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Comparison of cardiovascular events among treatments for overactive bladder: a Danish nationwide cohort study

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Abstract
Purpose The purpose of this study is to explore the cardiovascular safety of antimuscarinic drugs to treat overactive bladder (OAB) in Denmark.
Methods This was a cohort study using data recorded in Danish registries from patients newly exposed to darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium in 2004–2012. We estimated crude and standardized incidence rates (IRs) for acute myocardial infarction (AMI); stroke; cardiovascular mortality; major adverse cardiac events (MACE, a combined endpoint of the previous three outcomes); and all-cause death for the individual and combined drugs. We also estimated crude, standardized, and propensity score-stratified incidence rate ratios (IRRs) comparing individual antimuscarinic drugs to tolterodine as the reference.
Results Among 72,917 new users of OAB drugs (mean age, 66 years; 60% women), the standardized IR (95% confidence interval) per 1000 person-years for current use of any OAB drug was 2.7 (2.5–2.9) for AMI, 1.3 (1.2–1.5) for stroke, 7.8 (7.5–8.1) for MACE, 4.8 (4.5–5.0) for cardiovascular mortality, and 15.2 (14.8–15.6) for all-cause mortality. Propensity score-stratified IRRs for current use (reference, tolterodine) were close to the null for all drugs and endpoints.
Conclusions We did not identify differences in the risk of cardiovascular events or mortality among users of individual antimuscarinic OAB drugs.

Keywords Denmark · Pharmacoepidemiology · Urinary bladder, overactive · Cardiovascular diseases · Muscarinic antagonists

Introduction

Overactive bladder syndrome (OAB) involves voiding urgency with or without urge incontinence, usually experienced with nocturia and increased voiding frequency [1]. The prevalence of urgency urinary incontinence has been reported to be between 2 and 36% in Europe and the USA, in populations of varying sex and age composition [2]. One study administered a single questionnaire to residents of Canada, Germany, Italy, Sweden, and the UK aged 18 years or older and found a prevalence of OAB of 12% [3]. In Denmark, 7% of women aged 40–60 years reported having urge incontinence, and 30%, lower urinary tract symptoms, at least weekly [4]. Another study reported urge incontinence more than once per month in 19% of women in Denmark, with 32% suffering from urinary incontinence of any type [5]. In both studies, urinary tract symptoms were more common with increasing age.

OAB symptoms are attributed to involuntary contractions of the detrusor muscle of the bladder due to a complex pathophysiology involving myogenic, neurogenic, and/or urothelial changes [6]. Until 2012, antimuscarinic drugs were the only class of drugs approved for the pharmacologic treatment for OAB. These drugs block muscarinic receptors at the

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neuromuscular junction and prevent acetylcholine-mediated bladder contraction [7]. Even though antimuscarinic drugs have a safe pharmacological profile, muscarinic receptors are present throughout the body. Blocking these receptors can lead to a variety of adverse effects, including effects on the cardiovascular system [8].

The cardiovascular safety of antimuscarinic drugs used in the treatment of OAB is currently not well characterized. Therefore, we investigated the incidence rates of cardiovascular events and all-cause mortality among new users of previously available antimuscarinic OAB medication and explored any differences in risk among them.

Methods

Using information collected in Danish nationwide health registries, we conducted a cohort study of adults newly exposed to antimuscarinic drugs used to treat OAB. Potential confounders were adjusted by standardization and by stratifying on propensity scores. The study period was January 1, 2004 through December 31, 2012.

Data sources

Routine health care information, vital status, and demographic data on Danish residents collected from five national registries were used. All data sources were linked within Statistics Denmark using the Danish Civil Registry number, a unique identifier assigned to all Danish residents [9].

Dates of birth, death, and emigration were obtained from the Danish Civil Registry [9]. Prescription data were obtained from the Danish National Prescription Registry, which contains data on all drugs dispensed at community pharmacies to Danish residents since 1995 [10]. The data include substance name, brand name and quantity of the drug, and date of dispensing. The Danish Cancer Registry contains records of all new malignant neoplasms in the Danish population since 1943 [11]. The Danish National Registry of Patients contains data on all secondary care contacts in Denmark since 1977; from 1995 onward, outpatient diagnoses have been included systematically [12]. Virtually, all medical care in Denmark is provided by the public health authorities and is included in this registry [12]. The Cause of Death Registry collects information on the underlying and contributing causes of death of all residents of Denmark since 1875 [13]. Data are retrieved from death certificates, which include information from autopsies (when performed).

Study population

We included patients who had at least 12 months of residence in Denmark, followed by an index prescription for darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium, provided that the same agent was not prescribed during the previous 12 months and the patient was aged 18 years or older. Patients were excluded if they had a diagnosis of cancer other than non-melanoma skin cancer before the index prescription.

The cohort entry date was defined by the date of the index prescription. Follow-up started on the cohort entry date and finished at the earliest of end of study period, death, emigration, cancer (except non-melanoma skin cancer), or cardiovascular event. For the composite major adverse cardiac events (MACE), follow-up was terminated at the first occurrence of any of its components, while for the individual endpoints, person-time at risk continued to accumulate until the date of occurrence of the specific endpoint or a censoring event; e.g., the occurrence of acute myocardial infarction (AMI) in an individual did not terminate follow-up with respect to a stroke.

Variables

Exposure to OAB antimuscarinic drugs darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium was ascertained from dispensed prescriptions in the Danish National Prescription Registry [10]. These drugs were available only under prescription during the study period. Cardiovascular effects of OAB drugs were expected to present shortly after first exposure, continue during current exposure, and decline shortly after discontinuation of the medication. Therefore, exposure to OAB drugs was classified as current (during a therapy episode), recent (the 60 days after the estimated end of current exposure, or until a new exposure), or past (from the day after recent exposure until a new exposure or the end of follow-up). We assigned exposure periods to each prescription by the methods described by Pottegård and Hallas [14]. Two prescriptions were considered to belong to the same treatment episode if there was overlap between the exposure periods assigned to each prescription.

Study endpoints were (1) AMI, including out-of-hospital coronary heart disease death; (2) stroke, including out-of-hospital stroke-related death; (3) cardiovascular mortality, including death from coronary heart disease and cerebrovascular disease; (4) MACE (composite of non-fatal AMI, non-fatal stroke, and cardiovascular mortality); and (5) all-cause mortality. Cardiovascular events were identified through hospitalization discharge records or outpatient hospital diagnoses in any position in the National Danish Patient Registry [12].

Patient characteristics, including demographics, lifestyle factors, prescription-related information, and diagnoses were ascertained using one or more of the six registries. Increased cardiovascular risk at baseline was defined by the presence of (1) at least one of the following hospital or hospital outpatient clinic-based diagnoses: diabetes, peripheral arterial disease, coronary heart disease, transient ischemic attack, or atrial fibrillation or flutter, heart failure, prior AMI, or stroke, or (2) at

least two of the following conditions: a proxy for smoking (diagnosis of chronic obstructive pulmonary disease [COPD] or use of smoking cessation drugs), dyslipidemia (diagnosis or treatment), or hypertension (diagnosis or treatment).

Statistical methods

Incidence rates

We estimated crude and age-sex-standardized incidence rates (IRs) for current exposure to any OAB drug and to individual OAB drugs using exact 95% confidence intervals (CI) for the Poisson distribution. The reference for standardization was the age and sex composition of the entire Danish population as of January 1, 2008 (retrieved from Statistics Denmark). All IRs and 95% CIs are reported per 1000 person-years.

Incidence rate ratios

For comparisons among drugs, we estimated crude, age-sex-standardized, and propensity score-stratified incidence rate ratios (IRRs) for current exposure to OAB drugs with reference to current exposure to tolterodine. Tolterodine was selected because it is a commonly used drug for this indication worldwide. Propensity scores for initiating individual OAB drugs versus initiating tolterodine were estimated using multivariable logistic regression models, separately for each of the five individual drugs and for the five drugs combined. In these six models, the dependent variable was drug initiation, and the independent variables were those listed in the footnote to Table 1, selected a priori based on biological and clinical considerations. All variables included were ascertained at cohort entry, and no interaction terms were included.

For each combination of exposure and outcome (e.g., solifenacin versus tolterodine for the risk of AMI), we first estimated a propensity score for drug initiation. Second, we applied the asymmetrical trimming approach [15]: patients with propensity scores below the 2.5 percentile of propensity score for the exposed or above the 97.5 percentile for the unexposed were excluded. Third, a conventional stratified Cox analysis was performed within deciles of propensity score with no added covariates. Lastly, estimates and 95% CIs from the deciles were pooled using conventional Mantel-Haenszel techniques. The reference was current exposure to tolterodine.

The protocol for this study was registered in the EU PAS Register prior to the start of the study (EUPAS8441) [16].

Results

The study population comprised 72,917 patients. The most common index prescription was for solifenacin (42%), followed by tolterodine (33%), trospium (12%), fesoterodine (8%), darifenacin (4%), and oxybutynin (1%) (Table 2). Less than 1% entered the cohort with multiple OAB drugs. Of the entire cohort, 92% had not been exposed to other study drugs prior to cohort entry. The mean duration of completed index episodes (index episodes that ended before the end of follow-up for the patient) ranged from 4.9 months (fesoterodine) to 7.3 months (tolterodine). Solifenacin, tolterodine, and trospium were in use in 2004, the beginning of our study period. We observed the first dispensing of darifenacin and oxybutynin in 2005, and of fesoterodine in 2008.

The study population was 60% female, and the mean age at cohort entry was 66 years; 59% of patients were aged 65 years or older. At cohort entry, 24% of patients had a history of AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, or pulmonary artery disease; 22% had hypertension, 11% had proxies for smoking, 9% had diabetes, 7% had a hospital diagnosis code for obesity, and 6% had codes for alcohol abuse and related conditions.

Of the 72,917 study patients, 1698 (2.3%) had an AMI during follow-up, 637 (0.9%) had a stroke, and 3488 (4.8%) died of cardiovascular causes. A total of 5074 patients (7.0%) experienced an event in the MACE definition, and 11,044 patients (15.1%) died of any cause.

Incidence rates

Standardized IRs for current use of all study drugs combined were highest for all-cause mortality, 15.2 per 1000 person-years (95% CI, 14.8–15.6); followed by MACE, cardiovascular mortality, AMI, and stroke (Table 3). Results for individual drugs are shown in Table 3. No individual drug showed consistently elevated IRs, but point estimates for tolterodine were generally among the two or three highest for all endpoints.

Incidence rate ratios

We estimated IRRs for current use of antimuscarinic OAB drugs relative to current use of tolterodine. Propensity score-stratified IRRs were generally similar to crude and standardized IRRs (Table 1). Point estimates for IRRs for all study endpoints were close to 1.0. No increased risk was seen consistently across endpoints with any of the individual study drugs or for the pooled group of all OAB drugs compared to tolterodine.

Discussion

In this population-based cohort of 72,917 new users of antimuscarinic OAB drugs, 60% were women and mean age at cohort entry was 66 years; 24% had history of AMI, stroke, or other cardiovascular conditions. Solifenacin accounted for 42% of index prescriptions and tolterodine for 33%. We found

Table 1 Crude, standardized, and propensity score-stratified incidence rate ratios for current use of antimuscarinic drugs for overactive bladder, Denmark, 2004–2012

	Crude incidence rate ratio	95% confidence interval	Standardized incidence rate ratio	95% Confidence interval	Propensity score-stratified incidence rate ratio[a]	95% confidence interval
Acute myocardial infarction						
Tolterodine	Reference					
Any OAB drug except tolterodine	0.88	0.83–0.93	0.97	0.91–1.03	0.94	0.80–1.11
Darifenacin	0.80	0.57–1.12	0.83	0.59–1.16	0.89	0.57–1.39
Fesoterodine	0.74	0.56–0.97	0.65	0.49–0.86	0.83	0.56–1.25
Oxybutynin	0.45	0.21–0.97	0.54	0.25–1.16	0.43	0.11–1.73
Solifenacin	0.91	0.84–0.98	1.06	0.98–1.15	0.93	0.78–1.12
Trospium	0.99	0.83–1.18	0.99	0.83–1.18	1.02	0.77–1.35
Stroke						
Tolterodine	Reference					
Any OAB drug except tolterodine	0.97	0.89–1.05	0.80	0.73–0.87	1.06	0.82–1.36
Darifenacin	1.02	0.64–1.62	0.78	0.49–1.24	1.03	0.52–2.03
Fesoterodine	0.87	0.58–1.29	0.62	0.41–0.92	1.17	0.65–2.12
Oxybutynin	0.58	0.21–1.65	0.45	0.16–1.28	0.42	0.06–3.02
Solifenacin	0.97	0.86–1.09	0.89	0.79–1.00	1.05	0.79–1.39
Trospium	0.99	0.74–1.31	0.76	0.57–1.00	0.93	0.60–1.45
Cardiovascular mortality					0.94	0.80–1.11
Tolterodine	Reference					
Any OAB drug except tolterodine	0.87	0.84–0.90	0.75	0.72–0.78	1.04	0.93–1.16
Darifenacin	0.72	0.57–0.92	0.63	0.49–0.80	0.90	0.65–1.23
Fesoterodine	0.67	0.55–0.81	0.62	0.51–0.75	1.10	0.84–1.44
Oxybutynin	0.88	0.61–1.28	1.11	0.76–1.61	1.13	0.63–2.01
Solifenacin	0.90	0.85–0.95	0.78	0.74–0.82	1.08	0.95–1.22
Trospium	0.88	0.77–1.00	0.73	0.64–0.83	0.99	0.82–1.19
MACE						
Tolterodine	Reference					
Any OAB drug except tolterodine	0.88	0.85–0.91	0.82	0.79–0.85	1.00	0.92–1.10
Darifenacin	0.76	0.62–0.92	0.71	0.58–0.86	0.87	0.67–1.13
Fesoterodine	0.73	0.62–0.85	0.65	0.56–0.76	1.03	0.83–1.29
Oxybutynin	0.75	0.53–1.05	0.92	0.66–1.29	0.96	0.57–1.61
Solifenacin	0.90	0.86–0.94	0.87	0.83–0.91	1.02	0.92–1.13
Trospium	0.92	0.83–1.02	0.81	0.73–0.90	0.99	0.85–1.16
All-cause mortality						
Tolterodine	Reference					
Any OAB drug except tolterodine	0.84	0.82–0.86	0.85	0.83–0.87	0.95	0.90–1.02
Darifenacin	0.74	0.64–0.85	0.67	0.58–0.77	0.96	0.81–1.14
Fesoterodine	0.66	0.59–0.74	0.64	0.57–0.72	0.93	0.79–1.09
Oxybutynin	0.79	0.63–1.00	1.98	1.57–2.49	1.22	0.88–1.68
Solifenacin	0.87	0.84–0.90	0.84	0.81–0.87	0.97	0.90–1.04
Trospium	0.88	0.82–0.95	0.89	0.83–0.96	0.97	0.87–1.08

MACE major adverse cardiac events, *OAB* overactive bladder

[a] Variables in propensity scores were dichotomous and measured using patients' entire health care history, except where noted: income (in quartiles), obesity, hypertension, smoking, alcohol abuse and related conditions, all components of the Charlson score except cancers, ischemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate to severe renal disease, diabetes with end-organ damage, moderate to severe liver disease, renal impairment, dialysis, fractures, arthritis (rheumatoid arthritis, ankylosing spondylitis, juvenile arthritis, psoriatic arthritis), organ transplantation, polycystic ovary syndrome, endometrial polyps or other benign growths of the uterine lining, unspecified incontinence, stress incontinence, other specified forms of incontinence, polyuria, other diseases of the bladder, prescriptions before cohort entry for hormone-replacement therapy, tamoxifen, thyroid hormone replacement, nitrates, digoxin, antidiabetic drugs, statins, non-aspirin NSAIDs, lipid-lowering drugs, low-dose aspirin, antiplatelets (including aspirin in low doses), immunosuppressive agents, antigout drugs; number of hospitalizations in 12 months before cohort entry, number of sigmoidoscopies in 12 months before cohort entry (the last two representing health resource utilization)

no evidence of an increased cardiovascular or mortality risk associated with current use of any of the individual OAB drugs.

Published data about the association between OAB and cardiovascular morbidity are scarce. Higher baseline prevalence of cardiovascular comorbidity, including hypertension, diabetes, ischemic heart disease, and cardiac conduction disorders, was found in patients with OAB diagnoses or treated with OAB antimuscarinic drugs (39%) than in age-sex-matched patients without codes for either OAB or OAB antimuscarinic treatment (21%) [17]. In addition, the prevalence of use of non-OAB drugs with antimuscarinic effect was also higher in the OAB group than in the non-OAB group (33 versus 17%). The

Table 2 Patient characteristics at cohort entry by antimuscarinic drug for overactive bladder received at cohort entry, Denmark, 2004–2012

	Darifenacin *n* = 2698 *n* (%)	Fesoterodine *n* = 5749 *n* (%)	Oxybutynin *n* = 740 *n* (%)	Solifenacin *n* = 30,792 *n* (%)	Tolterodine *n* = 23,776 *n* (%)	Trospium *n* = 9105 *n* (%)
Age at cohort entry (years), median (interquartile range)	69 (59–78)	67 (56–76)	66 (55–76)	68 (57–77)	69 (58–78)	68 (56–77)
Female sex	1768 (65.5%)	3407 (59.3%)	597 (80.7%)	18,353 (59.6%)	13,812 (58.1%)	5466 (60.0%)
Smoking (proxy)[a]	246 (9.1%)	666 (11.6%)	72 (9.7%)	3437 (11.2%)	2347 (9.9%)	937 (10.3%)
Obesity indicator	176 (6.5%)	548 (9.5%)	64 (8.6%)	2215 (7.2%)	1327 (5.6%)	624 (6.9%)
Hypertension indicator[b]	561 (20.8%)	1416 (24.6%)	175 (23.6%)	6974 (22.6%)	5012 (21.1%)	1903 (20.9%)
Alcohol abuse and related conditions	137 (5.1%)	363 (6.3%)	38 (5.1%)	1822 (5.9%)	1407 (5.9%)	561 (6.2%)
Diabetes	207 (7.7%)	500 (8.7%)	55 (7.4%)	2413 (7.8%)	1881 (7.9%)	713 (7.8%)
Ischemic heart disease	152 (5.6%)	315 (5.5%)	33 (4.5%)	1890 (6.1%)	1464 (6.2%)	486 (5.3%)
Congestive heart failure	133 (4.9%)	272 (4.7%)	29 (3.9%)	1508 (4.9%)	1344 (5.7%)	425 (4.7%)
Peripheral vascular disease	148 (5.5%)	362 (6.3%)	54 (7.3%)	1941 (6.3%)	1488 (6.3%)	498 (5.5%)
Cerebrovascular disease	353 (13.1%)	719 (12.5%)	121 (16.4%)	4179 (13.6%)	3806 (16.0%)	1268 (13.9%)
History of CV disease[c]	608 (22.5%)	1323 (23.0%)	190 (25.7%)	7297 (23.7%)	6280 (26.4%)	2091 (23.0%)
Dementia	61 (2.3%)	105 (1.8%)	25 (3.4%)	649 (2.1%)	613 (2.6%)	214 (2.4%)
Chronic pulmonary disease	268 (9.9%)	628 (10.9%)	89 (12.0%)	3274 (10.6%)	2364 (9.9%)	904 (9.9%)
Moderate to severe renal disease	51 (1.9%)	168 (2.9%)	17 (2.3%)	711 (2.3%)	551 (2.3%)	188 (2.1%)
Arthritis (rheumatoid arthritis, ankylosing spondylitis, juvenile arthritis, psoriatic arthritis)	52 (1.9%)	104 (1.8%)	11 (1.5%)	504 (1.6%)	376 (1.6%)	140 (1.5%)
Hospitalizations before cohort entry, median (interquartile range)	14 (8–24)	18 (10–30)	19 (11–30)	16 (9–26)	14 (8–24)	15 (8–26)
Prescriptions before cohort entry						
Hormone-replacement therapy	1237 (45.8%)	2286 (39.8%)	449 (60.7%)	11,931 (38.7%)	8370 (35.2%)	3522 (38.7%)
Nitrates, digoxin, antidiabetic drugs, statins	1079 (40.0%)	2476 (43.1%)	285 (38.5%)	12,647 (41.1%)	9046 (38.0%)	3459 (38.0%)
Non-aspirin NSAIDs	2259 (83.7%)	4945 (86.0%)	619 (83.6%)	26,175 (85.0%)	19,537 (82.2%)	7646 (84.0%)
Lipid-lowering drug	814 (30.2%)	1996 (34.7%)	203 (27.4%)	9829 (31.9%)	6223 (26.2%)	2532 (27.8%)
Low-dose aspirin	994 (36.8%)	2053 (35.7%)	287 (38.8%)	11,280 (36.6%)	8829 (37.1%)	3209 (35.2%)
Antiplatelets (including aspirin in low doses)	1014 (37.6%)	2092 (36.4%)	294 (39.7%)	11,498 (37.3%)	8968 (37.7%)	3264 (35.8%)
Antigout drugs	111 (4.1%)	276 (4.8%)	29 (3.9%)	1413 (4.6%)	1066 (4.5%)	385 (4.2%)

57 patients who entered the cohort on multiple study drugs started simultaneously are not shown in this table

AMI acute myocardial infarction, *CV* cardiovascular, *NSAIDs* non-steroidal anti-inflammatory drugs, *OAB* overactive bladder

[a] Smoking proxy: diagnosis of chronic obstructive pulmonary disease or use of smoking cessation drugs before cohort entry

[b] Diagnosis or treatment

[c] Comprising AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, pulmonary artery disease

prevalence of cardiovascular comorbidity was similar in patients with OAB treated with OAB antimuscarinic drugs (39%) and age- and sex-matched patients with OAB but no such treatment (38%). A related study found that patients with OAB treated with OAB antimuscarinic drugs had baseline heart rate distributions similar to those with no such treatment [18], but treated patients with OAB also had higher prevalence of cardiovascular comorbidity (59%) than untreated OAB patients (54%).

The main limitation of this study was the lack of primary health care data, including patient lifestyle factors and covariates. The strategy implemented to overcome the lack of data that may not have been well recorded in hospital data (e.g., smoking, obesity) was to search for these diagnoses in secondary hospital discharge records. Prescriptions for drugs to help with smoking cessation and diagnosis codes for COPD were included as proxies for smoking. Although this approach captured the most serious cases and those that explicitly required health care, it would have missed mild and moderate cases. Another limitation pertains to the results for oxybutynin and darifenacin, which are imprecise, and possibly uninformative, due to low prevalence of use (1 and 4%, respectively). Outcomes in this study share risk factors and may not be clinically independent; however, individual outcomes are analyzed statistically as if they were independent. Finally, we have not in our analysis accounted for the entire anticholinergic burden from other drugs, e.g., COPD medication, antiparkinsonian drugs, antidepressants, antihistamines, and others. We do, however, not expect it to be distributed differently among the included OAB drugs.

Table 3 Crude and age-sex-standardized incidence rates for current use of antimuscarinic drugs for overactive bladder, Denmark, 2004–2012

	Events	Individuals contributing person-time	Person-time (years)	Crude incidence rate per 1000 person-years	95% confidence interval	Standardized incidence rate per 1000 person-years[a]	95% confidence interval
Acute myocardial infarction							
Any OAB drug	742	72,917	111,647	6.7	6.2–7.1	2.7	2.5–2.9
Darifenacin	30	4643	5204	5.8	3.9–8.2	2.2	1.5–3.2
Fesoterodine	43	10,591	8105	5.3	3.8–7.1	1.8	1.3–2.4
Oxybutynin	6	2604	1841	3.3	1.2–7.1	1.5	0.5–3.2
Solifenacin	296	38,667	45,587	6.5	5.8–7.3	2.9	2.6–3.2
Tolterodine	293	27,583	40,863	7.2	6.4–8	2.7	2.4–3
Trospium	91	12,932	12,811	7.1	5.7–8.7	2.7	2.2–3.3
Stroke							
Any OAB drug	310	72,917	112,359	2.8	2.5–3.1	1.3	1.2–1.5
Darifenacin	15	4657	5230	2.9	1.6–4.7	1.2	0.7–2
Fesoterodine	20	10,635	8143	2.5	1.5–3.8	0.9	0.6–1.4
Oxybutynin	3	2611	1850	1.6	0.3–4.7	0.7	0.1–2
Solifenacin	126	38,737	45,867	2.8	2.3–3.3	1.4	1.1–1.6
Tolterodine	116	27,600	41,156	2.8	2.3–3.4	1.5	1.3–1.8
Trospium	36	12,955	12,890	2.8	2–3.9	1.2	0.8–1.6
Cardiovascular mortality							
Any OAB drug	1656	72,917	112,768	14.7	14–15.4	4.8	4.5–5
Darifenacin	60	4660	5244	11.4	8.7–14.7	3.9	3–5
Fesoterodine	88	10,650	8173	10.8	8.6–13.3	3.8	3.1–4.7
Oxybutynin	26	2614	1856	14.0	9.2–20.5	6.9	4.5–10.1
Solifenacin	664	38,754	46,030	14.4	13.3–15.6	4.9	4.5–5.2
Tolterodine	659	27,609	41,303	16.0	14.8–17.2	6.2	5.8–6.7
Trospium	182	12,969	12,957	14.1	12.1–16.2	4.6	3.9–5.3
MACE							
Any OAB drug	2382	72,917	111,249	21.4	20.6–22.3	7.8	7.5–8.1
Darifenacin	91	4640	5191	17.5	14.1–21.5	6.6	5.3–8.1
Fesoterodine	136	10,576	8075	16.8	14.1–19.9	6.1	5.1–7.2
Oxybutynin	32	2602	1838	17.4	11.9–24.6	8.6	5.9–12.1
Solifenacin	949	38,651	45,430	20.9	19.6–22.3	8.1	7.6–8.7
Tolterodine	945	27,574	40,717	23.2	21.8–24.7	9.4	8.8–10
Trospium	273	12,918	12,745	21.4	19–24.1	7.6	6.7–8.6
All-cause mortality							
Any OAB drug	4799	72,917	112,768	42.6	41.4–43.8	15.2	14.8–15.6
Darifenacin	183	4660	5244	34.9	30–40.3	11.7	10–13.5
Fesoterodine	257	10,650	8173	31.5	27.7–35.5	11.2	9.8–12.6
Oxybutynin	69	2614	1856	37.2	28.9–47.1	34.5	26.9–43.7
Solifenacin	1889	38,754	46,030	41.0	39.2–42.9	14.6	13.9–15.2
Tolterodine	1954	27,609	41,303	47.3	45.2–49.5	17.4	16.6–18.2
Trospium	538	12,969	12,957	41.5	38.1–45.2	15.6	14.3–16.9

MACE major adverse cardiac events, *OAB* overactive bladder

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

Use of the nationwide Danish registries was a strength of this study. These data sources have complete population coverage in Denmark. A review of several validation studies confirms the suitability of Danish registry data for the study of cardiovascular events [12, 19]. For AMI, positive predictive values for different time periods, subsets of patients, and

types of AMI were between 82 and 100%. For stroke (including all types), positive predictive values between 79 and 97% have been reported [12]. The use of census data allowed for tracking of all patients and accounted for migration in or out of the population. Another strength of this study is that we compared users of different OAB medications rather than users and non-users, thus reducing possible confounding by indication at the design stage. These comparative safety results are the most relevant information for clinicians that need to treat patients with OAB.

In conclusion, we did not find differences in the risk of the targeted cardiovascular endpoints or all-cause mortality among users of individual OAB drugs, and we did not observe a consistently increased cardiovascular or mortality risk for any individual OAB drug.

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Author's contributions All authors fulfilled the ICMJE authorship criteria. Additionally, the authors were involved as follows: substantial contribution to the design of the study: AVM, JH, AP, NSK, WJA, CVL, SPG and AA; acquisition and analysis of the data: JH, AP, NSK; interpretation of the data: all authors; drafting or revising critically for important intellectual content: all authors; final approval: all authors; agreement to be accountable for all parts of the work: all authors.

Compliance with ethical standards

Ethical approval Retrospective registry studies do not require ethics committee notification or approval, since they do not fall under the Danish definition of health science research.

Conflict of interest The study was funded by Astellas Pharma Global Development, Inc., of which Willem Jan Atsma, Billy Franks, and Milbhor D'Silva are employees. Andrea Margulis, Alejandro Arana, and Susana Perez-Gutthann are full-time employees of RTI International, an independent non-profit research organization that does work for government agencies and pharmaceutical companies. Cristina Varas-Lorenzo was a full-time employee of RTI International at the time of the conduct of the study. Jesper Hallas, Nina Sahlertz. Kristiansen, and Anton Pottegård have worked on a project commissioned by Astellas, with funding paid to their employer. The contract granted the research team independent publication rights.

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