
Darifenacin	69	4,651	3,838	17.98	13.99	22.75	20.37	15.50	25.23
Fesoterodine	51	7,500	5,218	9.77	7.28	12.85	11.81	8.45	15.17
Oxybutynin	31	2,395	1,470	21.09	14.33	29.93	23.52	15.11	31.94
Solifenacin	290	20,518	17,329	16.73	14.86	18.78	17.97	15.90	20.05
Tolterodine	511	20,246	17,345	29.46	26.96	32.13	26.19	23.88	28.50
Female with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	572	21,854	22,340	25.60	23.55	27.79	25.54	23.45	27.63
Darifenacin	43	2,199	1,912	22.49	16.27	30.29	24.63	17.19	32.08
Fesoterodine	33	3,620	2,510	13.15	9.05	18.46	15.96	10.29	21.64
Oxybutynin	14	1,223	797	17.58	9.60	29.46	21.11	9.81	32.42
Solifenacin	171	9,971	8,667	19.73	16.88	22.92	21.53	18.28	24.78
Tolterodine	318	9,814	8,799	36.14	32.28	40.34	32.12	28.52	35.72

Table CV3. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Current Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
All-cause mortality									
Male with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,116	52,952	44,669	24.98	23.54	26.49	24.94	23.48	26.40
Darifenacin	98	4,441	3,472	28.23	22.91	34.40	26.89	21.56	32.23
Fesoterodine	90	8,248	5,253	17.13	13.78	21.06	19.50	15.33	23.66
Oxybutynin	20	2,815	1,769	11.31	6.90	17.45	17.19	9.16	25.23
Solifenacin	330	20,164	14,855	22.21	19.88	24.75	22.89	20.42	25.37
Tolterodine	591	26,729	19,975	29.59	27.25	32.07	27.61	25.38	29.85
Male aged over 65 with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,022	31,924	27,919	36.61	34.40	38.92	36.56	34.32	38.80
Darifenacin	92	2,868	2,368	38.85	31.31	47.64	40.03	31.85	48.21
Fesoterodine	85	5,010	3,271	25.98	20.75	32.13	29.75	23.21	36.29
Oxybutynin	15	1,145	665	22.57	12.62	37.19	23.96	11.68	36.25
Solifenacin	301	12,093	9,333	32.25	28.71	36.11	33.61	29.81	37.41
Tolterodine	541	16,578	12,670	42.70	39.18	46.45	40.13	36.73	43.53
Male with high CV risk with current exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	711	19,895	18,338	38.77	35.97	41.73	38.69	35.84	41.53
Darifenacin	51	1,720	1,495	34.11	25.39	44.84	63.97	43.50	84.43
Fesoterodine	65	3,089	2,091	31.08	23.99	39.62	34.89	26.12	43.67
Oxybutynin	16	778	495	32.30	18.45	52.41	36.40	17.73	55.08
Solifenacin	210	7,679	6,157	34.11	29.65	39.04	35.60	30.78	40.43
Tolterodine	379	10,110	8,380	45.23	40.79	50.02	42.87	38.54	47.21

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

a. Standardized to sex and age distribution of the study population person-years.

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Acute myocardial infarction	.				.	.	.	.	.	.
Darifenacin										
Cumulative dose Q1	443	23	12,335	2,071	11.11	7.04	16.66	10.71	6.33	15.09
Cumulative dose Q2	1,361	22	7,602	2,247	9.79	6.13	14.82	9.18	5.33	13.02
Cumulative dose Q3	3,885	34	4,084	2,607	13.04	9.03	18.22	12.66	8.37	16.95
Cumulative dose Q4	11,780	33	1,846	2,662	12.40	8.53	17.41	14.28	9.18	19.39
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	50	24	12,335	1,991	12.05	7.72	17.93	11.56	6.93	16.19
Cumulative duration Q2	131	19	7,720	2,261	8.40	5.06	13.12	8.03	4.41	11.64
Cumulative duration Q3	354	39	4,285	2,611	14.94	10.62	20.42	14.40	9.85	18.94
Cumulative duration Q4	955	30	1,877	2,724	11.01	7.43	15.72	12.86	8.07	17.66
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	57	27	12,335	2,052	13.16	8.67	19.14	12.57	7.83	17.32
Time since first exposure Q2	170	19	7,657	2,183	8.70	5.24	13.58	8.29	4.55	12.04
Time since first exposure Q3	458	34	4,430	2,635	12.90	8.93	18.03	12.50	8.28	16.72
Time since first exposure Q4	1,171	32	2,185	2,716	11.78	8.06	16.63	13.98	8.95	19.01
	.	.	.	.	.	.	.	.	.	.
Fesoterodine										
Cumulative dose Q1	242	30	21,922	3,654	8.21	5.54	11.72	8.54	5.47	11.61
Cumulative dose Q2	698	29	12,307	3,404	8.52	5.70	12.23	8.67	5.50	11.84
Cumulative dose Q3	1,738	25	7,480	3,665	6.82	4.41	10.07	6.89	4.16	9.62
Cumulative dose Q4	4,611	24	3,875	3,734	6.43	4.12	9.56	7.71	4.47	10.94
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	51	30	21,922	3,646	8.23	5.55	11.74	8.51	5.45	11.58
Cumulative duration Q2	126	30	13,836	3,400	8.82	5.95	12.59	8.96	5.74	12.19
Cumulative duration Q3	305	27	7,834	3,732	7.23	4.77	10.52	7.36	4.56	10.17
Cumulative duration Q4	705	21	3,829	3,679	5.71	3.53	8.72	6.93	3.82	10.03

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Acute myocardial infarction	.	.	.	.	.	.	.	.	.	.
Fesoterodine										
Time since first exposure Q1	58	32	21,922	3,706	8.63	5.90	12.19	8.80	5.73	11.86
Time since first exposure Q2	162	26	13,592	3,277	7.93	5.18	11.62	8.19	5.02	11.37
Time since first exposure Q3	383	29	8,090	3,772	7.69	5.15	11.04	7.80	4.93	10.66
Time since first exposure Q4	856	21	4,479	3,703	5.67	3.51	8.67	6.78	3.71	9.86
	.	.	.	.	.	.	.	.	.	.
Oxybutynin										
Cumulative dose Q1	456	9	8,142	1,590	5.66	2.58	10.72	7.35	2.32	12.38
Cumulative dose Q2	1,018	7	4,644	951	7.36	2.95	15.10	9.95	2.32	17.58
Cumulative dose Q3	2,529	8	2,350	1,340	5.97	2.57	11.72	7.77	2.17	13.37
Cumulative dose Q4	8,984	9	887	1,099	8.19	3.74	15.51	11.57	3.28	19.87
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	65	11	8,142	1,751	6.28	3.13	11.22	8.18	3.13	13.23
Cumulative duration Q2	129	6	5,570	942	6.37	2.33	13.78	8.30	1.39	15.20
Cumulative duration Q3	303	7	2,651	1,138	6.15	2.47	12.63	8.55	1.98	15.12
Cumulative duration Q4	841	9	983	1,149	7.83	3.57	14.82	10.60	3.23	17.97
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	72	11	8,142	1,755	6.27	3.12	11.19	8.21	3.15	13.27
Time since first exposure Q2	157	7	5,469	838	8.35	3.35	17.13	11.21	2.62	19.80
Time since first exposure Q3	389	5	2,543	1,193	4.19	1.35	9.71	5.58	0.44	10.72
Time since first exposure Q4	1,071	10	1,214	1,194	8.38	4.01	15.37	11.23	3.80	18.65

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Acute myocardial infarction	.	.	.	.	.	.	.	.	.	.
Solifenacin										
Cumulative dose Q1	369	121	57,112	12,093	10.01	8.30	11.96	10.51	8.64	12.39
Cumulative dose Q2	1,107	98	31,555	10,674	9.18	7.45	11.19	9.61	7.69	11.52
Cumulative dose Q3	2,789	122	17,251	11,177	10.92	9.06	13.03	11.47	9.43	13.52
Cumulative dose Q4	7,508	80	8,179	10,766	7.43	5.89	9.25	8.89	6.88	10.89
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	64	130	57,112	11,998	10.84	9.05	12.87	11.33	9.38	13.28
Cumulative duration Q2	171	98	30,703	10,771	9.10	7.39	11.09	9.60	7.69	11.50
Cumulative duration Q3	417	113	17,583	11,226	10.07	8.30	12.10	10.60	8.63	12.57
Cumulative duration Q4	993	80	8,172	10,716	7.47	5.92	9.29	8.87	6.88	10.86
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	66	123	57,112	10,999	11.18	9.29	13.34	11.67	9.60	13.73
Time since first exposure Q2	215	107	29,993	11,429	9.36	7.67	11.31	9.71	7.86	11.55
Time since first exposure Q3	541	113	18,592	11,172	10.11	8.34	12.16	10.64	8.66	12.62
Time since first exposure Q4	1,228	78	10,289	11,111	7.02	5.55	8.76	8.54	6.61	10.48
	.	.	.	.	.	.	.	.	.	.
Tolterodine										
Cumulative dose Q1	200	217	59,805	14,149	15.34	13.36	17.52	12.92	11.16	14.68
Cumulative dose Q2	616	177	30,710	10,563	16.76	14.38	19.41	14.05	11.95	16.16
Cumulative dose Q3	1,555	144	15,800	11,154	12.91	10.89	15.20	11.42	9.54	13.31
Cumulative dose Q4	4,076	168	7,797	11,228	14.96	12.79	17.40	15.97	13.53	18.41
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	71	202	59,805	13,669	14.78	12.81	16.96	12.91	11.10	14.72
Cumulative duration Q2	199	190	30,216	11,792	16.11	13.90	18.57	13.85	11.85	15.85
Cumulative duration Q3	476	160	16,055	11,167	14.33	12.19	16.73	12.79	10.78	14.79
Cumulative duration Q4	1,081	154	7,577	10,466	14.71	12.48	17.23	14.72	12.38	17.05

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Acute myocardial infarction										
Tolterodine	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	75	195	59,805	13,040	14.95	12.93	17.21	13.02	11.16	14.88
Time since first exposure Q2	253	194	28,754	11,548	16.80	14.52	19.34	14.26	12.21	16.30
Time since first exposure Q3	611	158	17,492	11,155	14.16	12.04	16.55	12.67	10.67	14.67
Time since first exposure Q4	1,318	159	10,349	11,352	14.01	11.91	16.36	14.34	12.10	16.58
	.	.	.	.	.	.	.	.	.	.
Stroke										
Darifenacin										
Cumulative dose Q1	443	43	12,335	2,069	20.78	15.04	27.99	20.63	14.44	26.82
Cumulative dose Q2	1,361	45	7,590	2,242	20.07	14.64	26.86	19.09	13.49	24.69
Cumulative dose Q3	3,885	33	4,060	2,590	12.74	8.77	17.89	12.57	8.25	16.90
Cumulative dose Q4	11,744	50	1,837	2,624	19.06	14.14	25.12	18.51	13.30	23.72
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	50	47	12,335	1,989	23.63	17.36	31.42	23.34	16.65	30.03
Cumulative duration Q2	131	32	7,701	2,256	14.19	9.70	20.02	13.51	8.82	18.20
Cumulative duration Q3	354	43	4,269	2,594	16.58	12.00	22.33	16.18	11.31	21.05
Cumulative duration Q4	954	49	1,861	2,686	18.24	13.50	24.12	17.62	12.61	22.62
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	57	47	12,335	2,050	22.93	16.85	30.49	22.46	16.02	28.89
Time since first exposure Q2	170	31	7,640	2,178	14.24	9.67	20.20	13.53	8.75	18.31
Time since first exposure Q3	458	45	4,409	2,616	17.20	12.54	23.01	16.52	11.67	21.37
Time since first exposure Q4	1,171	48	2,164	2,680	17.91	13.20	23.74	17.88	12.71	23.05

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Stroke	.	.	.	.	.	.	.	.	.	.
Fesoterodine										
Cumulative dose Q1	241	76	21,922	3,649	20.83	16.41	26.07	21.30	16.50	26.10
Cumulative dose Q2	697	58	12,270	3,389	17.11	12.99	22.12	17.24	12.78	21.70
Cumulative dose Q3	1,738	58	7,431	3,633	15.96	12.12	20.63	16.51	12.20	20.82
Cumulative dose Q4	4,609	41	3,834	3,683	11.13	7.99	15.10	12.27	8.32	16.22
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	51	76	21,922	3,641	20.87	16.45	26.13	21.09	16.33	25.85
Cumulative duration Q2	126	55	13,792	3,385	16.25	12.24	21.15	16.51	12.11	20.92
Cumulative duration Q3	305	57	7,800	3,704	15.39	11.66	19.94	16.04	11.82	20.26
Cumulative duration Q4	704	45	3,793	3,625	12.41	9.05	16.61	13.60	9.44	17.76
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	58	83	21,922	3,701	22.43	17.86	27.80	22.57	17.70	27.45
Time since first exposure Q2	162	49	13,545	3,263	15.02	11.11	19.85	15.36	11.03	19.70
Time since first exposure Q3	383	51	8,049	3,743	13.62	10.14	17.91	14.30	10.32	18.29
Time since first exposure Q4	855	50	4,439	3,648	13.71	10.17	18.07	14.55	10.34	18.75
	.	.	.	.	.	.	.	.	.	.
Oxybutynin										
Cumulative dose Q1	456	20	8,142	1,588	12.59	7.69	19.44	17.96	9.91	26.00
Cumulative dose Q2	1,018	6	4,638	950	6.31	2.31	13.67	8.52	1.60	15.44
Cumulative dose Q3	2,527	16	2,350	1,337	11.96	6.83	19.41	15.22	6.89	23.56
Cumulative dose Q4	8,958	15	881	1,079	13.90	7.77	22.90	19.91	9.16	30.66
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	65	20	8,142	1,749	11.43	6.98	17.65	14.93	8.05	21.81
Cumulative duration Q2	129	14	5,565	941	14.88	8.13	24.94	22.48	10.61	34.36
Cumulative duration Q3	303	8	2,643	1,133	7.06	3.04	13.87	7.93	2.08	13.77
Cumulative duration Q4	837	15	977	1,132	13.25	7.41	21.83	19.58	9.18	29.98

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Stroke										
Oxybutynin	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	72	21	8,142	1,754	11.97	7.41	18.29	15.87	8.75	22.99
Time since first exposure Q2	157	13	5,464	837	15.53	8.26	26.52	22.91	10.35	35.46
Time since first exposure Q3	389	8	2,537	1,187	6.74	2.90	13.23	7.74	2.05	13.43
Time since first exposure Q4	1,068	15	1,206	1,177	12.74	7.13	21.00	18.71	8.74	28.68
	.	.	.	.	.	.	.	.	.	.
Solifenacin										
Cumulative dose Q1	369	210	57,112	12,081	17.38	15.11	19.90	18.09	15.64	20.55
Cumulative dose Q2	1,106	185	31,481	10,632	17.40	14.98	20.10	17.65	15.10	20.20
Cumulative dose Q3	2,788	167	17,144	11,085	15.07	12.87	17.53	15.43	13.07	17.79
Cumulative dose Q4	7,476	150	8,080	10,569	14.19	12.01	16.65	15.88	13.26	18.50
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	64	219	57,112	11,985	18.27	15.93	20.86	18.96	16.44	21.47
Cumulative duration Q2	171	186	30,625	10,721	17.35	14.94	20.03	17.76	15.20	20.32
Cumulative duration Q3	417	159	17,473	11,129	14.29	12.15	16.69	14.75	12.44	17.05
Cumulative duration Q4	991	148	8,082	10,532	14.05	11.88	16.51	15.44	12.89	17.99
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	66	205	57,112	10,988	18.66	16.19	21.39	19.30	16.66	21.95
Time since first exposure Q2	215	196	29,925	11,373	17.23	14.91	19.82	17.51	15.05	19.97
Time since first exposure Q3	541	166	18,489	11,068	15.00	12.80	17.46	15.61	13.22	18.00
Time since first exposure Q4	1,227	145	10,191	10,938	13.26	11.19	15.60	14.50	12.07	16.94

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Stroke	.	.	.	.	.	.	.	.	.	.
Tolterodine										
Cumulative dose Q1	200	406	59,805	14,115	28.76	26.03	31.70	25.51	22.96	28.06
Cumulative dose Q2	616	275	30,575	10,487	26.22	23.22	29.51	23.76	20.89	26.63
Cumulative dose Q3	1,554	212	15,670	11,018	19.24	16.74	22.01	17.71	15.30	20.12
Cumulative dose Q4	4,073	169	7,693	11,049	15.30	13.08	17.78	15.98	13.55	18.41
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	70	413	59,805	13,641	30.28	27.43	33.34	27.44	24.74	30.14
Cumulative duration Q2	199	266	30,078	11,710	22.72	20.07	25.62	20.75	18.21	23.29
Cumulative duration Q3	476	219	15,906	11,031	19.85	17.31	22.66	18.13	15.70	20.56
Cumulative duration Q4	1,080	164	7,470	10,287	15.94	13.60	18.58	15.94	13.49	18.38
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	75	401	59,805	13,011	30.82	27.88	33.99	28.07	25.26	30.87
Time since first exposure Q2	253	292	28,616	11,453	25.50	22.66	28.59	22.68	20.02	25.34
Time since first exposure Q3	611	196	17,350	11,017	17.79	15.39	20.46	16.12	13.84	18.40
Time since first exposure Q4	1,318	173	10,247	11,189	15.46	13.24	17.95	15.52	13.20	17.84
	.	.	.	.	.	.	.	.	.	.
Cardiovascular mortality										
Darifenacin										
Cumulative dose Q1	443	2	12,335	2,073	0.96	0.11	3.36	0.93	0.00	2.22
Cumulative dose Q2	1,361	18	7,621	2,256	7.98	4.73	12.60	7.46	4.00	10.92
Cumulative dose Q3	3,888	16	4,100	2,626	6.09	3.48	9.89	6.47	3.27	9.68
Cumulative dose Q4	11,798	26	1,864	2,698	9.64	6.29	14.12	10.90	6.49	15.31

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Cardiovascular mortality										
Darifenacin	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	50	6	12,335	1,993	3.01	1.10	6.52	2.91	0.58	5.23
Cumulative duration Q2	131	14	7,736	2,269	6.17	3.37	10.34	5.91	2.81	9.01
Cumulative duration Q3	354	18	4,303	2,629	6.85	4.06	10.81	7.18	3.83	10.53
Cumulative duration Q4	956	24	1,896	2,762	8.69	5.56	12.92	9.46	5.53	13.40
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	57	6	12,335	2,054	2.92	1.07	6.32	2.82	0.56	5.08
Time since first exposure Q2	170	12	7,676	2,191	5.48	2.83	9.55	5.17	2.23	8.11
Time since first exposure Q3	458	17	4,447	2,655	6.40	3.73	10.24	6.65	3.46	9.83
Time since first exposure Q4	1,172	27	2,202	2,753	9.81	6.46	14.26	11.29	6.87	15.72
	.	.	.	.	.	.	.	.	.	.
Fesoterodine										
Cumulative dose Q1	242	3	21,922	3,657	0.82	0.16	2.35	0.90	0.00	1.92
Cumulative dose Q2	698	14	12,327	3,412	4.10	2.24	6.88	4.14	1.96	6.32
Cumulative dose Q3	1,739	17	7,503	3,684	4.62	2.69	7.38	4.87	2.52	7.22
Cumulative dose Q4	4,607	20	3,897	3,759	5.32	3.25	8.21	6.43	3.44	9.41
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	51	7	21,922	3,649	1.92	0.77	3.94	2.09	0.53	3.64
Cumulative duration Q2	126	11	13,854	3,408	3.23	1.61	5.76	3.16	1.28	5.05
Cumulative duration Q3	305	15	7,861	3,748	4.00	2.24	6.59	4.06	1.99	6.13
Cumulative duration Q4	705	21	3,854	3,706	5.67	3.51	8.66	7.13	3.93	10.34
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	58	8	21,922	3,709	2.16	0.93	4.24	2.21	0.67	3.76
Time since first exposure Q2	162	7	13,612	3,285	2.13	0.85	4.37	2.23	0.55	3.90
Time since first exposure Q3	383	20	8,113	3,788	5.28	3.22	8.15	5.40	3.00	7.79
Time since first exposure Q4	856	19	4,504	3,729	5.10	3.07	7.95	6.45	3.39	9.51

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Cardiovascular mortality	.	.	.	.	.	.	.	.	.	.
Oxybutynin										
Cumulative dose Q1	456	1	8,142	1,591	0.63	0.01	3.18	0.95	0.00	2.83
Cumulative dose Q2	1,018	2	4,647	952	2.10	0.24	7.32	3.44	0.00	8.22
Cumulative dose Q3	2,530	6	2,352	1,344	4.46	1.63	9.66	6.63	1.14	12.12
Cumulative dose Q4	8,992	5	890	1,104	4.53	1.46	10.49	8.61	0.73	16.49
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	65	2	8,142	1,752	1.14	0.13	3.98	1.70	0.00	4.06
Cumulative duration Q2	129	1	5,576	943	1.06	0.01	5.36	1.72	0.00	5.10
Cumulative duration Q3	303	6	2,655	1,140	5.26	1.92	11.39	7.78	1.33	14.23
Cumulative duration Q4	841	5	987	1,156	4.33	1.39	10.02	7.84	0.72	14.97
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	72	2	8,142	1,756	1.14	0.13	3.97	1.71	0.00	4.10
Time since first exposure Q2	157	3	5,475	839	3.58	0.72	10.26	5.50	0.00	11.75
Time since first exposure Q3	390	5	2,548	1,195	4.18	1.35	9.69	6.38	0.55	12.21
Time since first exposure Q4	1,072	4	1,217	1,201	3.33	0.90	8.43	6.56	0.00	13.27
	.	.	.	.	.	.	.	.	.	.
Solifenacin										
Cumulative dose Q1	369	37	57,112	12,104	3.06	2.15	4.21	3.20	2.16	4.23
Cumulative dose Q2	1,107	54	31,615	10,706	5.04	3.79	6.58	5.14	3.77	6.51
Cumulative dose Q3	2,790	79	17,325	11,258	7.02	5.56	8.75	7.44	5.79	9.10
Cumulative dose Q4	7,515	46	8,241	10,878	4.23	3.10	5.64	5.39	3.79	6.99
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	64	53	57,112	12,008	4.41	3.31	5.77	4.62	3.38	5.87
Cumulative duration Q2	171	50	30,757	10,800	4.63	3.44	6.10	4.77	3.45	6.10
Cumulative duration Q3	417	59	17,661	11,300	5.22	3.97	6.73	5.55	4.12	6.97
Cumulative duration Q4	994	54	8,246	10,837	4.98	3.74	6.50	6.25	4.55	7.95

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Cardiovascular mortality	.	.	.	.	.	.	.	.	.	.
Solifenacin										
Time since first exposure Q1	66	50	57,112	11,008	4.54	3.37	5.99	4.76	3.44	6.08
Time since first exposure Q2	215	53	30,044	11,464	4.62	3.46	6.05	4.73	3.46	6.01
Time since first exposure Q3	542	65	18,671	11,248	5.78	4.46	7.37	6.19	4.68	7.71
Time since first exposure Q4	1,229	48	10,361	11,226	4.28	3.15	5.67	5.23	3.72	6.75
	.	.	.	.	.	.	.	.	.	.
Tolterodine										
Cumulative dose Q1	201	82	59,805	14,174	5.79	4.60	7.18	4.63	3.60	5.66
Cumulative dose Q2	616	101	30,803	10,630	9.50	7.74	11.54	7.67	6.14	9.20
Cumulative dose Q3	1,555	123	15,928	11,276	10.91	9.07	13.02	9.45	7.76	11.13
Cumulative dose Q4	4,079	119	7,894	11,447	10.40	8.61	12.44	11.17	9.15	13.20
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	71	89	59,805	13,689	6.50	5.22	8.00	5.46	4.30	6.62
Cumulative duration Q2	199	99	30,311	11,857	8.35	6.79	10.17	6.90	5.52	8.28
Cumulative duration Q3	476	112	16,184	11,293	9.92	8.17	11.93	8.60	6.99	10.21
Cumulative duration Q4	1,082	125	7,688	10,688	11.70	9.73	13.93	11.59	9.55	13.63
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	75	83	59,805	13,059	6.36	5.06	7.88	5.32	4.15	6.49
Time since first exposure Q2	253	108	28,843	11,618	9.30	7.63	11.22	7.60	6.13	9.07
Time since first exposure Q3	611	116	17,622	11,284	10.28	8.49	12.33	8.86	7.23	10.48
Time since first exposure Q4	1,319	118	10,459	11,566	10.20	8.44	12.22	10.38	8.50	12.26
	.	.	.	.	.	.	.	.	.	.

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Composite cardiovascular endpoint										
Darifenacin										
Cumulative dose Q1	442	64	12,335	2,067	30.96	23.84	39.54	30.35	22.90	37.81
Cumulative dose Q2	1,361	59	7,573	2,233	26.42	20.11	34.07	25.11	18.68	31.55
Cumulative dose Q3	3,883	67	4,049	2,576	26.01	20.16	33.03	25.49	19.34	31.65
Cumulative dose Q4	11,737	81	1,821	2,593	31.24	24.81	38.83	32.96	25.52	40.39
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	50	67	12,335	1,987	33.71	26.12	42.81	32.93	25.03	40.84
Cumulative duration Q2	131	47	7,688	2,248	20.90	15.36	27.80	19.97	14.25	25.69
Cumulative duration Q3	354	80	4,254	2,579	31.02	24.60	38.61	30.17	23.51	36.83
Cumulative duration Q4	954	77	1,845	2,654	29.01	22.90	36.26	30.53	23.48	37.57
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	57	70	12,335	2,048	34.18	26.65	43.19	33.15	25.37	40.93
Time since first exposure Q2	170	46	7,624	2,171	21.19	15.51	28.26	20.20	14.34	26.07
Time since first exposure Q3	457	77	4,394	2,600	29.62	23.37	37.02	28.65	22.22	35.09
Time since first exposure Q4	1,170	78	2,151	2,650	29.43	23.26	36.73	31.90	24.57	39.23
	.	.	.	.	.	.	.	.	.	.
Fesoterodine										
Cumulative dose Q1	241	105	21,922	3,647	28.79	23.55	34.85	29.51	23.85	35.17
Cumulative dose Q2	697	83	12,251	3,382	24.54	19.55	30.43	24.71	19.37	30.06
Cumulative dose Q3	1,737	80	7,409	3,616	22.12	17.54	27.53	22.66	17.62	27.70
Cumulative dose Q4	4,613	64	3,813	3,658	17.50	13.47	22.34	19.92	14.78	25.07
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	51	103	21,922	3,638	28.31	23.11	34.33	28.65	23.09	34.20
Cumulative duration Q2	126	84	13,775	3,377	24.87	19.84	30.79	25.27	19.82	30.71
Cumulative duration Q3	305	80	7,773	3,689	21.69	17.20	26.99	22.36	17.40	27.32
Cumulative duration Q4	704	65	3,770	3,599	18.06	13.94	23.02	20.52	15.28	25.76

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Composite cardiovascular endpoint										
Fesoterodine										
Time since first exposure Q1	58	112	21,922	3,698	30.29	24.94	36.44	30.52	24.85	36.20
Time since first exposure Q2	162	74	13,526	3,254	22.74	17.86	28.55	23.20	17.88	28.53
Time since first exposure Q3	383	77	8,026	3,728	20.65	16.30	25.81	21.36	16.52	26.19
Time since first exposure Q4	855	69	4,415	3,622	19.05	14.82	24.11	21.05	15.82	26.28
	.	.	.	.	.	.	.	.	.	.
Oxybutynin										
Cumulative dose Q1	456	29	8,142	1,587	18.27	12.23	26.24	25.27	15.80	34.75
Cumulative dose Q2	1,018	13	4,635	949	13.70	7.29	23.39	18.46	8.17	28.74
Cumulative dose Q3	2,526	24	2,348	1,334	18.00	11.53	26.77	23.02	12.99	33.04
Cumulative dose Q4	8,950	22	878	1,074	20.48	12.83	30.99	28.69	15.70	41.69
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	65	31	8,142	1,748	17.73	12.05	25.16	23.08	14.56	31.60
Cumulative duration Q2	129	20	5,559	939	21.29	13.00	32.86	30.69	17.00	44.39
Cumulative duration Q3	303	15	2,639	1,131	13.27	7.42	21.86	16.53	7.71	25.35
Cumulative duration Q4	837	22	973	1,126	19.54	12.24	29.58	27.61	15.39	39.83
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	72	32	8,142	1,753	18.26	12.49	25.77	24.05	15.33	32.76
Time since first exposure Q2	157	20	5,458	836	23.92	14.60	36.92	34.01	18.86	49.17
Time since first exposure Q3	389	13	2,532	1,185	10.97	5.84	18.74	13.33	5.67	21.00
Time since first exposure Q4	1,067	23	1,203	1,170	19.66	12.46	29.48	27.24	15.42	39.06

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Composite cardiovascular endpoint										
Solifenacin										
Cumulative dose Q1	369	323	57,112	12,070	26.76	23.92	29.84	27.87	24.83	30.92
Cumulative dose Q2	1,106	276	31,423	10,601	26.03	23.05	29.29	26.68	23.52	29.84
Cumulative dose Q3	2,787	278	17,072	11,008	25.25	22.37	28.40	26.19	23.09	29.29
Cumulative dose Q4	7,474	217	8,021	10,468	20.73	18.06	23.68	23.73	20.47	26.98
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	64	342	57,112	11,974	28.56	25.61	31.75	29.63	26.48	32.77
Cumulative duration Q2	171	276	30,571	10,692	25.81	22.86	29.05	26.69	23.53	29.84
Cumulative duration Q3	417	261	17,398	11,058	23.60	20.82	26.65	24.56	21.56	27.57
Cumulative duration Q4	990	215	8,012	10,423	20.63	17.96	23.58	23.35	20.15	26.56
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	66	321	57,112	10,979	29.24	26.13	32.62	30.25	26.93	33.56
Time since first exposure Q2	215	295	29,874	11,339	26.02	23.13	29.16	26.60	23.56	29.64
Time since first exposure Q3	541	271	18,413	10,996	24.65	21.80	27.76	25.79	22.69	28.88
Time since first exposure Q4	1,227	207	10,122	10,833	19.11	16.59	21.90	21.68	18.64	24.72
	.	.	.	.	.	.	.	.	.	.
Tolterodine										
Cumulative dose Q1	200	602	59,805	14,091	42.72	39.38	46.27	37.26	34.20	40.32
Cumulative dose Q2	615	435	30,489	10,425	41.72	37.90	45.84	36.80	33.27	40.33
Cumulative dose Q3	1,554	338	15,551	10,905	31.00	27.78	34.48	28.15	25.12	31.18
Cumulative dose Q4	4,070	303	7,604	10,855	27.91	24.86	31.24	29.57	26.21	32.93
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	70	595	59,805	13,623	43.68	40.24	47.33	39.12	35.92	42.33
Cumulative duration Q2	199	437	29,992	11,651	37.51	34.07	41.20	33.47	30.27	36.66
Cumulative duration Q3	476	359	15,787	10,914	32.89	29.58	36.48	29.82	26.70	32.94
Cumulative duration Q4	1,079	287	7,368	10,089	28.45	25.25	31.94	28.55	25.24	31.87

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
Composite cardiovascular endpoint										
Tolterodine	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	75	577	59,805	12,993	44.41	40.86	48.19	39.90	36.57	43.23
Time since first exposure Q2	252	467	28,534	11,388	41.01	37.37	44.90	35.87	32.54	39.20
Time since first exposure Q3	611	331	17,230	10,898	30.37	27.19	33.83	27.46	24.46	30.45
Time since first exposure Q4	1,318	303	10,145	10,999	27.55	24.53	30.83	27.98	24.81	31.14
	.	.	.	.	.	.	.	.	.	.
All-cause mortality										
Darifenacin										
Cumulative dose Q1	443	9	12,335	2,073	4.34	1.98	8.22	4.26	1.47	7.05
Cumulative dose Q2	1,361	51	7,621	2,256	22.60	16.83	29.71	21.28	15.42	27.14
Cumulative dose Q3	3,888	56	4,100	2,626	21.33	16.11	27.69	21.34	15.70	26.99
Cumulative dose Q4	11,798	56	1,864	2,698	20.76	15.68	26.95	24.37	17.64	31.10
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	50	19	12,335	1,993	9.53	5.74	14.88	9.23	5.07	13.38
Cumulative duration Q2	131	45	7,736	2,269	19.83	14.46	26.53	19.07	13.48	24.65
Cumulative duration Q3	354	53	4,303	2,629	20.16	15.10	26.37	20.16	14.68	25.65
Cumulative duration Q4	956	55	1,896	2,762	19.91	15.00	25.91	22.78	16.51	29.05
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	57	24	12,335	2,054	11.68	7.48	17.38	11.25	6.74	15.75
Time since first exposure Q2	170	40	7,676	2,191	18.25	13.04	24.85	17.41	11.99	22.83
Time since first exposure Q3	458	48	4,447	2,655	18.08	13.33	23.97	17.95	12.84	23.06
Time since first exposure Q4	1,172	60	2,202	2,753	21.79	16.63	28.05	26.03	19.19	32.87

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
All-cause mortality	.	.	.	.	.	.	.	.	.	.
Fesoterodine										
Cumulative dose Q1	242	27	21,922	3,657	7.38	4.86	10.74	7.75	4.81	10.69
Cumulative dose Q2	698	33	12,327	3,412	9.67	6.66	13.58	10.34	6.77	13.90
Cumulative dose Q3	1,739	45	7,503	3,684	12.22	8.91	16.35	13.22	9.29	17.15
Cumulative dose Q4	4,607	48	3,897	3,759	12.77	9.41	16.93	16.21	11.31	21.11
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	51	33	21,922	3,649	9.04	6.22	12.70	9.49	6.23	12.75
Cumulative duration Q2	126	31	13,854	3,408	9.10	6.18	12.91	9.77	6.28	13.26
Cumulative duration Q3	305	37	7,861	3,748	9.87	6.95	13.61	10.54	7.09	13.99
Cumulative duration Q4	705	52	3,854	3,706	14.03	10.48	18.40	17.78	12.69	22.87
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	58	37	21,922	3,709	9.97	7.02	13.75	10.52	7.11	13.93
Time since first exposure Q2	162	26	13,612	3,285	7.91	5.17	11.59	8.24	5.04	11.45
Time since first exposure Q3	383	45	8,113	3,788	11.88	8.67	15.90	12.70	8.93	16.48
Time since first exposure Q4	856	45	4,504	3,729	12.07	8.80	16.15	15.98	11.03	20.94
	.	.	.	.	.	.	.	.	.	.
Oxybutynin										
Cumulative dose Q1	456	11	8,142	1,591	6.91	3.45	12.35	10.64	4.34	16.93
Cumulative dose Q2	1,018	8	4,647	952	8.40	3.62	16.50	12.02	3.64	20.39
Cumulative dose Q3	2,530	21	2,352	1,344	15.62	9.67	23.87	21.04	11.17	30.91
Cumulative dose Q4	8,992	13	890	1,104	11.78	6.26	20.11	17.77	7.23	28.31
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	65	14	8,142	1,752	7.99	4.37	13.39	11.75	5.55	17.95
Cumulative duration Q2	129	8	5,576	943	8.48	3.65	16.65	10.81	2.76	18.86
Cumulative duration Q3	303	14	2,655	1,140	12.28	6.71	20.58	18.57	8.16	28.97
Cumulative duration Q4	841	17	987	1,156	14.71	8.56	23.53	21.38	10.52	32.23

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
All-cause mortality	.	.	.	.	.	.	.	.	.	.
Oxybutynin										
Time since first exposure Q1	72	13	8,142	1,756	7.40	3.94	12.64	11.13	5.05	17.22
Time since first exposure Q2	157	12	5,475	839	14.30	7.38	24.95	17.84	6.97	28.71
Time since first exposure Q3	390	13	2,548	1,195	10.88	5.79	18.58	16.64	7.01	26.27
Time since first exposure Q4	1,072	15	1,217	1,201	12.49	6.99	20.58	19.98	8.99	30.96
	.	.	.	.	.	.	.	.	.	.
Solifenacin										
Cumulative dose Q1	369	94	57,112	12,104	7.77	6.28	9.50	8.22	6.55	9.88
Cumulative dose Q2	1,107	171	31,615	10,706	15.97	13.67	18.55	16.38	13.92	18.84
Cumulative dose Q3	2,790	209	17,325	11,258	18.57	16.13	21.26	19.82	17.12	22.53
Cumulative dose Q4	7,515	168	8,241	10,878	15.44	13.20	17.96	19.50	16.45	22.54
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	64	129	57,112	12,008	10.74	8.97	12.76	11.31	9.35	13.26
Cumulative duration Q2	171	166	30,757	10,800	15.37	13.12	17.89	15.98	13.54	18.42
Cumulative duration Q3	417	170	17,661	11,300	15.04	12.87	17.48	16.15	13.71	18.59
Cumulative duration Q4	994	177	8,246	10,837	16.33	14.02	18.92	20.25	17.19	23.30
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	66	120	57,112	11,008	10.90	9.04	13.03	11.44	9.39	13.49
Time since first exposure Q2	215	175	30,044	11,464	15.27	13.09	17.70	15.79	13.45	18.14
Time since first exposure Q3	542	174	18,671	11,248	15.47	13.26	17.95	16.57	14.09	19.05
Time since first exposure Q4	1,229	173	10,361	11,226	15.41	13.20	17.89	18.95	16.05	21.85

Table CV3(2). Person-time, Frequency, and Incidence Rates of Acute Myocardial Infarction Endpoint Definition for Dose and Duration During Current Use, by OAB Medication

	Mean Dose, Mean Duration, or Mean Time Since First Exposure	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	95% CI		Standardized Incidence Rate[a]	95% CI	
All-cause mortality	.	.	.	.	.	.	.	.	.	.
Tolterodine										
Cumulative dose Q1	201	227	59,805	14,174	16.02	14.00	18.24	12.98	11.24	14.72
Cumulative dose Q2	616	295	30,803	10,630	27.75	24.67	31.11	22.59	19.95	25.24
Cumulative dose Q3	1,555	332	15,928	11,276	29.44	26.36	32.79	25.87	23.06	28.68
Cumulative dose Q4	4,079	301	7,894	11,447	26.29	23.41	29.44	28.09	24.88	31.30
	.	.	.	.	.	.	.	.	.	.
Cumulative duration Q1	71	265	59,805	13,689	19.36	17.10	21.84	16.54	14.51	18.57
Cumulative duration Q2	199	269	30,311	11,857	22.69	20.06	25.57	19.14	16.80	21.47
Cumulative duration Q3	476	310	16,184	11,293	27.45	24.48	30.68	24.08	21.37	26.80
Cumulative duration Q4	1,082	311	7,688	10,688	29.10	25.95	32.52	28.89	25.67	32.11
	.	.	.	.	.	.	.	.	.	.
Time since first exposure Q1	75	254	59,805	13,059	19.45	17.13	22.00	16.49	14.41	18.56
Time since first exposure Q2	253	280	28,843	11,618	24.10	21.36	27.10	20.16	17.74	22.59
Time since first exposure Q3	611	329	17,622	11,284	29.16	26.09	32.48	25.43	22.64	28.21
Time since first exposure Q4	1,319	292	10,459	11,566	25.25	22.43	28.31	25.53	22.59	28.48

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

a. Standardized to sex and age distribution of the study population person-years.

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Acute myocardial infarction									
Overall with recent exposure to				.	.	.	.	.	.
Any OAB medication	487	123,515	35,613	13.67	12.49	14.95	13.67	12.45	14.88
Darifenacin	36	11,847	2,837	12.69	8.89	17.57	12.70	8.54	16.86
Fesoterodine	29	20,122	4,267	6.80	4.55	9.76	7.76	4.89	10.64
Oxybutynin	21	7,251	1,628	12.90	7.98	19.70	16.51	9.13	23.89
Solifenacin	164	53,179	12,838	12.78	10.89	14.89	13.77	11.65	15.88
Tolterodine	245	57,264	14,490	16.91	14.86	19.16	15.15	13.24	17.07
Overall aged over 65 with recent exposure to									
Any OAB medication	436	71,647	20,951	20.81	18.90	22.86	20.79	18.84	22.74
Darifenacin	35	7,172	1,729	20.24	14.10	28.15	20.82	13.91	27.73
Fesoterodine	27	11,430	2,440	11.06	7.29	16.09	12.44	7.66	17.22
Oxybutynin	17	3,275	759	22.41	13.05	35.85	24.26	12.29	36.23
Solifenacin	148	30,153	7,365	20.10	16.99	23.61	21.25	17.81	24.68
Tolterodine	216	35,006	8,928	24.19	21.07	27.64	22.35	19.34	25.35
Overall with high CV risk with recent exposure to									
Any OAB medication	320	38,971	11,010	29.06	25.97	32.43	29.04	25.85	32.22
Darifenacin	26	3,715	887	29.30	19.13	42.92	34.05	17.57	50.53
Fesoterodine	14	6,113	1,293	10.83	5.92	18.15	12.09	5.65	18.54
Oxybutynin	16	1,804	413	38.72	22.12	62.83	38.89	19.42	58.37
Solifenacin	107	16,242	3,864	27.69	22.69	33.46	29.12	23.58	34.65
Tolterodine	162	18,842	4,697	34.49	29.39	40.23	32.24	27.23	37.24

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Acute myocardial infarction									
Female with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	230	74,103	22,544	10.20	8.93	11.61	10.20	8.88	11.51
Darifenacin	13	7,625	1,886	6.89	3.67	11.77	6.79	3.09	10.48
Fesoterodine	21	12,659	2,760	7.61	4.71	11.63	9.02	5.09	12.96
Oxybutynin	16	4,837	1,110	14.41	8.23	23.38	17.56	8.81	26.31
Solifenacin	77	34,659	8,670	8.88	7.01	11.10	9.39	7.29	11.49
Tolterodine	107	31,880	8,419	12.71	10.42	15.36	11.27	9.11	13.42
Female aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	209	42,066	13,085	15.97	13.88	18.29	15.96	13.79	18.12
Darifenacin	13	4,469	1,117	11.64	6.19	19.87	11.69	5.33	18.06
Fesoterodine	20	6,933	1,537	13.01	7.94	20.08	14.97	8.28	21.65
Oxybutynin	12	2,235	533	22.51	11.62	39.26	24.19	10.34	38.04
Solifenacin	71	19,168	4,885	14.54	11.35	18.33	15.02	11.52	18.52
Tolterodine	96	19,415	5,191	18.49	14.98	22.59	16.98	13.56	20.41
Female with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	140	20,602	6,140	22.80	19.18	26.91	22.78	19.00	26.55
Darifenacin	9	2,097	519	17.33	7.91	32.81	17.22	5.96	28.48
Fesoterodine	8	3,349	736	10.87	4.68	21.34	12.47	3.64	21.31
Oxybutynin	13	1,111	262	49.68	26.43	84.84	52.02	23.42	80.61
Solifenacin	46	9,289	2,306	19.95	14.60	26.61	20.69	14.70	26.69
Tolterodine	67	9,355	2,401	27.91	21.63	35.44	25.75	19.52	31.97

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Acute myocardial infarction									
Male with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	257	49,412	13,068	19.67	17.33	22.22	19.67	17.26	22.07
Darifenacin	23	4,222	950	24.20	15.33	36.29	22.92	13.54	32.29
Fesoterodine	8	7,463	1,507	5.31	2.29	10.42	5.59	1.66	9.52
Oxybutynin	5	2,414	518	9.65	3.11	22.35	14.68	1.39	27.97
Solifenacin	87	18,520	4,167	20.88	16.72	25.75	21.34	16.85	25.83
Tolterodine	138	25,384	6,070	22.73	19.10	26.86	21.87	18.21	25.53
Male aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	227	29,581	7,866	28.86	25.23	32.87	28.84	25.09	32.60
Darifenacin	22	2,703	612	35.95	22.52	54.40	36.04	20.98	51.10
Fesoterodine	7	4,497	903	7.75	3.11	15.90	8.24	2.05	14.43
Oxybutynin	5	1,040	225	22.18	7.15	51.35	24.38	2.31	46.45
Solifenacin	77	10,985	2,480	31.05	24.50	38.80	31.63	24.56	38.69
Tolterodine	120	15,591	3,738	32.11	26.62	38.39	31.28	25.67	36.89
Male with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	180	18,369	4,871	36.96	31.75	42.77	36.94	31.54	42.33
Darifenacin	17	1,618	368	46.18	26.89	73.89	46.03	18.29	73.78
Fesoterodine	6	2,764	557	10.78	3.94	23.33	11.62	2.23	21.00
Oxybutynin	3	693	152	19.80	3.98	56.80	22.33	0.00	47.60
Solifenacin	61	6,953	1,558	39.15	29.94	50.29	39.75	29.77	49.73
Tolterodine	95	9,487	2,296	41.38	33.48	50.58	40.43	32.28	48.58

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Stroke									
Overall with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	612	123,515	35,569	17.21	15.87	18.63	17.20	15.84	18.57
Darifenacin	66	11,847	2,833	23.30	18.02	29.64	23.32	17.67	28.96
Fesoterodine	66	20,122	4,263	15.48	11.97	19.70	17.23	12.99	21.48
Oxybutynin	15	7,251	1,628	9.21	5.15	15.18	13.05	6.17	19.93
Solifenacin	174	53,179	12,828	13.56	11.62	15.74	14.19	12.07	16.31
Tolterodine	296	57,264	14,476	20.45	18.18	22.92	18.70	16.55	20.85
Overall aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	530	71,647	20,914	25.34	23.23	27.59	25.33	23.17	27.48
Darifenacin	59	7,172	1,727	34.17	26.01	44.08	34.94	26.01	43.87
Fesoterodine	55	11,430	2,437	22.57	17.00	29.38	25.17	18.38	31.96
Oxybutynin	13	3,275	758	17.15	9.12	29.28	19.65	8.53	30.77
Solifenacin	155	30,153	7,355	21.07	17.89	24.67	21.76	18.32	25.20
Tolterodine	253	35,006	8,918	28.37	24.98	32.09	26.70	23.38	30.01
Overall with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	376	38,971	10,984	34.23	30.86	37.87	34.21	30.75	37.67
Darifenacin	42	3,715	885	47.44	34.19	64.12	46.52	27.10	65.95
Fesoterodine	45	6,113	1,289	34.91	25.46	46.71	38.52	27.05	49.99
Oxybutynin	7	1,804	414	16.91	6.78	34.70	21.66	4.64	38.69
Solifenacin	92	16,242	3,861	23.83	19.21	29.22	24.56	19.52	29.59
Tolterodine	193	18,842	4,685	41.19	35.59	47.43	39.40	33.80	45.00

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Stroke									
Female with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	308	74,103	22,519	13.68	12.19	15.29	13.67	12.15	15.20
Darifenacin	30	7,625	1,883	15.93	10.75	22.74	15.81	10.14	21.48
Fesoterodine	33	12,659	2,758	11.97	8.24	16.80	13.35	8.70	17.99
Oxybutynin	7	4,837	1,111	6.30	2.52	12.93	7.61	1.87	13.34
Solifenacin	105	34,659	8,663	12.12	9.91	14.67	12.57	10.16	14.98
Tolterodine	136	31,880	8,411	16.17	13.57	19.13	14.69	12.20	17.18
Female aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	267	42,066	13,065	20.44	18.06	23.04	20.43	17.98	22.88
Darifenacin	28	4,469	1,115	25.11	16.68	36.29	25.49	16.03	34.94
Fesoterodine	27	6,933	1,536	17.58	11.58	25.57	19.53	12.02	27.04
Oxybutynin	6	2,235	533	11.25	4.11	24.35	11.59	2.17	21.02
Solifenacin	90	19,168	4,878	18.45	14.84	22.68	18.80	14.91	22.69
Tolterodine	119	19,415	5,185	22.95	19.01	27.46	21.52	17.63	25.42
Female with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	181	20,602	6,125	29.55	25.40	34.18	29.53	25.22	33.83
Darifenacin	17	2,097	518	32.85	19.12	52.55	32.25	16.90	47.59
Fesoterodine	25	3,349	734	34.05	22.03	50.25	37.63	22.53	52.72
Oxybutynin	3	1,111	263	11.41	2.29	32.74	11.14	0.00	23.80
Solifenacin	50	9,289	2,303	21.71	16.11	28.62	22.30	16.11	28.50
Tolterodine	88	9,355	2,395	36.74	29.47	45.26	34.67	27.37	41.97

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Stroke									
Male with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	304	49,412	13,050	23.29	20.75	26.07	23.30	20.68	25.92
Darifenacin	36	4,222	949	37.92	26.56	52.49	36.30	24.41	48.18
Fesoterodine	33	7,463	1,505	21.93	15.09	30.79	23.96	15.62	32.30
Oxybutynin	8	2,414	517	15.47	6.66	30.37	22.47	6.52	38.41
Solifenacin	69	18,520	4,166	16.56	12.89	20.96	16.99	12.97	21.00
Tolterodine	160	25,384	6,065	26.38	22.45	30.80	25.62	21.65	29.60
Male aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	263	29,581	7,850	33.50	29.58	37.81	33.50	29.45	37.54
Darifenacin	31	2,703	612	50.68	34.43	71.92	50.70	32.85	68.55
Fesoterodine	28	4,497	901	31.08	20.65	44.91	34.57	21.49	47.64
Oxybutynin	7	1,040	225	31.14	12.48	63.89	33.08	7.93	58.23
Solifenacin	65	10,985	2,477	26.24	20.25	33.44	26.69	20.20	33.18
Tolterodine	134	15,591	3,733	35.90	30.08	42.52	35.32	29.33	41.31
Male with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	195	18,369	4,859	40.13	34.70	46.18	40.12	34.49	45.76
Darifenacin	25	1,618	368	67.98	43.98	100.30	67.60	31.55	103.70
Fesoterodine	20	2,764	555	36.04	22.01	55.64	39.65	22.02	57.28
Oxybutynin	4	693	151	26.49	7.13	67.05	34.94	0.00	69.99
Solifenacin	42	6,953	1,558	26.96	19.43	36.44	27.40	19.11	35.69
Tolterodine	105	9,487	2,290	45.85	37.50	55.51	45.38	36.69	54.07

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Cardiovascular mortality									
Overall with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	311	123,515	35,669	8.72	7.78	9.74	8.71	7.74	9.68
Darifenacin	18	11,847	2,841	6.34	3.75	10.01	6.39	3.43	9.35
Fesoterodine	22	20,122	4,270	5.15	3.23	7.80	6.52	3.75	9.30
Oxybutynin	7	7,251	1,631	4.29	1.72	8.81	7.40	1.56	13.25
Solifenacin	93	53,179	12,852	7.24	5.84	8.86	7.85	6.25	9.45
Tolterodine	174	57,264	14,512	11.99	10.27	13.91	10.65	9.05	12.24
Overall aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	296	71,647	21,000	14.10	12.54	15.80	14.08	12.47	15.68
Darifenacin	17	7,172	1,734	9.81	5.71	15.69	10.09	5.29	14.90
Fesoterodine	22	11,430	2,443	9.00	5.64	13.63	11.07	6.36	15.78
Oxybutynin	6	3,275	760	7.89	2.88	17.08	11.63	1.88	21.38
Solifenacin	88	30,153	7,377	11.93	9.57	14.70	12.66	10.01	15.32
Tolterodine	166	35,006	8,948	18.55	15.84	21.60	17.15	14.52	19.78
Overall with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	217	38,971	11,046	19.65	17.12	22.44	19.62	17.01	22.23
Darifenacin	11	3,715	891	12.34	6.15	22.04	13.25	2.30	24.19
Fesoterodine	13	6,113	1,294	10.04	5.34	17.15	12.73	5.70	19.75
Oxybutynin	6	1,804	415	14.46	5.28	31.29	19.40	3.04	35.75
Solifenacin	60	16,242	3,873	15.49	11.82	19.94	16.39	12.23	20.54
Tolterodine	128	18,842	4,710	27.18	22.67	32.31	25.44	20.99	29.88

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Cardiovascular mortality									
Female with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	162	74,103	22,571	7.18	6.11	8.37	7.17	6.07	8.27
Darifenacin	8	7,625	1,888	4.24	1.82	8.32	4.24	1.29	7.18
Fesoterodine	13	12,659	2,762	4.71	2.50	8.04	6.05	2.70	9.39
Oxybutynin	3	4,837	1,112	2.70	0.54	7.74	3.56	0.00	7.70
Solifenacin	49	34,659	8,677	5.65	4.18	7.47	6.11	4.39	7.82
Tolterodine	91	31,880	8,428	10.80	8.69	13.26	9.37	7.43	11.32
Female aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	156	42,066	13,108	11.90	10.11	13.92	11.88	10.02	13.75
Darifenacin	8	4,469	1,119	7.15	3.08	14.04	7.29	2.23	12.35
Fesoterodine	13	6,933	1,540	8.44	4.49	14.42	10.41	4.65	16.17
Oxybutynin	2	2,235	535	3.74	0.42	13.04	4.62	0.00	11.09
Solifenacin	47	19,168	4,890	9.61	7.06	12.78	10.13	7.23	13.03
Tolterodine	88	19,415	5,199	16.93	13.57	20.85	15.48	12.22	18.74
Female with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	106	20,602	6,154	17.22	14.10	20.83	17.19	13.92	20.47
Darifenacin	5	2,097	521	9.60	3.09	22.23	9.26	1.14	17.38
Fesoterodine	6	3,349	737	8.14	2.97	17.61	10.39	1.89	18.89
Oxybutynin	3	1,111	263	11.40	2.29	32.70	13.32	0.00	28.72
Solifenacin	30	9,289	2,309	12.99	8.76	18.54	13.80	8.85	18.75
Tolterodine	63	9,355	2,406	26.19	20.12	33.50	24.10	18.09	30.11

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Cardiovascular mortality									
Male with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	149	49,412	13,099	11.38	9.62	13.36	11.37	9.55	13.20
Darifenacin	10	4,222	953	10.49	5.02	19.25	10.10	3.83	16.38
Fesoterodine	9	7,463	1,508	5.97	2.72	11.30	7.34	2.45	12.23
Oxybutynin	4	2,414	518	7.72	2.08	19.53	14.04	0.00	28.30
Solifenacin	44	18,520	4,176	10.54	7.66	14.14	10.86	7.65	14.07
Tolterodine	83	25,384	6,084	13.64	10.87	16.91	12.85	10.08	15.62
Male aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	140	29,581	7,892	17.74	14.92	20.93	17.73	14.79	20.66
Darifenacin	9	2,703	615	14.64	6.68	27.72	14.75	5.11	24.40
Fesoterodine	9	4,497	904	9.96	4.54	18.85	12.18	4.06	20.29
Oxybutynin	4	1,040	226	17.71	4.76	44.83	23.30	0.00	46.95
Solifenacin	41	10,985	2,487	16.49	11.83	22.36	16.88	11.71	22.05
Tolterodine	78	15,591	3,749	20.81	16.45	25.97	19.92	15.49	24.36
Male with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	111	18,369	4,891	22.69	18.67	27.33	22.67	18.45	26.89
Darifenacin	6	1,618	371	16.19	5.91	35.04	24.90	0.66	49.13
Fesoterodine	7	2,764	557	12.57	5.03	25.78	15.67	3.95	27.40
Oxybutynin	3	693	152	19.76	3.97	56.68	27.05	0.00	58.52
Solifenacin	30	6,953	1,564	19.18	12.94	27.37	19.64	12.61	26.67
Tolterodine	65	9,487	2,304	28.21	21.77	35.95	27.12	20.51	33.73

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Composite cardiovascular endpoint									
Overall with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	1,033	123,515	35,517	29.08	27.34	30.91	29.08	27.30	30.85
Darifenacin	95	11,847	2,829	33.58	27.17	41.05	33.76	26.95	40.57
Fesoterodine	88	20,122	4,260	20.66	16.57	25.45	22.85	17.98	27.72
Oxybutynin	35	7,251	1,626	21.52	14.99	29.93	28.65	18.72	38.57
Solifenacin	319	53,179	12,814	24.89	22.24	27.78	26.47	23.55	29.39
Tolterodine	507	57,264	14,455	35.07	32.09	38.27	31.86	29.06	34.65
Overall aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	906	71,647	20,870	43.41	40.63	46.33	43.38	40.56	46.20
Darifenacin	87	7,172	1,723	50.50	40.45	62.29	51.96	41.03	62.90
Fesoterodine	75	11,430	2,434	30.81	24.23	38.62	33.98	26.14	41.82
Oxybutynin	29	3,275	756	38.34	25.67	55.05	42.38	26.33	58.44
Solifenacin	288	30,153	7,343	39.22	34.82	44.02	41.05	36.29	45.81
Tolterodine	437	35,006	8,900	49.10	44.60	53.93	45.88	41.55	50.21
Overall with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	650	38,971	10,951	59.35	54.88	64.10	59.31	54.75	63.87
Darifenacin	63	3,715	882	71.45	54.90	91.41	76.69	51.40	102.00
Fesoterodine	56	6,113	1,288	43.49	32.85	56.47	47.92	35.12	60.71
Oxybutynin	23	1,804	412	55.82	35.37	83.72	60.74	34.80	86.69
Solifenacin	183	16,242	3,852	47.51	40.87	54.91	49.58	42.37	56.79
Tolterodine	332	18,842	4,672	71.05	63.62	79.12	67.40	60.09	74.70

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Composite cardiovascular endpoint									
Female with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	506	74,103	22,495	22.49	20.58	24.54	22.49	20.53	24.45
Darifenacin	38	7,625	1,882	20.19	14.29	27.71	20.09	13.69	26.49
Fesoterodine	50	12,659	2,756	18.14	13.47	23.92	20.73	14.85	26.60
Oxybutynin	23	4,837	1,109	20.74	13.14	31.10	25.20	14.73	35.67
Solifenacin	170	34,659	8,657	19.64	16.80	22.82	20.54	17.44	23.63
Tolterodine	230	31,880	8,403	27.37	23.95	31.15	24.65	21.44	27.87
Female aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	445	42,066	13,044	34.12	31.02	37.44	34.09	30.92	37.26
Darifenacin	36	4,469	1,114	32.33	22.64	44.75	32.87	22.11	43.63
Fesoterodine	43	6,933	1,534	28.03	20.28	37.75	31.68	22.01	41.36
Oxybutynin	18	2,235	532	33.84	20.04	53.44	35.84	19.06	52.62
Solifenacin	150	19,168	4,873	30.78	26.06	36.12	31.57	26.51	36.63
Tolterodine	202	19,415	5,178	39.01	33.82	44.78	36.26	31.22	41.30
Female with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	299	20,602	6,112	48.92	43.53	54.79	48.88	43.34	54.42
Darifenacin	23	2,097	516	44.54	28.22	66.80	43.98	25.98	61.97
Fesoterodine	31	3,349	733	42.28	28.72	60.00	47.23	30.19	64.26
Oxybutynin	16	1,111	261	61.21	34.97	99.32	63.26	31.94	94.59
Solifenacin	87	9,289	2,300	37.83	30.30	46.66	39.08	30.85	47.30
Tolterodine	146	9,355	2,390	61.08	51.57	71.83	57.22	47.86	66.58

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
Composite cardiovascular endpoint									
Male with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	527	49,412	13,021	40.47	37.09	44.08	40.48	37.03	43.94
Darifenacin	57	4,222	947	60.21	45.60	78.00	57.42	42.49	72.36
Fesoterodine	38	7,463	1,504	25.26	17.87	34.67	26.53	17.97	35.09
Oxybutynin	12	2,414	517	23.21	11.98	40.48	34.62	14.47	54.76
Solifenacin	149	18,520	4,157	35.84	30.32	42.08	36.74	30.83	42.64
Tolterodine	277	25,384	6,052	45.77	40.54	51.49	44.33	39.10	49.56
Male aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	461	29,581	7,826	58.91	53.65	64.54	58.88	53.51	64.26
Darifenacin	51	2,703	609	83.74	62.34	110.10	83.83	60.82	106.80
Fesoterodine	32	4,497	900	35.54	24.31	50.16	37.80	24.49	51.11
Oxybutynin	11	1,040	224	49.01	24.43	87.53	53.30	20.86	85.74
Solifenacin	138	10,985	2,470	55.86	46.93	66.00	56.87	47.38	66.37
Tolterodine	235	15,591	3,723	63.13	55.31	71.73	61.93	54.00	69.87
Male with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	351	18,369	4,839	72.53	65.14	80.53	72.50	64.92	80.09
Darifenacin	40	1,618	365	109.50	78.21	149.10	109.90	64.75	155.00
Fesoterodine	25	2,764	555	45.09	29.17	66.53	48.79	29.42	68.16
Oxybutynin	7	693	151	46.46	18.61	95.31	57.56	14.17	100.90
Solifenacin	96	6,953	1,552	61.85	50.10	75.53	62.87	50.28	75.45
Tolterodine	186	9,487	2,282	81.50	70.21	94.09	80.27	68.71	91.82

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
All-cause mortality									
Overall with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	889	123,515	35,669	24.92	23.31	26.62	24.90	23.26	26.54
Darifenacin	58	11,847	2,841	20.41	15.50	26.39	20.65	15.33	25.98
Fesoterodine	61	20,122	4,270	14.28	10.93	18.35	16.51	12.28	20.74
Oxybutynin	16	7,251	1,631	9.81	5.61	15.92	14.63	6.88	22.39
Solifenacin	271	53,179	12,852	21.09	18.65	23.75	22.72	20.01	25.44
Tolterodine	489	57,264	14,512	33.70	30.77	36.82	29.88	27.21	32.55
Overall aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	822	71,647	21,000	39.14	36.51	41.91	39.10	36.42	41.77
Darifenacin	55	7,172	1,734	31.72	23.90	41.29	33.02	24.28	41.76
Fesoterodine	57	11,430	2,443	23.33	17.67	30.22	26.56	19.53	33.60
Oxybutynin	14	3,275	760	18.41	10.06	30.85	22.96	10.06	35.86
Solifenacin	253	30,153	7,377	34.30	30.20	38.79	36.18	31.70	40.65
Tolterodine	449	35,006	8,948	50.18	45.65	55.04	45.97	41.69	50.26
Overall with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	543	38,971	11,046	49.16	45.11	53.47	49.09	44.96	53.22
Darifenacin	29	3,715	891	32.54	21.79	46.72	54.36	29.95	78.77
Fesoterodine	41	6,113	1,294	31.68	22.73	42.97	35.92	24.72	47.11
Oxybutynin	10	1,804	415	24.10	11.54	44.22	30.93	10.28	51.57
Solifenacin	163	16,242	3,873	42.08	35.87	49.06	44.19	37.38	50.99
Tolterodine	302	18,842	4,710	64.12	57.09	71.77	59.49	52.72	66.25

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
All-cause mortality									
Female with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	451	74,103	22,571	19.98	18.18	21.91	19.96	18.12	21.80
Darifenacin	25	7,625	1,888	13.24	8.57	19.54	13.44	8.16	18.72
Fesoterodine	32	12,659	2,762	11.58	7.92	16.35	14.06	9.08	19.05
Oxybutynin	9	4,837	1,112	8.09	3.69	15.32	9.44	3.17	15.72
Solifenacin	144	34,659	8,677	16.60	14.00	19.54	17.75	14.85	20.66
Tolterodine	245	31,880	8,428	29.07	25.54	32.95	25.24	22.05	28.43
Female aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	421	42,066	13,108	32.12	29.12	35.34	32.07	29.01	35.14
Darifenacin	24	4,469	1,119	21.45	13.74	31.90	22.26	13.33	31.19
Fesoterodine	29	6,933	1,540	18.84	12.61	27.05	22.48	14.13	30.84
Oxybutynin	7	2,235	535	13.09	5.25	26.87	13.23	3.27	23.18
Solifenacin	137	19,168	4,890	28.02	23.52	33.12	29.23	24.33	34.13
Tolterodine	228	19,415	5,199	43.85	38.35	49.93	39.70	34.50	44.89
Female with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	259	20,602	6,154	42.08	37.11	47.53	42.02	36.90	47.13
Darifenacin	13	2,097	521	24.97	13.28	42.63	24.79	11.30	38.28
Fesoterodine	17	3,349	737	23.06	13.42	36.89	27.31	13.98	40.63
Oxybutynin	6	1,111	263	22.80	8.33	49.35	24.45	4.53	44.37
Solifenacin	80	9,289	2,309	34.64	27.47	43.12	36.35	28.37	44.33
Tolterodine	144	9,355	2,406	59.85	50.47	70.46	54.48	45.50	63.47

Table CV4. Person-time, Frequency, and Incidence Rates for Each Outcome, by Sex for Recent Exposure

	Events	Individuals Contributing Person-time	Person-time (Years)	Crude Incidence Rate	(95% CI)		Standardized Incidence Rate[a]	(95% CI)	
All-cause mortality									
Male with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	438	49,412	13,099	33.44	30.38	36.72	33.43	30.30	36.56
Darifenacin	33	4,222	953	34.62	23.83	48.61	33.12	21.80	44.44
Fesoterodine	29	7,463	1,508	19.23	12.88	27.61	20.73	13.06	28.40
Oxybutynin	7	2,414	518	13.50	5.41	27.70	23.60	5.45	41.76
Solifenacin	127	18,520	4,176	30.41	25.35	36.19	31.31	25.86	36.76
Tolterodine	244	25,384	6,084	40.11	35.23	45.47	37.90	33.13	42.67
Male aged over 65 with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	401	29,581	7,892	50.81	45.96	56.04	50.78	45.81	55.75
Darifenacin	31	2,703	615	50.43	34.26	71.57	50.93	33.00	68.87
Fesoterodine	28	4,497	904	30.98	20.58	44.77	33.35	20.78	45.91
Oxybutynin	7	1,040	226	30.99	12.42	63.59	39.16	9.03	69.28
Solifenacin	116	10,985	2,487	46.64	38.54	55.95	47.74	39.05	56.44
Tolterodine	221	15,591	3,749	58.95	51.44	67.26	56.41	48.96	63.87
Male with high CV risk with recent exposure to	.	.	.	.	.	.	.	.	.
Any OAB medication	284	18,369	4,891	58.06	51.50	65.22	58.01	51.27	64.76
Darifenacin	16	1,618	371	43.18	24.66	70.05	84.25	37.17	131.30
Fesoterodine	24	2,764	557	43.09	27.60	64.08	46.77	27.83	65.70
Oxybutynin	4	693	152	26.34	7.09	66.68	39.10	0.00	78.43
Solifenacin	83	6,953	1,564	53.06	42.26	65.78	54.06	42.42	65.70
Tolterodine	158	9,487	2,304	68.57	58.29	80.13	65.80	55.52	76.08

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

a. Standardized to sex and age distribution of the study population person-years.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Acute myocardial infarction						
Overall with current exposure to	.	.	.	.	.	.
Any OAB medication	0.76	0.69	0.83	0.86	0.78	0.93
Darifenacin	0.78	0.62	0.93	0.87	0.70	1.04
Fesoterodine	0.50	0.40	0.60	0.61	0.49	0.74
Oxybutynin	0.44	0.29	0.60	0.69	0.45	0.92
Solifenacin	0.63	0.55	0.70	0.77	0.68	0.86
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.79	0.71	0.86	0.86	0.78	0.94
Darifenacin	0.77	0.61	0.93	0.88	0.70	1.07
Fesoterodine	0.51	0.40	0.62	0.61	0.47	0.74
Oxybutynin	0.56	0.34	0.78	0.66	0.40	0.92
Solifenacin	0.66	0.57	0.74	0.77	0.67	0.87
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.80	0.71	0.89	0.87	0.77	0.96
Darifenacin	0.73	0.54	0.92	1.24	0.93	1.54
Fesoterodine	0.54	0.40	0.68	0.64	0.47	0.80
Oxybutynin	0.70	0.41	0.98	0.86	0.51	1.21
Solifenacin	0.66	0.56	0.76	0.77	0.66	0.89
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Acute myocardial infarction						
Female with current exposure to	.	.	.	.	.	.
Any OAB medication	0.69	0.60	0.78	0.80	0.69	0.90
Darifenacin	0.72	0.52	0.93	0.85	0.60	1.09
Fesoterodine	0.43	0.30	0.56	0.57	0.39	0.74
Oxybutynin	0.57	0.32	0.81	0.87	0.49	1.24
Solifenacin	0.50	0.41	0.59	0.63	0.51	0.74
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.72	0.62	0.82	0.80	0.69	0.91
Darifenacin	0.72	0.50	0.94	0.85	0.59	1.10
Fesoterodine	0.44	0.30	0.59	0.55	0.37	0.73
Oxybutynin	0.69	0.36	1.02	0.84	0.44	1.25
Solifenacin	0.54	0.44	0.65	0.64	0.52	0.76
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.72	0.60	0.84	0.80	0.67	0.94
Darifenacin	0.72	0.45	0.98	0.83	0.52	1.14
Fesoterodine	0.47	0.29	0.66	0.61	0.37	0.85
Oxybutynin	0.80	0.38	1.22	1.01	0.48	1.55
Solifenacin	0.50	0.38	0.61	0.60	0.46	0.74
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Acute myocardial infarction						
Male with current exposure to	.	.	.	.	.	.
Any OAB medication	0.87	0.76	0.98	0.92	0.80	1.03
Darifenacin	0.89	0.64	1.14	0.89	0.65	1.14
Fesoterodine	0.61	0.44	0.77	0.66	0.48	0.84
Oxybutynin	0.33	0.13	0.52	0.50	0.20	0.81
Solifenacin	0.85	0.71	0.99	0.91	0.76	1.05
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.88	0.76	0.99	0.91	0.79	1.03
Darifenacin	0.86	0.61	1.10	0.92	0.65	1.18
Fesoterodine	0.61	0.43	0.78	0.66	0.47	0.85
Oxybutynin	0.45	0.13	0.76	0.48	0.14	0.82
Solifenacin	0.84	0.70	0.99	0.90	0.74	1.05
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.89	0.75	1.02	0.92	0.78	1.06
Darifenacin	0.76	0.49	1.04	1.26	0.84	1.68
Fesoterodine	0.61	0.40	0.82	0.66	0.44	0.89
Oxybutynin	0.60	0.20	1.00	0.72	0.24	1.20
Solifenacin	0.87	0.70	1.05	0.93	0.75	1.12
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Stroke						
Overall with current exposure to	.	.	.	.	.	.
Any OAB medication	0.82	0.76	0.88	0.89	0.83	0.96
Darifenacin	0.79	0.66	0.92	0.84	0.70	0.97
Fesoterodine	0.71	0.61	0.81	0.83	0.71	0.95
Oxybutynin	0.51	0.37	0.64	0.76	0.56	0.97
Solifenacin	0.71	0.64	0.77	0.80	0.73	0.88
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.85	0.78	0.92	0.90	0.83	0.97
Darifenacin	0.81	0.67	0.95	0.87	0.72	1.02
Fesoterodine	0.72	0.61	0.84	0.82	0.69	0.94
Oxybutynin	0.68	0.48	0.89	0.79	0.55	1.03
Solifenacin	0.73	0.66	0.81	0.81	0.73	0.90
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.85	0.77	0.93	0.88	0.81	0.96
Darifenacin	0.81	0.65	0.97	1.12	0.90	1.33
Fesoterodine	0.77	0.63	0.90	0.84	0.69	0.99
Oxybutynin	0.70	0.47	0.93	0.83	0.56	1.10
Solifenacin	0.72	0.63	0.80	0.77	0.68	0.86
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Stroke						
Female with current exposure to	.	.	.	.	.	.
Any OAB medication	0.81	0.73	0.90	0.88	0.79	0.98
Darifenacin	0.75	0.58	0.93	0.81	0.62	1.00
Fesoterodine	0.71	0.57	0.86	0.84	0.67	1.01
Oxybutynin	0.51	0.32	0.70	0.70	0.44	0.96
Solifenacin	0.71	0.62	0.81	0.80	0.70	0.91
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.84	0.74	0.94	0.88	0.78	0.98
Darifenacin	0.78	0.58	0.97	0.85	0.64	1.06
Fesoterodine	0.72	0.56	0.88	0.82	0.63	1.00
Oxybutynin	0.58	0.33	0.84	0.65	0.36	0.93
Solifenacin	0.74	0.63	0.84	0.80	0.68	0.91
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.84	0.73	0.96	0.87	0.75	0.99
Darifenacin	0.82	0.58	1.06	0.86	0.61	1.12
Fesoterodine	0.68	0.49	0.87	0.75	0.54	0.96
Oxybutynin	0.59	0.29	0.89	0.62	0.31	0.93
Solifenacin	0.74	0.61	0.87	0.78	0.65	0.92
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Stroke						
Male with current exposure to	.	.	.	.	.	.
Any OAB medication	0.87	0.79	0.96	0.90	0.81	0.99
Darifenacin	0.88	0.69	1.08	0.86	0.67	1.05
Fesoterodine	0.76	0.61	0.91	0.82	0.66	0.98
Oxybutynin	0.54	0.33	0.74	0.83	0.51	1.14
Solifenacin	0.77	0.67	0.88	0.80	0.69	0.91
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.89	0.79	0.99	0.92	0.81	1.02
Darifenacin	0.87	0.66	1.08	0.90	0.68	1.11
Fesoterodine	0.75	0.58	0.92	0.81	0.63	0.99
Oxybutynin	0.92	0.53	1.30	0.93	0.54	1.32
Solifenacin	0.79	0.67	0.91	0.83	0.70	0.95
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.88	0.78	0.99	0.90	0.79	1.00
Darifenacin	0.83	0.61	1.05	1.14	0.85	1.42
Fesoterodine	0.86	0.66	1.05	0.91	0.70	1.12
Oxybutynin	0.88	0.50	1.25	0.99	0.57	1.42
Solifenacin	0.74	0.62	0.86	0.76	0.64	0.88
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Cardiovascular mortality						
Overall with current exposure to	.	.	.	.	.	.
Any OAB medication	0.71	0.63	0.80	0.82	0.72	0.92
Darifenacin	0.72	0.53	0.91	0.84	0.62	1.07
Fesoterodine	0.42	0.30	0.53	0.54	0.39	0.69
Oxybutynin	0.31	0.15	0.48	0.57	0.27	0.88
Solifenacin	0.54	0.45	0.63	0.68	0.57	0.79
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.74	0.65	0.83	0.82	0.72	0.92
Darifenacin	0.71	0.52	0.90	0.85	0.62	1.09
Fesoterodine	0.42	0.30	0.55	0.53	0.37	0.68
Oxybutynin	0.45	0.20	0.71	0.59	0.27	0.92
Solifenacin	0.56	0.47	0.66	0.68	0.57	0.80
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.76	0.65	0.87	0.84	0.72	0.96
Darifenacin	0.69	0.46	0.92	1.65	1.14	2.16
Fesoterodine	0.51	0.34	0.68	0.64	0.43	0.86
Oxybutynin	0.50	0.20	0.81	0.70	0.28	1.12
Solifenacin	0.58	0.47	0.70	0.70	0.56	0.84
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Cardiovascular mortality						
Female with current exposure to	.	.	.	.	.	.
Any OAB medication	0.66	0.55	0.78	0.78	0.64	0.92
Darifenacin	0.62	0.37	0.87	0.80	0.48	1.12
Fesoterodine	0.32	0.18	0.47	0.47	0.26	0.68
Oxybutynin	0.27	0.05	0.48	0.51	0.09	0.92
Solifenacin	0.50	0.38	0.62	0.64	0.49	0.79
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.70	0.57	0.83	0.79	0.65	0.94
Darifenacin	0.65	0.38	0.92	0.83	0.49	1.18
Fesoterodine	0.31	0.16	0.47	0.44	0.22	0.65
Oxybutynin	0.39	0.07	0.71	0.55	0.10	1.00
Solifenacin	0.54	0.41	0.68	0.66	0.50	0.82
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.71	0.55	0.86	0.80	0.62	0.98
Darifenacin	0.68	0.34	1.02	0.84	0.43	1.26
Fesoterodine	0.37	0.16	0.59	0.55	0.23	0.86
Oxybutynin	0.36	0.00	0.72	0.55	0.00	1.11
Solifenacin	0.52	0.36	0.68	0.65	0.45	0.85
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Cardiovascular mortality						
Male with current exposure to	.	.	.	.	.	.
Any OAB medication	0.80	0.67	0.92	0.85	0.72	0.99
Darifenacin	0.87	0.56	1.18	0.88	0.57	1.20
Fesoterodine	0.54	0.34	0.74	0.61	0.39	0.83
Oxybutynin	0.39	0.11	0.66	0.63	0.19	1.08
Solifenacin	0.64	0.50	0.79	0.71	0.55	0.88
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.80	0.67	0.93	0.85	0.71	0.99
Darifenacin	0.80	0.51	1.09	0.87	0.55	1.19
Fesoterodine	0.54	0.34	0.75	0.61	0.38	0.84
Oxybutynin	0.60	0.15	1.06	0.63	0.16	1.11
Solifenacin	0.63	0.48	0.78	0.70	0.54	0.87
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.82	0.67	0.98	0.87	0.71	1.03
Darifenacin	0.73	0.41	1.05	1.65	1.00	2.30
Fesoterodine	0.64	0.38	0.90	0.72	0.43	1.01
Oxybutynin	0.70	0.17	1.23	0.82	0.20	1.43
Solifenacin	0.67	0.49	0.84	0.74	0.55	0.94
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Composite cardiovascular endpoint						
Overall with current exposure to	.	.	.	.	.	.
Any OAB medication	0.80	0.76	0.85	0.88	0.83	0.93
Darifenacin	0.79	0.69	0.89	0.85	0.74	0.96
Fesoterodine	0.64	0.56	0.72	0.76	0.67	0.85
Oxybutynin	0.49	0.39	0.60	0.74	0.58	0.90
Solifenacin	0.68	0.63	0.74	0.80	0.74	0.86
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.83	0.78	0.88	0.89	0.83	0.94
Darifenacin	0.80	0.69	0.90	0.88	0.76	1.00
Fesoterodine	0.65	0.56	0.73	0.74	0.64	0.84
Oxybutynin	0.64	0.49	0.80	0.75	0.56	0.93
Solifenacin	0.71	0.65	0.77	0.80	0.74	0.87
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.84	0.77	0.90	0.88	0.82	0.95
Darifenacin	0.77	0.64	0.89	1.15	0.97	1.32
Fesoterodine	0.69	0.59	0.79	0.77	0.66	0.89
Oxybutynin	0.70	0.52	0.89	0.84	0.62	1.05
Solifenacin	0.70	0.64	0.77	0.78	0.70	0.85
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Composite cardiovascular endpoint						
Female with current exposure to	.	.	.	.	.	.
Any OAB medication	0.77	0.70	0.83	0.85	0.78	0.92
Darifenacin	0.74	0.60	0.88	0.82	0.67	0.97
Fesoterodine	0.60	0.49	0.70	0.72	0.60	0.85
Oxybutynin	0.55	0.39	0.71	0.79	0.56	1.01
Solifenacin	0.63	0.56	0.70	0.73	0.65	0.81
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.79	0.72	0.86	0.85	0.77	0.92
Darifenacin	0.75	0.60	0.90	0.84	0.68	1.00
Fesoterodine	0.60	0.48	0.71	0.70	0.56	0.83
Oxybutynin	0.65	0.44	0.86	0.75	0.51	0.99
Solifenacin	0.65	0.57	0.73	0.73	0.64	0.81
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.79	0.70	0.88	0.84	0.75	0.93
Darifenacin	0.77	0.59	0.95	0.84	0.64	1.03
Fesoterodine	0.59	0.45	0.72	0.68	0.52	0.83
Oxybutynin	0.70	0.45	0.95	0.79	0.50	1.08
Solifenacin	0.64	0.55	0.73	0.70	0.60	0.81
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Composite cardiovascular endpoint						
Male with current exposure to	.	.	.	.	.	.
Any OAB medication	0.88	0.81	0.96	0.92	0.84	0.99
Darifenacin	0.90	0.74	1.06	0.89	0.73	1.04
Fesoterodine	0.73	0.61	0.85	0.79	0.66	0.92
Oxybutynin	0.46	0.31	0.61	0.70	0.47	0.93
Solifenacin	0.82	0.74	0.91	0.86	0.77	0.95
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.90	0.82	0.98	0.93	0.85	1.01
Darifenacin	0.87	0.71	1.04	0.92	0.75	1.09
Fesoterodine	0.72	0.59	0.85	0.79	0.64	0.93
Oxybutynin	0.72	0.45	0.98	0.74	0.47	1.02
Solifenacin	0.84	0.74	0.93	0.88	0.78	0.98
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.90	0.81	0.98	0.92	0.83	1.01
Darifenacin	0.79	0.62	0.97	1.17	0.93	1.41
Fesoterodine	0.80	0.65	0.95	0.86	0.69	1.02
Oxybutynin	0.76	0.48	1.05	0.88	0.55	1.20
Solifenacin	0.81	0.70	0.91	0.84	0.73	0.95
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
All-cause mortality						
Overall with current exposure to	.	.	.	.	.	.
Any OAB medication	0.74	0.69	0.79	0.84	0.78	0.90
Darifenacin	0.73	0.62	0.85	0.85	0.71	0.98
Fesoterodine	0.43	0.36	0.51	0.58	0.48	0.68
Oxybutynin	0.44	0.32	0.56	0.73	0.53	0.93
Solifenacin	0.59	0.53	0.64	0.73	0.66	0.80
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.77	0.72	0.83	0.86	0.79	0.92
Darifenacin	0.74	0.62	0.86	0.89	0.74	1.03
Fesoterodine	0.46	0.38	0.54	0.59	0.49	0.70
Oxybutynin	0.61	0.43	0.80	0.75	0.53	0.97
Solifenacin	0.63	0.57	0.70	0.76	0.68	0.84
Tolterodine (REF)	1.00	.	.	1.00	.	.
Overall with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.78	0.71	0.85	0.85	0.77	0.93
Darifenacin	0.68	0.53	0.83	1.50	1.20	1.81
Fesoterodine	0.52	0.41	0.64	0.66	0.52	0.80
Oxybutynin	0.57	0.36	0.78	0.76	0.48	1.03
Solifenacin	0.63	0.55	0.71	0.75	0.66	0.85
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
All-cause mortality						
Female with current exposure to	.	.	.	.	.	.
Any OAB medication	0.67	0.60	0.74	0.78	0.70	0.86
Darifenacin	0.58	0.44	0.73	0.73	0.55	0.91
Fesoterodine	0.33	0.25	0.42	0.46	0.34	0.58
Oxybutynin	0.50	0.32	0.68	0.83	0.54	1.12
Solifenacin	0.51	0.44	0.58	0.64	0.55	0.73
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.72	0.64	0.80	0.81	0.72	0.89
Darifenacin	0.61	0.46	0.76	0.78	0.58	0.97
Fesoterodine	0.33	0.24	0.43	0.45	0.32	0.58
Oxybutynin	0.72	0.46	0.98	0.90	0.57	1.22
Solifenacin	0.57	0.49	0.65	0.69	0.59	0.79
Tolterodine (REF)	1.00	.	.	1.00	.	.
Female with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.71	0.61	0.81	0.80	0.69	0.90
Darifenacin	0.62	0.42	0.82	0.77	0.52	1.01
Fesoterodine	0.36	0.23	0.49	0.50	0.32	0.68
Oxybutynin	0.49	0.23	0.75	0.66	0.31	1.01
Solifenacin	0.55	0.44	0.65	0.67	0.55	0.79
Tolterodine (REF)	1.00	.	.	1.00	.	.

Table CV5a. Crude and Standardized Incidence Rate Ratios for Acute Myocardial Infarction, With Tolterodine as Reference, Current Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
All-cause mortality						
Male with current exposure to	.	.	.	.	.	.
Any OAB medication	0.84	0.76	0.93	0.90	0.81	0.99
Darifenacin	0.95	0.75	1.16	0.97	0.77	1.18
Fesoterodine	0.58	0.45	0.71	0.71	0.55	0.86
Oxybutynin	0.38	0.21	0.55	0.62	0.35	0.90
Solifenacin	0.75	0.65	0.85	0.83	0.72	0.94
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male aged over 65 with current exposure to	.	.	.	.	.	.
Any OAB medication	0.86	0.77	0.95	0.91	0.82	1.01
Darifenacin	0.91	0.71	1.11	1.00	0.78	1.22
Fesoterodine	0.61	0.47	0.75	0.74	0.57	0.91
Oxybutynin	0.53	0.26	0.80	0.60	0.29	0.90
Solifenacin	0.76	0.65	0.86	0.84	0.72	0.96
Tolterodine (REF)	1.00	.	.	1.00	.	.
Male with high CV risk with current exposure to	.	.	.	.	.	.
Any OAB medication	0.86	0.75	0.96	0.90	0.79	1.01
Darifenacin	0.75	0.53	0.97	1.49	1.09	1.89
Fesoterodine	0.69	0.51	0.87	0.81	0.60	1.03
Oxybutynin	0.71	0.36	1.07	0.85	0.42	1.27
Solifenacin	0.75	0.63	0.88	0.83	0.69	0.97
Tolterodine (REF)	1.00	.	.	1.00	.	.

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

a. Standardized to sex and age distribution of the study population person-years.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Acute myocardial infarction						
Overall with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.81	0.68	0.93	0.90	0.76	1.04
Darifenacin	0.75	0.49	1.01	0.84	0.54	1.13
Fesoterodine	0.40	0.25	0.56	0.51	0.32	0.71
Oxybutynin	0.76	0.42	1.10	1.09	0.60	1.57
Solifenacin	0.76	0.61	0.90	0.91	0.73	1.09
Tolterodine	1.00	.	.	1.00	.	.
Overall aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.86	0.72	1.00	0.93	0.78	1.08
Darifenacin	0.84	0.54	1.14	0.93	0.60	1.26
Fesoterodine	0.46	0.27	0.64	0.56	0.33	0.78
Oxybutynin	0.93	0.47	1.38	1.09	0.55	1.62
Solifenacin	0.83	0.66	1.00	0.95	0.75	1.15
Tolterodine	1.00	.	.	1.00	.	.
Overall with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.84	0.68	1.00	0.90	0.73	1.07
Darifenacin	0.85	0.50	1.20	1.06	0.63	1.48
Fesoterodine	0.31	0.14	0.49	0.38	0.17	0.58
Oxybutynin	1.12	0.55	1.70	1.21	0.59	1.83
Solifenacin	0.80	0.61	1.00	0.90	0.68	1.12
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Acute myocardial infarction						
Female with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.80	0.62	0.99	0.90	0.70	1.11
Darifenacin	0.54	0.23	0.85	0.60	0.26	0.95
Fesoterodine	0.60	0.32	0.88	0.80	0.43	1.18
Oxybutynin	1.13	0.54	1.73	1.56	0.74	2.38
Solifenacin	0.70	0.49	0.90	0.83	0.59	1.08
Tolterodine	1.00	.	.	1.00	.	.
Female aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.86	0.65	1.07	0.94	0.71	1.17
Darifenacin	0.63	0.26	0.99	0.69	0.29	1.09
Fesoterodine	0.70	0.36	1.04	0.88	0.46	1.31
Oxybutynin	1.22	0.49	1.95	1.42	0.57	2.28
Solifenacin	0.79	0.54	1.03	0.88	0.61	1.16
Tolterodine	1.00	.	.	1.00	.	.
Female with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.82	0.58	1.05	0.88	0.63	1.14
Darifenacin	0.62	0.19	1.05	0.67	0.20	1.13
Fesoterodine	0.39	0.10	0.67	0.48	0.13	0.84
Oxybutynin	1.78	0.72	2.84	2.02	0.82	3.22
Solifenacin	0.71	0.45	0.98	0.80	0.50	1.11
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Acute myocardial infarction						
Male with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.87	0.69	1.04	0.90	0.71	1.09
Darifenacin	1.06	0.59	1.53	1.05	0.59	1.51
Fesoterodine	0.23	0.07	0.40	0.26	0.07	0.44
Oxybutynin	0.42	0.05	0.80	0.67	0.07	1.27
Solifenacin	0.92	0.67	1.16	0.98	0.71	1.24
Tolterodine	1.00	.	.	1.00	.	.
Male aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.90	0.70	1.10	0.92	0.72	1.13
Darifenacin	1.12	0.61	1.63	1.15	0.63	1.68
Fesoterodine	0.24	0.06	0.43	0.26	0.06	0.46
Oxybutynin	0.69	0.07	1.31	0.78	0.08	1.48
Solifenacin	0.97	0.69	1.24	1.01	0.72	1.30
Tolterodine	1.00	.	.	1.00	.	.
Male with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.89	0.67	1.12	0.91	0.69	1.14
Darifenacin	1.12	0.54	1.69	1.14	0.56	1.71
Fesoterodine	0.26	0.05	0.48	0.29	0.05	0.52
Oxybutynin	0.48	0.00	1.03	0.55	0.00	1.19
Solifenacin	0.95	0.64	1.25	0.98	0.67	1.30
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Stroke						
Overall with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.84	0.72	0.96	0.92	0.79	1.05
Darifenacin	1.14	0.84	1.44	1.25	0.91	1.58
Fesoterodine	0.76	0.56	0.96	0.92	0.68	1.17
Oxybutynin	0.45	0.22	0.68	0.70	0.34	1.06
Solifenacin	0.66	0.54	0.79	0.76	0.62	0.90
Tolterodine	1.00	.	.	1.00	.	.
Overall aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.89	0.76	1.03	0.95	0.81	1.09
Darifenacin	1.20	0.86	1.55	1.31	0.94	1.68
Fesoterodine	0.80	0.56	1.03	0.94	0.67	1.22
Oxybutynin	0.60	0.27	0.94	0.74	0.33	1.15
Solifenacin	0.74	0.59	0.89	0.82	0.65	0.98
Tolterodine	1.00	.	.	1.00	.	.
Overall with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.83	0.69	0.98	0.87	0.72	1.02
Darifenacin	1.15	0.77	1.54	1.18	0.79	1.57
Fesoterodine	0.85	0.57	1.12	0.98	0.66	1.29
Oxybutynin	0.41	0.10	0.72	0.55	0.14	0.96
Solifenacin	0.58	0.43	0.72	0.62	0.47	0.78
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Stroke						
Female with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.85	0.68	1.02	0.93	0.74	1.12
Darifenacin	0.99	0.60	1.37	1.08	0.65	1.50
Fesoterodine	0.74	0.46	1.02	0.91	0.56	1.25
Oxybutynin	0.39	0.09	0.69	0.52	0.12	0.91
Solifenacin	0.75	0.56	0.94	0.86	0.64	1.07
Tolterodine	1.00	.	.	1.00	.	.
Female aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.89	0.70	1.08	0.95	0.74	1.15
Darifenacin	1.09	0.64	1.54	1.18	0.70	1.67
Fesoterodine	0.77	0.45	1.09	0.91	0.53	1.29
Oxybutynin	0.49	0.09	0.89	0.54	0.10	0.98
Solifenacin	0.80	0.58	1.02	0.87	0.63	1.11
Tolterodine	1.00	.	.	1.00	.	.
Female with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.80	0.60	1.01	0.85	0.63	1.07
Darifenacin	0.89	0.43	1.36	0.93	0.45	1.41
Fesoterodine	0.93	0.52	1.34	1.09	0.60	1.57
Oxybutynin	0.31	0.00	0.67	0.32	0.00	0.69
Solifenacin	0.59	0.39	0.80	0.64	0.42	0.87
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Stroke						
Male with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.88	0.71	1.05	0.91	0.74	1.08
Darifenacin	1.44	0.92	1.96	1.42	0.90	1.93
Fesoterodine	0.83	0.52	1.14	0.94	0.58	1.29
Oxybutynin	0.59	0.17	1.00	0.88	0.25	1.50
Solifenacin	0.63	0.45	0.81	0.66	0.48	0.85
Tolterodine	1.00	.	.	1.00	.	.
Male aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.93	0.74	1.13	0.95	0.75	1.15
Darifenacin	1.41	0.86	1.96	1.44	0.87	2.00
Fesoterodine	0.87	0.51	1.22	0.98	0.58	1.38
Oxybutynin	0.87	0.21	1.53	0.94	0.22	1.65
Solifenacin	0.73	0.51	0.95	0.76	0.53	0.98
Tolterodine	1.00	.	.	1.00	.	.
Male with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.88	0.67	1.08	0.88	0.67	1.09
Darifenacin	1.48	0.84	2.13	1.49	0.86	2.12
Fesoterodine	0.79	0.41	1.16	0.87	0.46	1.29
Oxybutynin	0.58	0.00	1.15	0.77	0.00	1.54
Solifenacin	0.59	0.38	0.80	0.60	0.39	0.82
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Cardiovascular mortality						
Overall with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.73	0.59	0.86	0.82	0.67	0.97
Darifenacin	0.53	0.27	0.78	0.60	0.31	0.89
Fesoterodine	0.43	0.24	0.62	0.61	0.34	0.88
Oxybutynin	0.36	0.09	0.63	0.70	0.17	1.22
Solifenacin	0.60	0.45	0.76	0.74	0.55	0.92
Tolterodine	1.00	.	.	1.00	.	.
Overall aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.76	0.62	0.90	0.82	0.66	0.98
Darifenacin	0.53	0.26	0.79	0.59	0.29	0.88
Fesoterodine	0.49	0.27	0.70	0.65	0.36	0.93
Oxybutynin	0.43	0.08	0.77	0.68	0.13	1.23
Solifenacin	0.64	0.48	0.81	0.74	0.55	0.93
Tolterodine	1.00	.	.	1.00	.	.
Overall with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.72	0.57	0.88	0.77	0.60	0.94
Darifenacin	0.45	0.17	0.73	0.52	0.20	0.84
Fesoterodine	0.37	0.16	0.58	0.50	0.21	0.79
Oxybutynin	0.53	0.10	0.97	0.76	0.14	1.39
Solifenacin	0.57	0.40	0.74	0.64	0.45	0.84
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Cardiovascular mortality						
Female with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.66	0.49	0.84	0.76	0.57	0.96
Darifenacin	0.39	0.11	0.68	0.45	0.13	0.78
Fesoterodine	0.44	0.18	0.69	0.65	0.27	1.02
Oxybutynin	0.25	0.00	0.54	0.38	0.00	0.82
Solifenacin	0.52	0.34	0.70	0.65	0.43	0.88
Tolterodine	1.00	.	.	1.00	.	.
Female aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.70	0.52	0.89	0.77	0.57	0.97
Darifenacin	0.42	0.12	0.73	0.47	0.13	0.81
Fesoterodine	0.50	0.21	0.79	0.67	0.28	1.06
Oxybutynin	0.22	0.00	0.53	0.30	0.00	0.72
Solifenacin	0.57	0.37	0.77	0.65	0.42	0.89
Tolterodine	1.00	.	.	1.00	.	.
Female with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.66	0.45	0.86	0.71	0.49	0.94
Darifenacin	0.37	0.03	0.70	0.38	0.03	0.73
Fesoterodine	0.31	0.05	0.57	0.43	0.07	0.79
Oxybutynin	0.44	0.00	0.94	0.55	0.00	1.19
Solifenacin	0.50	0.28	0.71	0.57	0.32	0.82
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Cardiovascular mortality						
Male with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.83	0.61	1.06	0.89	0.65	1.12
Darifenacin	0.77	0.26	1.27	0.79	0.27	1.30
Fesoterodine	0.44	0.14	0.74	0.57	0.18	0.96
Oxybutynin	0.57	0.00	1.13	1.09	0.00	2.19
Solifenacin	0.77	0.49	1.05	0.85	0.54	1.15
Tolterodine	1.00	.	.	1.00	.	.
Male aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.85	0.62	1.09	0.89	0.64	1.14
Darifenacin	0.70	0.22	1.19	0.74	0.23	1.25
Fesoterodine	0.48	0.15	0.81	0.61	0.19	1.03
Oxybutynin	0.85	0.00	1.71	1.17	0.00	2.34
Solifenacin	0.79	0.49	1.09	0.85	0.53	1.17
Tolterodine	1.00	.	.	1.00	.	.
Male with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.80	0.56	1.05	0.84	0.58	1.09
Darifenacin	0.57	0.09	1.05	0.92	0.20	1.63
Fesoterodine	0.45	0.10	0.79	0.58	0.13	1.03
Oxybutynin	0.70	0.00	1.51	1.00	0.00	2.15
Solifenacin	0.68	0.39	0.97	0.72	0.41	1.04
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Composite cardiovascular endpoint						
Overall with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.83	0.74	0.92	0.91	0.82	1.01
Darifenacin	0.96	0.75	1.17	1.06	0.83	1.29
Fesoterodine	0.59	0.46	0.72	0.72	0.55	0.88
Oxybutynin	0.61	0.40	0.82	0.90	0.59	1.21
Solifenacin	0.71	0.61	0.81	0.83	0.71	0.95
Tolterodine	1.00	.	.	1.00	.	.
Overall aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.88	0.78	0.99	0.95	0.84	1.05
Darifenacin	1.03	0.79	1.27	1.13	0.87	1.39
Fesoterodine	0.63	0.47	0.78	0.74	0.56	0.92
Oxybutynin	0.78	0.49	1.07	0.92	0.58	1.27
Solifenacin	0.80	0.68	0.92	0.89	0.76	1.03
Tolterodine	1.00	.	.	1.00	.	.
Overall with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.84	0.72	0.95	0.88	0.76	1.00
Darifenacin	1.01	0.73	1.28	1.14	0.84	1.44
Fesoterodine	0.61	0.44	0.79	0.71	0.51	0.91
Oxybutynin	0.79	0.45	1.12	0.90	0.52	1.28
Solifenacin	0.67	0.55	0.79	0.74	0.60	0.87
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Composite cardiovascular endpoint						
Female with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.82	0.69	0.95	0.91	0.77	1.05
Darifenacin	0.74	0.48	0.99	0.81	0.54	1.09
Fesoterodine	0.66	0.46	0.87	0.84	0.58	1.10
Oxybutynin	0.76	0.43	1.08	1.02	0.58	1.46
Solifenacin	0.72	0.58	0.86	0.83	0.67	1.00
Tolterodine	1.00	.	.	1.00	.	.
Female aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.87	0.73	1.02	0.94	0.78	1.10
Darifenacin	0.83	0.53	1.12	0.91	0.59	1.23
Fesoterodine	0.72	0.48	0.95	0.87	0.59	1.16
Oxybutynin	0.87	0.45	1.29	0.99	0.51	1.47
Solifenacin	0.79	0.62	0.96	0.87	0.69	1.05
Tolterodine	1.00	.	.	1.00	.	.
Female with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.80	0.64	0.96	0.85	0.69	1.02
Darifenacin	0.73	0.41	1.05	0.77	0.43	1.11
Fesoterodine	0.69	0.42	0.96	0.83	0.51	1.15
Oxybutynin	1.00	0.48	1.52	1.11	0.53	1.68
Solifenacin	0.62	0.45	0.78	0.68	0.50	0.86
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
Composite cardiovascular endpoint						
Male with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.88	0.76	1.01	0.91	0.78	1.05
Darifenacin	1.32	0.94	1.69	1.30	0.93	1.66
Fesoterodine	0.55	0.36	0.74	0.60	0.40	0.80
Oxybutynin	0.51	0.21	0.80	0.78	0.33	1.23
Solifenacin	0.78	0.63	0.94	0.83	0.66	0.99
Tolterodine	1.00	.	.	1.00	.	.
Male aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.93	0.79	1.08	0.95	0.80	1.10
Darifenacin	1.33	0.92	1.73	1.35	0.94	1.76
Fesoterodine	0.56	0.36	0.77	0.61	0.38	0.84
Oxybutynin	0.78	0.31	1.25	0.86	0.34	1.38
Solifenacin	0.88	0.70	1.07	0.92	0.73	1.11
Tolterodine	1.00	.	.	1.00	.	.
Male with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.89	0.73	1.05	0.90	0.74	1.06
Darifenacin	1.34	0.88	1.80	1.37	0.91	1.82
Fesoterodine	0.55	0.32	0.78	0.61	0.35	0.86
Oxybutynin	0.57	0.14	1.00	0.72	0.18	1.26
Solifenacin	0.76	0.57	0.95	0.78	0.59	0.98
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
All-cause mortality						
Overall with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.74	0.66	0.82	0.83	0.74	0.93
Darifenacin	0.61	0.44	0.77	0.69	0.50	0.88
Fesoterodine	0.42	0.31	0.54	0.55	0.41	0.70
Oxybutynin	0.29	0.15	0.44	0.49	0.25	0.73
Solifenacin	0.63	0.53	0.72	0.76	0.65	0.87
Tolterodine	1.00	.	.	1.00	.	.
Overall aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.78	0.69	0.87	0.85	0.75	0.95
Darifenacin	0.63	0.46	0.81	0.72	0.52	0.92
Fesoterodine	0.46	0.34	0.59	0.58	0.42	0.74
Oxybutynin	0.37	0.17	0.56	0.50	0.23	0.77
Solifenacin	0.68	0.58	0.79	0.79	0.67	0.91
Tolterodine	1.00	.	.	1.00	.	.
Overall with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.77	0.66	0.87	0.83	0.71	0.94
Darifenacin	0.51	0.31	0.70	0.91	0.58	1.25
Fesoterodine	0.49	0.33	0.66	0.60	0.41	0.80
Oxybutynin	0.38	0.14	0.61	0.52	0.19	0.85
Solifenacin	0.66	0.53	0.78	0.74	0.60	0.88
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
All-cause mortality						
Female with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.69	0.58	0.79	0.79	0.67	0.91
Darifenacin	0.46	0.27	0.64	0.53	0.31	0.75
Fesoterodine	0.40	0.25	0.55	0.56	0.35	0.76
Oxybutynin	0.28	0.09	0.46	0.37	0.13	0.62
Solifenacin	0.57	0.45	0.69	0.70	0.56	0.85
Tolterodine	1.00	.	.	1.00	.	.
Female aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.73	0.61	0.85	0.81	0.68	0.94
Darifenacin	0.49	0.28	0.69	0.56	0.32	0.80
Fesoterodine	0.43	0.26	0.60	0.57	0.35	0.79
Oxybutynin	0.30	0.07	0.52	0.33	0.08	0.58
Solifenacin	0.64	0.50	0.77	0.74	0.58	0.89
Tolterodine	1.00	.	.	1.00	.	.
Female with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.70	0.56	0.85	0.77	0.61	0.93
Darifenacin	0.42	0.18	0.65	0.46	0.20	0.71
Fesoterodine	0.39	0.19	0.58	0.50	0.25	0.75
Oxybutynin	0.38	0.07	0.69	0.45	0.08	0.82
Solifenacin	0.58	0.42	0.74	0.67	0.48	0.85
Tolterodine	1.00	.	.	1.00	.	.

Table CV5b. Crude and Standardized Incidence Rate Ratios for Each Outcome, With Tolterodine as Reference, Recent Exposure

	Crude Incidence Rate Ratio	95% CI		Standardized Incidence Rate Ratio[a]	95% CI	
All-cause mortality						
Male with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.83	0.70	0.96	0.88	0.74	1.02
Darifenacin	0.86	0.55	1.18	0.87	0.56	1.19
Fesoterodine	0.48	0.29	0.66	0.55	0.34	0.76
Oxybutynin	0.34	0.08	0.59	0.62	0.15	1.09
Solifenacin	0.76	0.60	0.92	0.83	0.65	1.00
Tolterodine	1.00	.	.	1.00	.	.
Male aged over 65 with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.86	0.72	1.00	0.90	0.75	1.05
Darifenacin	0.86	0.53	1.18	0.90	0.56	1.24
Fesoterodine	0.53	0.32	0.73	0.59	0.36	0.82
Oxybutynin	0.53	0.13	0.92	0.69	0.17	1.22
Solifenacin	0.79	0.61	0.97	0.85	0.66	1.04
Tolterodine	1.00	.	.	1.00	.	.
Male with high CV risk with recent exposure to	.	.	.	.	.	.
Any OAB medication	0.85	0.68	1.01	0.88	0.71	1.05
Darifenacin	0.63	0.31	0.95	1.28	0.68	1.88
Fesoterodine	0.63	0.36	0.90	0.71	0.41	1.02
Oxybutynin	0.38	0.00	0.77	0.59	0.00	1.18
Solifenacin	0.77	0.57	0.98	0.82	0.60	1.04
Tolterodine	1.00	.	.	1.00	.	.

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

a. Standardized to sex and age distribution of the study population person-years.

Table CV6. Adjusted Hazard Ratios for Cardiovascular Endpoints

	Reference =Tolterodine			Reference = Any Other Study OAB			Reference = Any Past Use of Any Study OAB		
	Adjusted Hazard Rate Ratio[a]	(95% CI)		Adjusted Hazard Ratio[a]	95% CI		Adjusted Hazard Ratio[a]	95% CI	
Current use									
Acute myocardial infarction	.	.	.	.	.	.	.	.	.
Any OAB medication	0.75	0.67	0.83	1.00	.	.	0.86	0.80	0.91
Darifenacin	0.84	0.69	1.03	0.98	0.81	1.19	0.84	0.70	1.02
Fesoterodine	0.63	0.52	0.78	0.72	0.59	0.88	0.65	0.54	0.79
Oxybutynin	0.75	0.53	1.06	0.87	0.62	1.23	0.76	0.54	1.08
Solifenacin	0.76	0.67	0.86	0.84	0.74	0.94	0.76	0.69	0.84
Tolterodine	1.00	.	.	1.35	1.21	1.50	1.00	0.92	1.08
Stroke	.	.	.	.	.	.	.	.	.
Any OAB medication	0.83	0.76	0.90	1.00	.	.	1.20	1.14	1.27
Darifenacin	0.84	0.71	0.99	0.92	0.79	1.08	1.11	0.95	1.30
Fesoterodine	0.83	0.72	0.96	0.90	0.79	1.03	1.12	0.98	1.28
Oxybutynin	0.74	0.57	0.97	0.80	0.62	1.05	1.02	0.79	1.33
Solifenacin	0.81	0.73	0.89	0.85	0.78	0.93	1.07	0.99	1.17
Tolterodine	1.00	.	.	1.22	1.12	1.32	1.32	1.23	1.41
Cardiovascular mortality	.	.	.	.	.	.	.	.	.
Any OAB medication	0.68	0.59	0.78	1.00	.	.	0.73	0.67	0.79
Darifenacin	0.81	0.62	1.06	0.99	0.76	1.28	0.72	0.56	0.93
Fesoterodine	0.61	0.46	0.81	0.73	0.55	0.97	0.56	0.43	0.73
Oxybutynin	0.63	0.37	1.07	0.77	0.45	1.31	0.57	0.33	0.96
Solifenacin	0.69	0.58	0.81	0.78	0.66	0.91	0.62	0.54	0.71
Tolterodine	1.00	.	.	1.48	1.29	1.71	0.88	0.79	0.98
Composite cardiovascular endpoint	.	.	.	.	.	.	.	.	.
Any OAB medication	0.81	0.75	0.86	1.00	.	.	1.06	1.01	1.10
Darifenacin	0.85	0.75	0.97	0.95	0.84	1.08	1.00	0.89	1.13
Fesoterodine	0.77	0.68	0.86	0.84	0.75	0.94	0.92	0.83	1.03
Oxybutynin	0.76	0.61	0.94	0.84	0.68	1.03	0.93	0.75	1.14
Solifenacin	0.80	0.74	0.86	0.85	0.79	0.91	0.94	0.89	1.01
Tolterodine	1.00	.	.	1.24	1.16	1.33	1.17	1.11	1.24

Table CV6. Adjusted Hazard Ratios for Cardiovascular Endpoints

	Reference =Tolterodine			Reference = Any Other Study OAB			Reference = Any Past Use of Any Study OAB		
	Adjusted Hazard Rate Ratio[a]	(95% CI)		Adjusted Hazard Ratio[a]	95% CI		Adjusted Hazard Ratio[a]	95% CI	
Current use									
All-cause mortality	.	.	.	.	.	.	.	.	.
Any OAB medication	0.73	0.68	0.80	1.00	.	.	0.69	0.66	0.73
Darifenacin	0.85	0.72	1.00	1.00	0.86	1.17	0.69	0.60	0.81
Fesoterodine	0.63	0.53	0.75	0.72	0.61	0.85	0.53	0.45	0.62
Oxybutynin	0.84	0.64	1.11	0.99	0.75	1.30	0.70	0.53	0.91
Solifenacin	0.75	0.68	0.83	0.82	0.75	0.90	0.61	0.56	0.66
Tolterodine	1.00	.	.	1.37	1.26	1.49	0.81	0.76	0.87
Recent use									
Acute myocardial infarction									
Any OAB medication	0.82	0.69	0.98	1.00	.	.	1.13	1.00	1.26
Darifenacin	0.83	0.58	1.17	0.92	0.66	1.30	1.04	0.74	1.46
Fesoterodine	0.50	0.34	0.74	0.53	0.36	0.77	0.63	0.44	0.92
Oxybutynin	1.19	0.76	1.86	1.34	0.87	2.08	1.49	0.96	2.30
Solifenacin	0.90	0.74	1.10	1.00	0.83	1.21	1.13	0.95	1.34
Tolterodine	1.00	.	.	1.21	1.02	1.45	1.26	1.08	1.46
Stroke	.	.	.	.	.	.	.	.	.
Any OAB medication	0.85	0.72	0.99	1.00	.	.	1.15	1.04	1.28
Darifenacin	1.22	0.93	1.59	1.37	1.06	1.77	1.52	1.18	1.95
Fesoterodine	0.89	0.68	1.16	0.97	0.75	1.25	1.12	0.87	1.44
Oxybutynin	0.64	0.38	1.08	0.69	0.41	1.16	0.82	0.49	1.36
Solifenacin	0.76	0.63	0.92	0.77	0.64	0.91	0.95	0.80	1.12
Tolterodine	1.00	.	.	1.18	1.01	1.39	1.25	1.09	1.42
Cardiovascular mortality	.	.	.	.	.	.	.	.	.
Any OAB medication	0.68	0.54	0.85	1.00	.	.	1.17	1.01	1.35
Darifenacin	0.60	0.37	0.98	0.72	0.45	1.16	0.86	0.54	1.38
Fesoterodine	0.59	0.38	0.92	0.69	0.45	1.06	0.85	0.55	1.30
Oxybutynin	0.61	0.28	1.29	0.73	0.34	1.54	0.87	0.41	1.84
Solifenacin	0.74	0.58	0.95	0.86	0.67	1.09	1.07	0.85	1.34
Tolterodine	1.00	.	.	1.49	1.19	1.86	1.42	1.19	1.69

Table CV6. Adjusted Hazard Ratios for Cardiovascular Endpoints

	Reference =Tolterodine			Reference = Any Other Study OAB			Reference = Any Past Use of Any Study OAB		
	Adjusted Hazard Rate Ratio[a]	(95% CI)		Adjusted Hazard Ratio[a]	95% CI		Adjusted Hazard Ratio[a]	95% CI	
Recent use									
Composite cardiovascular	.	.	.	.	.	.	.	.	.
Any OAB medication	0.84	0.75	0.95	1.00	.	.	1.10	1.02	1.19
Darifenacin	1.04	0.83	1.29	1.15	0.93	1.42	1.25	1.01	1.54
Fesoterodine	0.70	0.56	0.88	0.75	0.60	0.93	0.86	0.69	1.06
Oxybutynin	0.91	0.65	1.29	0.99	0.71	1.39	1.11	0.79	1.55
Solifenacin	0.83	0.72	0.95	0.86	0.76	0.99	1.00	0.88	1.12
Tolterodine	1.00	.	.	1.19	1.05	1.35	1.20	1.09	1.33
All-cause mortality	.	.	.	.	.	.	.	.	.
Any OAB medication	0.69	0.61	0.79	1.00	.	.	1.17	1.08	1.28
Darifenacin	0.68	0.52	0.90	0.81	0.62	1.06	0.98	0.75	1.27
Fesoterodine	0.56	0.43	0.73	0.65	0.50	0.85	0.81	0.63	1.05
Oxybutynin	0.49	0.30	0.80	0.58	0.35	0.95	0.69	0.42	1.13
Solifenacin	0.76	0.65	0.88	0.87	0.76	1.01	1.09	0.95	1.24
Tolterodine	1.00	.	.	1.45	1.27	1.65	1.41	1.27	1.57

CI = confidence interval; OAB = overactive bladder.

Table notes continue on next page.

Table CV6. Adjusted Hazard Ratios for Cardiovascular Endpoints

a. The hazard ratio for each outcome was adjusted for the variables marked in the following table with an X.

	Outcome				
Adjustment Variable	**Acute Myocardial Infarction**	**Stroke**	**Cardio-vascular Mortality**	**Composite Endpoint**	**All-Cause Mortality**
Age	X	X	X	X	X
Acute myocardial infarction	X		X		
Antiplatelets	X	X	X	X	X
Cerobrovascular disease	X	X	X	X	X
Dyslipidemia		X			
Coronary heart disease	X		X	X	X
Heart failure	X		X	X	X
Hormone replacement therapy	X	X		X	X
Education					X
Digoxin			X		
Hypertension	X	X	X	X	X
Low-dose aspirin	X	X	X	X	X
Nitrates	X		X		X
Number of OAB drugs during follow-up	X	X	X	X	X
Number of hospitalisations	X	X	X	X	X
Number of OAB drugs before cohort entry			X		X
Overactive bladder					X
Sex	X	X	X	X	X
Stroke	X	X	X	X	X

Table CV7. Results of Propensity Score–Matched Analysis for Cardiovascular Endpoints and All-Cause Mortality, With Tolterodine as Reference, Current Exposure and Recent Exposure

Use	Endpoint	Exposure	Hazard Ratio[a]	95% CI	
Current use					
	Acute myocardial infarction		.	.	.
		Any OAB medication (besides tolterodine)	0.80	0.71	0.90
		Darifenacin	0.96	0.77	1.19
		Fesoterodine	0.72	0.56	0.92
		Oxybutynin	0.79	0.53	1.19
		Solifenacin	0.84	0.73	0.96
	Stroke		.	.	.
		Any OAB medication (besides tolterodine)	0.87	0.80	0.96
		Darifenacin	0.94	0.79	1.12
		Fesoterodine	0.87	0.73	1.03
		Oxybutynin	0.87	0.65	1.16
		Solifenacin	0.88	0.79	0.98
	Cardiovascular mortality		.	.	.
		Any OAB medication (besides tolterodine)	0.83	0.70	0.98
		Darifenacin	0.96	0.71	1.28
		Fesoterodine	0.69	0.48	0.99
		Oxybutynin	0.79	0.43	1.45
		Solifenacin	0.84	0.69	1.01
	Composite cardiovascular endpoint		.	.	.
		Any OAB medication (besides tolterodine)	0.86	0.79	0.92
		Darifenacin	0.96	0.83	1.10
		Fesoterodine	0.82	0.71	0.94
		Oxybutynin	0.85	0.67	1.08
		Solifenacin	0.87	0.80	0.95
	All-cause mortality		.	.	.
		Any OAB medication (besides tolterodine)	0.83	0.75	0.92
		Darifenacin	1.04	0.88	1.23
		Fesoterodine	0.73	0.60	0.90
		Oxybutynin	0.90	0.64	1.25
		Solifenacin	0.85	0.76	0.95

Table CV7. Results of Propensity Score–Matched Analysis for Cardiovascular Endpoints and All-Cause Mortality, With Tolterodine as Reference, Current Exposure and Recent Exposure

Use	Endpoint	Exposure	Hazard Ratio[a]	95% CI	
Recent use					
	Acute myocardial infarction				
		Any OAB medication (besides tolterodine)	0.92	0.75	1.13
		Darifenacin	0.83	0.56	1.25
		Fesoterodine	0.54	0.33	0.87
		Oxybutynin	1.64	0.98	2.74
		Solifenacin	1.02	0.81	1.28
	Stroke		.	.	.
		Any OAB medication (besides tolterodine)	1.00	0.83	1.20
		Darifenacin	1.45	1.08	1.94
		Fesoterodine	1.30	0.93	1.80
		Oxybutynin	0.75	0.40	1.40
		Solifenacin	0.88	0.71	1.09
	Cardiovascular mortality		.	.	.
		Any OAB medication (besides tolterodine)	0.81	0.62	1.06
		Darifenacin	0.75	0.45	1.26
		Fesoterodine	0.64	0.36	1.16
		Oxybutynin	0.79	0.34	1.87
		Solifenacin	0.94	0.71	1.26
	Composite cardiovascular endpoint		.	.	.
		Any OAB medication (besides tolterodine)	0.96	0.83	1.10
		Darifenacin	1.19	0.93	1.51
		Fesoterodine	0.93	0.70	1.22
		Oxybutynin	1.16	0.78	1.72
		Solifenacin	0.94	0.80	1.11
	All-cause mortality		.	.	.
		Any OAB medication (besides tolterodine)	0.82	0.70	0.95
		Darifenacin	0.82	0.61	1.10
		Fesoterodine	0.70	0.52	0.95
		Oxybutynin	0.72	0.42	1.24
		Solifenacin	0.92	0.78	1.09

CI = confidence interval; OAB = overactive bladder.

Table notes continue on next page.

Table CV7. Results of Propensity Score–Matched Analysis for Cardiovascular Endpoints and All-Cause Mortality, With Tolterodine as Reference, Current Exposure and Recent Exposure

a. The hazard ratio for each outcome was adjusted for the variables marked in the following table with an X.

	Outcome				
Adjustment Variable	**Acute Myocardial Infarction**	**Stroke**	**Cardio-vascular Mortality**	**Composite Endpoint**	**All-Cause Mortality**
Age	X	X	X	X	X
Acute myocardial	X		X		
Antiplatelets	X	X	X	X	X
Cerobrovascular disease	X	X	X	X	X
Dyslipidemia		X			
Coronary heart disease	X		X	X	X
Heart failure	X		X	X	X
Hormone replacement therapy	X	X		X	X
Education					X
Digoxin			X		
Hypertension	X	X	X	X	X
Low-dose aspirin	X	X	X	X	X
Nitrates	X		X		X
Number of OAB drugs during follow-up	X	X	X	X	X
Number of hospitalisations	X	X	X	X	X
Number of OAB drugs before cohort entry			X		X
Overactive bladder					X
Sex	X	X	X	X	X
Stroke	X	X	X	X	X

Table 1 (InVes). Characteristics of Patients Ever Exposed to Intravesical Oxybutynin (N = 230) at FIRST Study Cohort Entry

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Age at cohort entry (years)							
	Mean (SD)	***45***	***(14.3)***	***73***	***(5.4)***	***56***	***(18.2)***
	18-24	17	12.1	0	0.0	17	7.4
	25-34	22	15.6	0	0.0	22	9.6
	35-44	26	18.4	0	0.0	26	11.3
	45-54	31	22.0	0	0.0	31	13.5
	55-64	45	31.9	0	0.0	45	19.6
	65-74	0	0.0	56	62.9	56	24.3
	75-84	0	0.0	30	33.7	30	13.0
	85+	0	0.0	3	3.4	3	1.3
Sex							
	Female	81	57.4	47	52.8	128	55.7
	Male	60	42.6	42	47.2	102	44.3
Calendar year at cohort entry							
	2006	29	20.6	14	15.7	43	18.7
	2007	38	27.0	27	30.3	65	28.3
	2008	20	14.2	19	21.3	39	17.0
	2009	22	15.6	10	11.2	32	13.9
	2010	14	9.9	6	6.7	20	8.7
	2011	11	7.8	9	10.1	20	8.7
	2012	7	5.0	4	4.5	11	4.8
Duration of enrollment prior to cohort entry							
	Mean (SD)	***1,131***	***(638.2)***	***1,133***	***(628.5)***	***1,132***	***(633.1)***
	1 to < 2 years	53	37.6	33	37.1	86	37.4
	2 to < 4 years	49	34.8	33	37.1	82	35.7
	4 to < 8 years	39	27.7	23	25.8	62	27.0
Duration of follow-up							
	Mean (SD)	***1,587***	***(636.7)***	***1,539***	***(630.4)***	***1,569***	***(633.3)***
	< 1 year	8	5.7	4	4.5	12	5.2
	1 to < 2 years	10	7.1	10	11.2	20	8.7
	2 to < 4 years	39	27.7	20	22.5	59	25.7
	4 to < 8 years	84	59.6	55	61.8	139	60.4

Table 1 (InVes). Characteristics of Patients Ever Exposed to Intravesical Oxybutynin (N = 230) at FIRST Study Cohort Entry

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Menopause	Yes	34	24.1	47	52.8	81	35.2
Number of study drugs during follow-up							
	1	27	19.1	11	12.4	38	16.5
	2	50	35.5	30	33.7	80	34.8
	3	49	34.8	28	31.5	77	33.5
	4	13	9.2	14	15.7	27	11.7
	5	2	1.4	6	6.7	8	3.5
Number of different study drugs to which patient was exposed in the 12 months before this study						230	100.0
	1	90	63.8	47	52.8	137	59.6
	2	41	29.1	29	32.6	70	30.4
	3	9	6.4	10	11.2	19	8.3
	4	1	0.7	2	2.2	3	1.3
	5	0	0.0	1	1.1	1	0.4
Education (years)						230	100.0
	Missing	22	15.6	11	12.4	33	14.3
	≤ 9	31	22.0	23	25.8	54	23.5
	< 9 to ≤ 12	55	39.0	33	37.1	88	38.3
	> 12	33	23.4	22	24.7	55	23.9
Income (in quartiles)							
	Missing	5	3.5	1	1.1	6	2.6
	Low	24	17.0	13	14.6	37	16.1
	Midlow	26	18.4	16	18.0	42	18.3
	Midhigh	28	19.9	22	24.7	50	21.7
	High	58	41.1	37	41.6	95	41.3
Hospitalizations							
	None	52	36.9	35	39.3	87	37.8
	< 5	69	48.9	44	49.4	113	49.1
	5-10	13	9.2	9	10.1	22	9.6
	11-25	6	4.3	1	1.1	7	3.0
	26-50	1	0.7	0	0.0	1	0.4
	> 50						

Table 1 (InVes). Characteristics of Patients Ever Exposed to Intravesical Oxybutynin (N = 230) at FIRST Study Cohort Entry

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Outpatient visits		12	8.5	8	9.0	20	8.7
	None	41	29.1	27	30.3	68	29.6
	< 5	49	34.8	26	29.2	75	32.6
	5-10	33	23.4	23	25.8	56	24.3
	11-25	5	3.5	5	5.6	10	4.3
	26-50	1	0.7	0	0.0	1	0.4
	> 50						
Comorbidities		3	2.1	0	0.0	3	1.3
Mild liver disease, Charlson	Yes	141	100.0	89	100.0	230	100.0
AIDS/HIV, Charlson	No	141	100.0	89	100.0	230	100.0
Cancer, Charlson	No	141	100.0	89	100.0	230	100.0
Metastatic carcinoma, Charlson	No	8	5.7	9	10.1	17	7.4
Diabetes without complications, Charlson	Yes	2	1.4	7	7.9	9	3.9
Diabetes with complications, Charlson	Yes	0	0.0	2	2.2	2	0.9
Alcohol abuse and related conditions	Yes	141	100.0	89	100.0	230	100.0
Polycystic ovary syndrome	No	6	4.3	0	0.0	6	2.6
Obesity	Yes	141	100.0	89	100.0	230	100.0
Dementia, Charlson	No	3	2.1	0	0.0	3	1.3
Drug abuse	Yes	1	0.7	2	2.2	3	1.3
Transient ischemic attack	Yes	7	5.0	9	10.1	16	7.0
Cerebrovascular disease, Charlson	Yes	25	17.7	3	3.4	28	12.2
Paraplegia and hemiplegia, Charlson	Yes	1	0.7	7	7.9	8	3.5
Heart failure	Yes	5	3.5	16	18.0	21	9.1
Coronary heart disease	Yes	3	2.1	7	7.9	10	4.3
Acute myocardial infarction	Yes	1	0.7	8	9.0	9	3.9
Congestive heart failure, Charlson	Yes	5	3.5	8	9.0	13	5.7
Stroke	Yes	2	1.4	6	6.7	8	3.5
Peripheral vascular disease, Charlson	Yes	8	5.7	7	7.9	15	6.5
Chronic pulmonary disease, Charlson	Yes	0	0.0	1	1.1	1	0.4
Peptic ulcer disease, Charlson	Yes	141	100.0	89	100.0	230	100.0
Moderate or severe liver disease, Charlson	No	3	2.1	6	6.7	9	3.9
Connective tissue disease-rheumatic disease, Charlson	Yes	2	1.4	4	4.5	6	2.6

Table 1 (InVes). Characteristics of Patients Ever Exposed to Intravesical Oxybutynin (N = 230) at FIRST Study Cohort Entry

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Arthritis	Yes	1	0.7	2	2.2	3	1.3
Gout	Yes	21	14.9	4	4.5	25	10.9
Fractures	Yes	8	5.7	5	5.6	13	5.7
Renal impairment	Yes	1	0.7	3	3.4	4	1.7
Renal disease, Charlson	Yes	1	0.7	0	0.0	1	0.4
Endometrial polyps or other benign growths of the uterus	Yes	33	23.4	34	38.2	67	29.1
Overactive bladder	Yes	141	100.0	89	100.0	230	100.0
Dialysis	No	10	7.1	14	15.7	24	10.4
Diabetes	Yes	9	6.4	10	11.2	19	8.3
Diabetes - diagnosis	Yes	8	5.7	13	14.6	21	9.1
Diabetes - drugs	Yes	14	9.9	31	34.8	45	19.6
Dyslipidemia	Yes	3	2.1	7	7.9	10	4.3
Dyslipidemia - diagnosis	Yes	14	9.9	29	32.6	43	18.7
Dyslipidemia - drugs	Yes	25	17.7	57	64.0	82	35.7
Hypertension	Yes	12	8.5	27	30.3	39	17.0
Hypertension - diagnosis	Yes	23	16.3	54	60.7	77	33.5
Hypertension - drugs	Yes	3	2.1	6	6.7	9	3.9
Peripheral artery disease	Yes	3	2.1	6	6.7	9	3.9
Peripheral artery disease - diagnosis	Yes	141	100.0	89	100.0	230	100.0
Peripheral artery disease - procedures	No	1	0.7	0	0.0	1	0.4
Organ transplantation	Yes	1	0.7	0	0.0	1	0.4
Organ transplantation - diagnosis	Yes	141	100.0	89	100.0	230	100.0
Organ transplantation - procedures	No	2	1.4	2	2.2	4	1.7
Smoking	Yes	141	100.0	89	100.0	230	100.0
Smoking - diagnosis	No	2	1.4	2	2.2	4	1.7
Smoking - drugs	Yes	21	14.9	46	51.7	67	29.1
Antiplatelets (including aspirin in low doses)	Yes	12	8.5	40	44.9	52	22.6
Low-dose aspirin	Yes	1	0.7	6	6.7	7	3.0
Digoxin	Yes	4	2.8	15	16.9	19	8.3
Nitrates	Yes	14	9.9	25	28.1	39	17.0
Statins	Yes	21	14.9	36	40.4	57	24.8
Hormone-replacement therapy	Yes	9	6.4	10	11.2	19	8.3

Table 1 (InVes). Characteristics of Patients Ever Exposed to Intravesical Oxybutynin (N = 230) at FIRST Study Cohort Entry

		Aged < 65 Years		Aged ≥ 65 Years		Total	
Variable	**Category**	**n**	**%**	**n**	**%**	**n**	**%**
Thyroid hormone replacement	Yes	141	100.0	89	100.0	230	100.0
Tamoxifen	No	4	2.8	4	4.5	8	3.5
Immunosuppressive agents	Yes	49	34.8	27	30.3	76	33.0
Non-aspirin NSAIDs	Yes	141	100.0	89	100.0	230	100.0
Mammograms	No	0	0.0	1	1.1	1	0.4
Sigmoidoscopies	Yes	0	0.0	1	1.1	1	0.4

HIV = human immunodeficiency virus; NSAIDs = nonsteroidal anti-inflammatory drugs; OAB = overactive bladder; SD = standard deviation.