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Original Research

Effect of phosphodiesterase type 5 inhibitors on major adverse cardiovascular events and overall mortality in a large nationwide cohort of men with erectile dysfunction and cardiovascular risk factors: A retrospective, observational study based on healthcare claims and national death index data

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Abstract

Background: Treatment with phosphodiesterase type 5 inhibitors (PDE-5is) is effective in treating erectile dysfunction (ED).

Aim: The objective of this study was to determine the effect of PDE-5is on the incidence of major adverse cardiovascular (CV) events (MACE; composite outcome of CV death, hospitalization for myocardial infarction, coronary revascularization, stroke, heart failure, and unstable angina pectoris) and overall mortality.

Methods: A retrospective observational cohort study was conducted in a large US claims database in men with ≥1 diagnosis of ED without prior MACE within 1 year, from January 1, 2006, to October 31, 2020. The exposed group had ≥1 claim for PDE-5i and the unexposed group had no claims for PDE-5i, and the groups were matched up to 1:4 on baseline risk variables.

Outcome: The primary outcome was MACE and the secondary outcomes were overall mortality and individual components of MACE, determined by multivariable Cox proportional hazard modeling.

Results: Matched plus multivariable analyses showed that MACE was lower by 13% in men exposed (n = 23 816) to PDE-5is (hazard ratio [HR] 0.87; 95% CI 0.79-0.95; $P = .001$) vs nonexposure (n = 48 682) over mean follow-up periods of 37 and 29 months, respectively, with lower incidence of coronary revascularization (HR 0.85; 95% CI 0.73-0.98; $P = .029$), heart failure (HR 0.83; 95% CI 0.72-0.97; $P = .016$), unstable angina (HR 0.78; 95% CI 0.64-0.96; $P = .021$), and CV death (HR 0.61; 95% CI 0.41-0.90; $P = .014$) with PDE-5i exposure. Phosphodiesterase type 5 inhibitor–exposed men had a 25% lower incidence of overall mortality (HR 0.75; 95% CI 0.65-0.87; $P < .001$). Men without coronary artery disease (CAD) but with CV risk factors at baseline showed a similar pattern. In the main study cohort, men in the highest quartile of PDE-5i exposure had the lowest incidence of MACE (HR 0.45; 95% CI 0.37-0.54; $P < .001$) and overall mortality (HR 0.51; 95% CI 0.37-0.71; $P < .001$) vs the lowest exposure quartile. In a subgroup with baseline type 2 diabetes (n = 6503), PDE-5i exposure was associated with a lower MACE risk (HR 0.79; 95% CI 0.64-0.97; $P = .022$).

Clinical Implications: PDE-5is may have cardioprotective effects.

Strengths and Limitations: Strengths are the large numbers of participants and consistency of the data; limitations include the retrospective nature of the study and unknown confounders.

Conclusions: In a large population of US men with ED, PDE-5i exposure was associated with lower incidence of MACE, CV death, and overall mortality risk compared to non-exposure. Risk reduction correlated with PDE-5i exposure level.

Keywords: Erectile dysfunction; phosphodiesterase inhibitors; cardio-protection; major adverse cardiovascular events; myocardial infarction.

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Introduction

Along with the worldwide adoption of oral phosphodiesterase type 5 inhibitors (PDE-5is) as a first-line therapy for erectile dysfunction (ED) over the past 2 decades, knowledge of the broader effects of PDE-5 inhibition on the vascular system has increased significantly.[1,2]

The clinical efficacy of PDE-5is in treating ED is well known to be related to the downregulation of PDE-5 release in systemic arteries, which in turn reduces the breakdown of cyclic guanosine monophosphate (cGMP) in the penis and other organs. This pharmacologic effect is mediated via a nitric oxide (NO) mechanism, thereby enhancing vasodilation of key arteries and sinusoids in the corpus cavernosum of the penis.[3,4]

Moreover, since the action of these drugs is achieved systemically, improving NO-mediated vasodilation and endothelial function with PDE-5is is not specific for the vasculature of the genitalia but involves the vasculature of all body systems.[5,6]

This systemic benefit in endothelial function led Rosano et al.[7] to postulate that patients with other disorders associated with known endothelial dysfunction, including coronary artery disease (CAD), as well as risk factors for atherosclerosis, including type 2 diabetes mellitus (T2DM), may show benefit from therapy with these agents.[8]

Consistent with the hypothesis presented by Rosano et al,[7] a limited number of studies in at-risk populations of men have reported a significant reduction in cardiac risk associated with chronic PDE-5i use.[9-13] Each of these studies, however, was restricted to men with T2DM or known CAD, and some studies included limited assessment of the frequency or duration of PDE-5i use in the study population.[9-13] Of note, there has been a gradual decline over the past 2 decades in the rate of hospitalization for acute myocardial infarction.[14] Additionally, in view of new therapies and interventions with cardioprotective effects (eg, high-intensity statin therapy, new low-density lipoprotein [LDL]–lowering agents, antidiabetic medications, and drug-eluting stents[15,16]) there is a need to assess the effects of chronic PDE-5i use in a more recent broad population of men with ED. The purpose of our study was to assess the effect of PDE-5i usage on the incidence of major adverse cardiovascular (CV) events (MACE; including CV mortality) and overall mortality (all-cause death) in a broad population of men with ED, including relevant subpopulations, using a large integrated medical and pharmacy claims database.

We hypothesized that men with ED who were exposed to PDE-5is would show a decreased risk of MACE and overall mortality, even after adjustment for relevant covariates and comorbidities. We aimed to achieve the following objectives: Objective 1: To determine if PDE-5i exposure will be associated with a decreased incidence of MACE and overall mortality in men with ED compared to unexposed controls; objective 2: To determine if PDE-5i exposure will be associated with reduced MACE and overall mortality among men diagnosed with ED and no overt CAD, but with known CV risk factors; objective 3: To determine if increased level of exposure to PDE-5is will lead to greater improvements in CV outcomes; and objective 4: To determine if men with diabetes and/or a history of overt CAD will show similar benefits in reduced MACE events and mortality, depending on exposure to PDE-5is during the study period. The primary endpoint was MACE and secondary endpoints were overall mortality and the individual components of MACE.

Methods

Study design

This was a retrospective observational cohort study using patient data from a large medical and pharmacy claims database that identified male patients ≥18 years old with ≥1 diagnosis of ED between January 1, 2006, and October 31, 2020 (study period). From this population, we identified an exposed group consisting of men who filled 1 or more prescriptions for an approved PDE-5i (sildenafil, vardenafil, tadalafil, or avanafil) after their diagnosis of ED during the patient identification period (January 1, 2007, to October 31, 2020), without any PDE-5i claim in the baseline period (12 months before the index date). The first claim date of PDE-5i was defined as the index date of the exposed group. From the same population, we identified an unexposed group of patients (controls) without any claims for PDE-5i during the study period. To ensure that patients in the exposed and unexposed groups had similar amounts of time between their first ED diagnosis date and their index date, the index date of the unexposed group was the date of any pharmacy claim closest to a randomly selected date based on the distribution of days between first ED diagnosis and the index date among the exposed group.

We opted for covariate matching in combination with multivariable regression adjustment on matched-pair differences to control for any inherent biases within treatment and comparison groups. PDE-5i–exposed men were matched to controls on the basis of age; index date; diagnoses of CAD, T2DM, hypertension, and hypercholesterolemia/dyslipidemia; and antiplatelet, statin, and antihypertensive therapy using a matching ratio of up to 1:4. These matching variables were selected from a prespecified list of potential matching variables as the most clinically important variables that could be used for matching, while still maintaining the desired sample size. A single variable indicating "current smoking" was initially considered as a potential matching variable, although matching on this variable was impractical due to an insufficient number of matches with this indicator present. To address potential imbalances in smoking that remained after matching, a broader assessment algorithm was used to identify any smoking history (eg, current, past), and this modified smoking-related variable was included in subsequent multivariable-adjusted analyses.

Continued eligibility and exclusion

Continuous eligibility was required for the 12-month baseline period and between the date of the initial ED diagnosis claim and the index date. Patients were excluded from analysis if they had any claim for MACE in the baseline period, if they received an index PDE-5i product specified for treatment of pulmonary hypertension, or if they had a claim for diagnosis of pulmonary hypertension and/or related treatment use during the baseline period. Patients were followed until they were censored, which was defined as the end of continuous enrollment, death, claim of outcomes (MACE), or study end date, whichever occurred earlier. Diagnoses were determined using International Classification of Diseases, Clinical Modification Ninth and Tenth Revision diagnosis codes (ICD-9-CM; ICD-10-CM). Procedures were determined using ICD-9 and ICD-10 procedure codes, Current Procedural Terminology codes, or Healthcare Common Procedure Coding System codes,[17,18] and drug therapies were classified using Generic Product Identifier codes.

Cohorts were created for comparisons of study outcomes in patients with vs without PDE-5i exposure in all patients (main study), and in 3 subgroups: patients without a baseline diagnosis of CAD but with 1 or more baseline risk variables (age ≥45 years, smoking, T2DM, hypertension, hypercholesterolemia/dyslipidemia, peripheral arterial disease, chronic kidney disease, or statin therapy), patients with baseline T2DM, and patients with baseline diagnosis of CAD. In addition, we explored the relationship between the level of PDE-5i exposure and outcomes in the main study cohort, the PDE-5i–exposed group. Quartiles of exposure were determined by the cumulative number of tablets received based on the quantity dispensed from pharmacy claims extending from the index date until the date of censoring, with the lowest quartile as the reference.

Data source

The HealthCore Integrated Research Database contains healthcare claims and other information from over 50 million members of commercial health plans in the United States and includes health maintenance organizations, point of service plans, preferred provider organizations, Medicare Advantage and consumer-directed health plans and indemnity plans since January 1, 2006. Death and cause of death data were obtained from the National Death Index (NDI), the federal database for all recorded deaths in the United States, maintained by the Centers for Disease Control (CDC).[19]

Outcome definition and assessment

The primary outcome was MACE, defined as a composite of CV death or hospitalization (≥1 inpatient claim) for myocardial infarction, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft), stroke, heart failure, or unstable angina pectoris during the follow-up period. Cardiovascular death was assessed by linkage to CDC-based NDI data, with utilization of NDI-defined underlying cause of death based on ICD-10-CM diagnosis codes. Cardiovascular death included death due to myocardial infarction, sudden cardiac death, heart failure, stroke, CV hemorrhage (including nontraumatic subarachnoid hemorrhage, aortic rupture, arterial rupture, or cardiac tamponade), or other CV causes (including peripheral arterial disease, coronary artery disease, pulmonary embolism, cardiogenic shock, ventricular tachycardia, or dilated cardiomyopathy), in alignment with consensus CV and stroke endpoint definitions.[20] The secondary outcomes were overall mortality and the individual components of MACE.

Statistical methods and sample size

Statistical methodology

All demographic data, baseline clinical characteristics, and outcomes of interest were described in bivariate statistics. Frequencies and percentages were provided for categorical variables. Relevant measures of centrality such as means and medians were presented for continuous measures, as well as variance measures such as SDs and percentiles.

Hazard ratios and 95% CIs from marginal Cox proportional hazards models were used to report associations between PDE-5i use and time-to-event outcomes, including MACE and mortality, for matched and multivariable-adjusted analyses.[21,22]

Exact matching plus multivariable adjustment was selected given its ability to account for residual imbalances that remain after matching alone in claims-based analyses.[23] Multivariable-adjusted models for MACE controlled for age on index date, insurance type, year of index drug claim, months between ED diagnosis and index date, baseline conditions (smoking, CAD, T2DM, hypertension, hypercholesterolemia/dyslipidemia, peripheral arterial disease, and hypogonadism), and baseline medications (antiplatelet therapy, short- and long-acting nitrates, high- and moderate-low–intensity statins, ezetimibe/cholesterol absorption inhibitors, eicosapentaenoic acid/docosahexaenoic acid, angiotensin receptor blockers, beta-blockers, calcium channel blockers, aldosterone receptor modulators, diuretics, thiazolidinediones, insulin, and androgen/testosterone replacement therapy). We defined "hypogonadism" as at least 1 medical claim with an ICD-9 or ICD-10 diagnosis code for hypogonadism (ICD-9: 257.2; ICD-10: E29.1), hypogonadotropic hypogonadism/hypopituitarism (ICD-9: 253.2, 253.7; ICD-10: E23.0, E23.1), or postprocedural testicular hypofunction (ICD-9: 257.1; ICD-10: E89.5).

Multivariable-adjusted models for mortality controlled for age on index date, baseline Quan-Charlson Comorbidity Index, and baseline conditions (smoking, CAD, T2DM, and hypertension).[24,25]

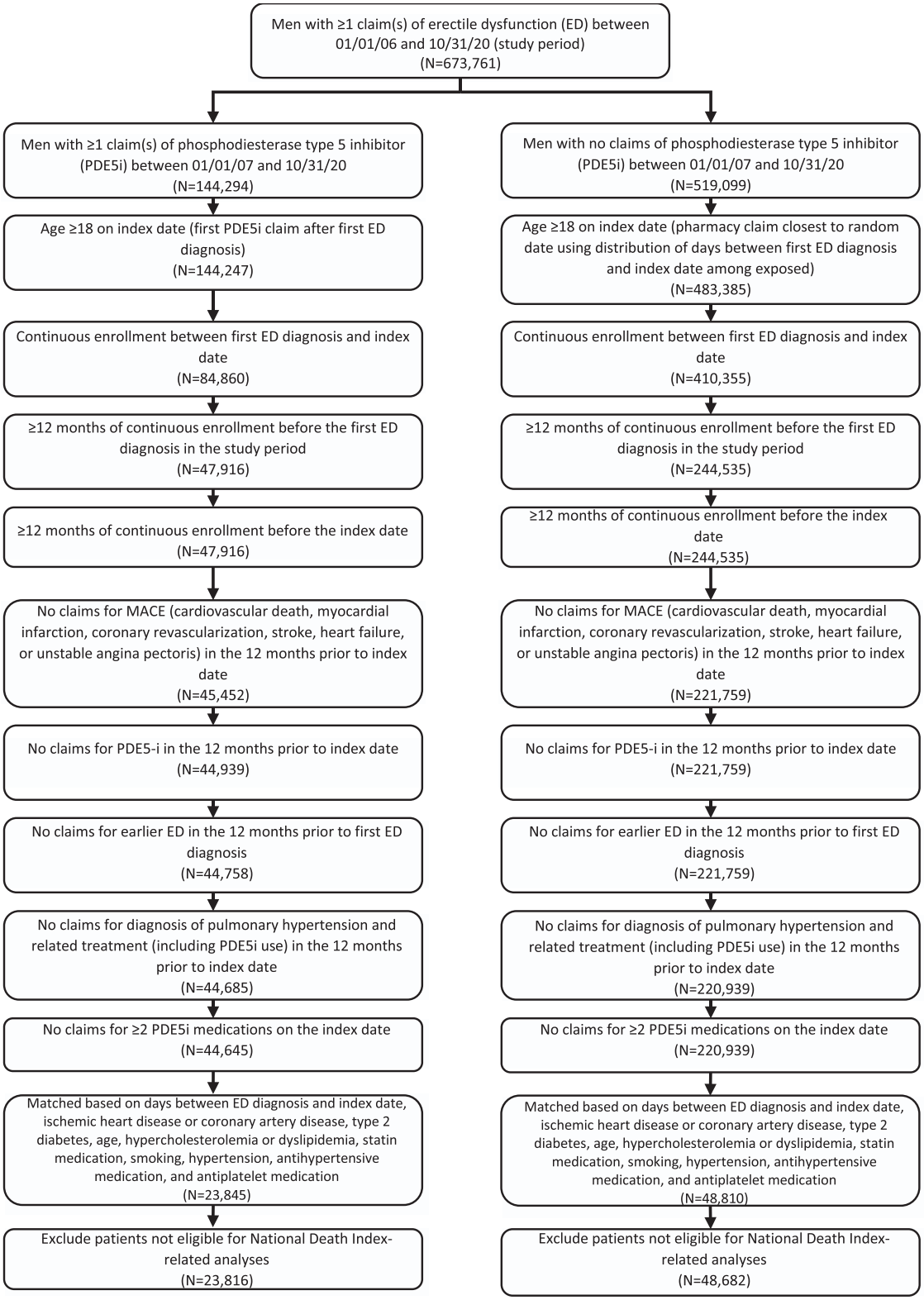
The same statistical approach was used to establish the association between quartiles of PDE-5i exposure and outcomes, with the exception that the multivariable-adjusted models for mortality additionally controlled for months between ED diagnosis and index date and baseline medications (antiplatelets, high- and moderate-low–intensity statins, angiotensin receptor blockers, beta-blockers, calcium channel blockers, aldosterone receptor modulators, and diuretics), since this analysis was conducted only among men exposed to PDE-5is and was thus not matched on the key variables that were used to match exposed and unexposed men in the main analysis. Kaplan-Meier curves were plotted to visualize event-free survival over the follow-up period. The study protocol with incorporated statistical analysis plan was specified a priori before review of the results. Analyses were completed using software from Instant Health Data (IHD; Panalgo) and SAS Enterprise Guide 8.3 (SAS Institute).

Study ethics

This study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor, and followed Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research.[26] A Health Insurance Portability and Accountability Act Waiver of Authorization was applied for from an Institutional Review Board (IRB) in order to access the NDI data. The protocol and applicable study materials were submitted to an IRB for review, and a waiver of authorization was granted (IRB # 20210336).

Results

In total, 673 761 men with at least 1 claim for ED during the study period were screened as potentially eligible for inclusion in the present study. After excluding those for whom NDI or other key endpoint data were not available (see Figure 1), a large subgroup ($n = 23\,816$) of men were selected as ED-confirmed patients with PDE-5is prescribed on their health plan and who met all eligibility criteria. An additional 48 682



Acronyms: ED= Erectile Dysfunction, n=number, PDE5i=Phosphodiesterase-5 inhibitors

Figure 1. Patient flow and attrition throughout the study.

men were selected as matched controls, but without PDE-5i exposure, as shown in the flowchart diagram (Figure 1).

Baseline demographic and clinical characteristics of the main study cohorts are shown in Table 1. As expected, the mean age of patients in the PDE-5i–exposed group was nearly identical to the average age in the control group (51.7 vs 52.0 years; P = not significant). Additional similarities between the groups can be seen in the time between

the ED diagnosis and index date, presence or absence of ischemic heart disease/CAD, T2DM, hypertension, hypercholesterolemia, dyslipidemia, antiplatelet drugs, statins, and antihypertensive medicines. Remaining differences at baseline were further accounted for in the preplanned, multivariable analysis.

Objective 1: To determine whether PDE-5i exposure will be associated with a decreased incidence of MACE and overall mortality in men with ED compared to unexposed controls

Results of adjusted multivariable regression models for MACE and mortality (Table 2) showed a 13% reduced incidence of cardiac events in the PDE-5i–exposed group (HR 0.87; 95% CI 0.79-0.95; $P = .001$) compared to the unexposed group. This reduction of cardiac events was associated with significantly lower incidences of coronary revascularization (HR 0.85, 95% CI 0.73-0.98, $P = .029$), heart failure (HR 0.83, 95% CI 0.72-0.97, $P = .016$), unstable angina (HR 0.78; 95% CI 0.64-0.96, $P = .021$), and CV mortality (HR 0.61; 95% CI 0.41-0.90, $P = .014$) in the PDE-5i–exposed men compared to the controls. We observed a numerically similar reduction of myocardial infarction and stroke rates in the PDE-5i–exposed group, which did not achieve statistical significance (see Table 2).

Men with ED who were exposed to PDE-5is had a statistically significant lower risk of dying from any cause (overall mortality) by 25% (HR 0.75; 95% CI 0.65-0.87; $P < .001$) compared to unexposed men, in addition to a 39% reduced risk of dying from CV causes (HR 0.61; 95% CI 0.41-0.90; $P = .014$), compared to men who were not exposed to PDE-5is during the same time period.

Objective 2: To determine if PDE-5i exposure will be associated with reduced MACE and overall mortality among men diagnosed with ED and no overt CAD, but with known CV risk factors

We observed a similar pattern and magnitude of differences to those seen in the full study cohort (Table 2). Specifically, we observed a lower incidence of MACE (HR 0.88; 95% CI 0.80-0.97; $P = .009$), overall mortality (HR 0.76; 95% CI 0.65-0.89; $P < .001$), and CV-related mortality (HR 0.66; 95% CI 0.43-1.02; $P = .059$) in men with compared to men without PDE-5i exposure.

Objective 3: To determine whether increased level of exposure to PDE-5is will lead to greater improvements in CV outcomes

The number of PDE-5i tablets dispensed was used as a proxy measure of drug exposure for purposes of testing this hypothesis. The mean (SD) numbers of PDE-5i tablets dispensed during follow-up were 5.5 (1.1) tablets in the lowest quartile, 12.6 (3.5) tablets in the second quartile, 32.0 (8.2) tablets in the third quartile; and 191.2 (251.1) tablets in the fourth or highest quartile of dosing. An apparent dose-response effect can be seen with increasing levels of exposure inferred from the number of pharmacy claims. Men with the highest level of exposure to the PDE-5is had the greatest magnitude of effect in comparison to men in the first and second quartiles of exposure (see Table 2). Hazard ratios were in the range of 0.33-0.53 for the main CV outcomes, most at the $P < .001$ level, except for CV-related mortality, which was nonsignificant at $P = .066$, compared to men with lower levels of PDE-5i exposure. MACE was lower in the group of men with the highest levels of exposure (HR 0.45; 95% CI 0.37-0.54; $P < .001$) compared to men with the lowest quartile of exposure. Incidences of myocardial infarction (HR 0.40; 95% CI 0.29-0.56; $P < .001$) and stroke (HR 0.53; 95% CI 0.38-0.75; $P < .001$) were also lower in patients with the highest exposure to of PDE-5i, according to our proxy measure.

Objective 4: To determine whether men with diabetes and/or a history of overt CAD will show similar benefits in reduced MACE events and mortality, depending on exposure to PDE-5is during the study period

In men with baseline T2DM, PDE-5i exposure was associated with a lower overall incidence of MACE (HR 0.79; 95% CI 0.64-0.97; $P = .022$), although individual components of MACE were not significantly different between the exposed and unexposed groups, as was overall mortality rates.

Patients with overt CAD

In men with known baseline CAD, there were no significant differences in adverse cardiac outcomes between men exposed vs not exposed to PDE-5, but there was a nonsignificant trend toward less cardiac mortality (HR 0.41; 95% CI 0.16-1.05; $P = .063$) in the PDE-5i exposed group. The lack of a statistically significant difference in this cohort may have been in part due to the lower number of patients in this subgroup.

Key findings from the matched and multivariable adjusted data are shown in Figure 2, demonstrating survival using Kaplan-Meier Curves and Figure 3, showing Forest plots of HRs.

Discussion

The major findings of the current retrospective observational study of a large US claims database were that in a general population of men with ED, exposure to PDE-5is was associated with significant and clinically meaningful lower incidence of MACE (by 13%), total mortality (by 25%) and CV mortality (by 39%), compared to our matched control group without exposure to PDE-5is. The reductions in MACE were largely driven by reductions in coronary revascularization, heart failure, unstable angina, and CV mortality. In men without known CAD, but who had risk factors for CAD, PDE-5i exposure was associated with similar reductions in MACE, total mortality, and CV mortality. In the main study cohort, men with the highest quartile of PDE-5i exposure had correspondingly greater reductions in MACE (by 55%) and overall mortality (by 49%) compared to the lowest quartile of PDE-5i use. The highest exposures were also associated with significantly greater reductions in myocardial infarction and stroke compared to lower exposures. In a subgroup of men with ED and T2DM, we observed a lower incidence of MACE, but not individual components of MACE, in those exposed to PDE-5i medications. In a subgroup of men with ED and with known CAD there was a nonsignificant trend toward lower CV mortality, but without a statistically significant reduction in MACE with PDE-5i exposure. As expected, the sample sizes for these latter 2 subgroups were limited compared to the size of the main study population, which may account in part for the less robust effects of the PDE-5is in these men.

Strengths of the current study

Our findings confirm and extend the findings of recent studies that investigated the effects of PDE-5is in subpopulations of men with ED, including those who had T2DM,[9-11] known CAD including past myocardial infarctions,[12,13] and rheumatoid arthritis.[27] Our findings also extend the findings from

Table 1. Baseline demographics, clinical conditions, treatment use in patients with erectile dysfunction (objective 1 cohort).

	Exposed group	Unexposed group	*P* value[a]
Number of patients, *n* (%)	23 816 (32.9%)	48 682 (67.1%)	—
Age on index date (years)[Matched]			
Mean (SD)	51.7 (10.4)	52.0 (10.4)	—
Median (IQR)	53.0 (45.0-59.0)	53.0 (46.0-59.0)	
Time between ED diagnosis and index date (in months)[Matched]			
Mean (SD)	2.0 (4.8)	1.5 (3.8)	—
Median (IQR)	0.2 (0.0-1.5)	0.2 (0.0-1.1)	
Smoking[b], *n* (%)			
Yes	2022 (8.5%)	5414 (11.1%)	**<.001**
No	21 794 (91.5%)	43 268 (88.9%)	
Clinical comorbidities, *n* (%)			
Ischemic heart disease/coronary artery disease[Matched]	505 (2.1%)	894 (1.8%)	—
Type 2 diabetes mellitus[Matched]	2187 (9.2%)	4316 (8.9%)	—
Hypertension[Matched]	8303 (34.9%)	17 215 (35.4%)	—
Hypercholesterolemia, dyslipidemia[Matched]	8894 (37.3%)	17 682 (36.3%)	—
Atrial fibrillation	401 (1.7%)	754 (1.5%)	.080
Ventricular arrhythmia	80 (0.3%)	130 (0.3%)	.061
Peripheral arterial disease	237 (1.0%)	598 (1.2%)	**<.001**
Benign prostatic hypertrophy	3768 (15.8%)	7571 (15.6%)	.551
Chronic kidney disease	387 (1.6%)	815 (1.7%)	.859
Hypogonadism	2039 (8.6%)	4957 (10.2%)	**<.001**
Postprocedural testicular hypofunction	20 (0.1%)	33 (0.1%)	.480
Hypogonadotropic hypogonadism/hypopituitarism	30 (0.1%)	85 (0.2%)	.228
Treatment use in baseline period, *n* (%)			
Implantable cardioverter-defibrillator	≤10	≤10	1.000
Cardiac resynchronization pacemakers	≤10	≤10	NA
Warfarin, direct oral anticoagulants	381 (1.6%)	796 (1.6%)	.878
Digoxin	34 (0.1%)	84 (0.2%)	.426
Antiplatelets including acetylsalicylic acid[Matched]	76 (0.3%)	118 (0.2%)	—
Antianginals			
Ranolazine	≤10	12 (0.0%)	.683
Nitrates, short and long acting	101 (0.4%)	255 (0.5%)	**.001**
Statins[Matched]			
High intensity	1139 (4.8%)	2436 (5.0%)	**.001**
Moderate-low intensity	4511 (18.9%)	8903 (18.3%)	**<.001**
Nonstatin lipid-lowering agents			
PCSK9 inhibitors	≤10	≤10	.564
Ezetimibe/cholesterol absorption inhibitors	426 (1.8%)	596 (1.2%)	**<.001**
Fibrates	727 (3.1%)	1488 (3.1%)	.909
Niacin	204 (0.9%)	318 (0.7%)	**.002**
EPA/DHA	193 (0.8%)	308 (0.6%)	**.009**
Adenosine triphosphate-citrate lyase inhibitors	0 (0.0%)	0 (0.0%)	NA
Bile acid sequestrants	92 (0.4%)	205 (0.4%)	.337
Antihypertensives[Matched]			
Angiotensin-converting enzyme inhibitors	4169 (17.5%)	8899 (18.3%)	.251
Angiotensin receptor blockers	2282 (9.6%)	4509 (9.3%)	**.002**
Angiotensin receptor-neprilysin inhibitor	0 (0.0%)	≤10	NA
Beta-blockers	2261 (9.5%)	4898 (10.1%)	**.007**
Calcium channel blockers	2300 (9.7%)	5137 (10.6%)	**<.001**
Renin inhibitor	29 (0.1%)	57 (0.1%)	.782
Aldosterone receptor modulators	295 (1.2%)	696 (1.4%)	**.017**
Antiadrenergics	473 (2.0%)	1004 (2.1%)	.063
Vasodilators	61 (0.3%)	144 (0.3%)	.108
Diuretics	1837 (7.7%)	3690 (7.6%)	**.009**
Type 2 diabetes mellitus therapy			
Metformin	1377 (5.8%)	2764 (5.7%)	.693
Dipeptidyl peptidase 4 inhibitors	302 (1.3%)	590 (1.2%)	.436
Glucagon-like peptide-1 receptor agonists	174 (0.7%)	354 (0.7%)	.810
Sodium-glucose cotransporter-2 inhibitors	117 (0.5%)	247 (0.5%)	.521
Sulphonylureas	685 (2.9%)	1377 (2.8%)	.701
Thiazolidinediones	310 (1.3%)	549 (1.1%)	**.035**
Insulin	464 (1.9%)	1003 (2.1%)	**.007**
Other[c]	34 (0.1%)	62 (0.1%)	.483
Androgen/testosterone replacement therapy	1222 (5.1%)	2922 (6.0%)	**<.001**
Non-PDE-5i ED therapy (prescription and nonpharmacologic)			
Alprostadil (injectable and MUSE)	49 (0.2%)	44 (0.1%)	**<.001**
Other injectables (papaverine, phentolamine)	17 (0.1%)	30 (0.1%)	.691
Nonpharmacologic (implant/pump, vacuum, revascularization)	118 (0.5%)	163 (0.3%)	**<.001**

ED, erectile dysfunction; EPA/DHA, eicosapentaenoic acid/docosahexaenoic acid; IQR, interquartile range; MUSE, medicated urethral system for erections; NA, not applicable; PCSK9, proprotein convertase subtilisin/kexin type 9 serine protease; PDE-5i, phosphodiesterase-5 inhibitor. [a] *P* values calculated using McNemar's tests. [b] Based on Desai et al. published algorithm. [c] Amylin analogs, meglitinide analogues, alpha-glucosidase inhibitors, dopamine receptor agonists.

Table 2. Summary of adjusted incidence rates and hazard ratios from multivariable regression models for MACE and mortality during follow-up period.

	Objective 1[a]		Objective 2[b]		Objective 3[c]				Objective 4, T2DM[d]		Objective 4, CAD[e]	
	Exposed (n = 23 816)	Unexposed (n = 48 682)	Exposed (n = 19 205)	Unexposed (n = 39 391)	Fourth Quartile (highest) (n = 5638)	Third Quartile (n = 5093)	Second Quartile (n = 6453)	First Quartile (lowest) (n = 6632)	Exposed (n = 2187)	Unexposed (n = 4316)	Exposed (n = 505)	Unexposed (n = 894)
Overall MACE[f]												
Cases/100 person-years	0.909	1.041	1.180	1.324	0.543	0.842	1.032	1.161	2.122	2.674	3.707	4.823
Hazard Ratio	0.87	Reference	0.88	Reference	0.45	0.72	0.89	Reference	0.79	Reference	0.78	Reference
95% CI	0.79-0.95		0.80-0.97		0.37-0.54	0.59-0.88	0.74-1.07		0.64-0.97		0.57-1.07	
P value	.001		.009		<.001	.001	.221		.022		.123	
Myocardial Infarction[f]												
Cases/100 person-years	0.310	0.327	0.414	0.431	0.206	0.391	0.463	0.491	0.752	0.687	1.522	1.673
Hazard Ratio	0.94	Reference	0.95	Reference	0.40	0.79	0.94	Reference	1.1061	Reference	0.9102	Reference
95% CI	0.81-1.09		0.81-1.11		0.29-0.56	0.58-1.08	0.70-1.27		0.80-1.53		0.57-1.45	
P value	.399		.529		<.001	.138	.698		.542		.693	
Coronary Revascularization[f]												
Cases/100 person-years	0.229	0.269	0.327	0.379	0.205	0.297	0.470	0.441	0.584	0.685	0.167	0.217
Hazard Ratio	0.85	Reference	0.86	Reference	0.45	0.67	1.06	Reference	0.85	Reference	0.76	Reference
95% CI	0.73-0.98		0.74-1.00		0.32-0.64	0.47-0.94	0.79-1.44		0.61-1.17		0.42-1.37	
P value	.029		.055		<.001	.022	.686		.318		.361	
Stroke[f]												
Cases/100 person-years	0.289	0.312	0.363	0.391	0.156	0.228	0.243	0.277	0.604	0.752	0.067	0.057
Hazard Ratio	0.92	Reference	0.92	Reference	0.53	0.81	0.87	Reference	0.80	Reference	1.18	Reference
95% CI	0.79-1.06		0.79-1.08		0.38-0.75	0.58-1.15	0.62-1.23		0.55-1.17		0.62-2.24	
P value	.254		.318		<.001	.248	.435		.254		.623	
Heart Failure [f]												
Cases/100 person-years	0.290	0.343	0.366	0.422	0.174	0.348	0.294	0.372	0.913	1.202	1.099	1.740
Hazard Ratio	0.83	Reference	0.85	Reference	0.43	0.91	0.79	Reference	0.76	Reference	0.63	Reference
95% CI	0.72-0.97		0.73-1.00		0.30-0.60	0.66-1.25	0.56-1.10		0.55-1.03		0.36-1.09	
P value	.016		.052		<.001	.549	.164		.080		.096	
Unstable Angina Pectoris [f]												
Cases/100 person-years	0.107	0.138	0.140	0.182	0.077	0.134	0.225	0.241	0.132	0.190	0.086	0.104
Hazard Ratio	0.78	Reference	0.78	Reference	0.33	0.56	0.94	Reference	0.70	Reference	0.79	Reference
95% CI	0.64-0.96		0.62-0.97		0.20-0.53	0.35-0.91	0.62-1.42		0.43-1.14		0.37-1.67	
P value	.021		.026		<.001	.018	.756		.156		.535	
Cardiovascular-Related Mortality [f]												
Cases/100 person-years	0.034	0.056	0.041	0.062	0.012	0.011	0.013	0.025	0.039	0.056	0.001	0.003
Hazard Ratio	0.61	Reference	0.66	Reference	0.46	0.41	0.53	Reference	0.70	Reference	0.41	Reference
95% CI	0.41-0.90		0.43-1.02		0.20-1.05	0.14-1.19	0.21-1.35		0.25-1.96		0.16-1.05	
P value	.014		.059		.066	.101	.185		.497		.063	
Overall Mortality [g]												
Cases/100 person-years	0.397	0.517	0.449	0.577	0.294	0.428	0.327	0.528	0.736	0.712	1.021	1.157
Hazard Ratio	0.75	Reference	0.76	Reference	0.51	0.79	0.61	Reference	1.02	Reference	0.88	Reference
95% CI	0.65-0.87		0.65-0.89		0.37-0.71	0.57-1.11	0.43-0.87		0.72-1.46		0.53-1.47	
P value	<.001		<.001		<.001	.169	.006		.902		.624	

CAD, coronary artery disease; MACE, major adverse cardiovascular events; T2DM, type 2 diabetes mellitus. MACE is defined as composite outcome of cardiovascular death, or hospitalization (≥1 inpatient claim) for myocardial infarction, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft), stroke, heart failure, or unstable angina pectoris during the follow-up period. [a]Patients in the study population with erectile dysfunction. [b]Population from objective 1 but without CAD diagnosis in the baseline period and with ≥1 of the following: age ≥45 years, smoking, T2DM, hypertension, hypercholesterolemia/dyslipidemia, peripheral arterial disease, chronic kidney disease, or statin use. [c]Population from objective 1 exposed to phosphodiesterase-type 5 inhibitors. [d]Population from objective 1 with T2DM in the baseline period. [e]Population from objective 1 with CAD in the baseline period. [f]Results are from models adjusted for age on index date, insurance type, year of index drug claim, months between erectile dysfunction diagnosis and index date, baseline smoking, ischemic heart disease/CAD, T2DM, hypertension, hypercholesterolemia/dyslipidemia, peripheral arterial disease, hypogonadism, antiplatelets including acetylsalicylic acid, short- and long-acting nitrates, high- and moderate-low–intensity statins, ezetimibe/cholesterol absorption inhibitors, eicosapentaenoic acid/docosahexaenoic acid, angiotensin receptor blockers, beta-blockers, calcium channel blockers, aldosterone receptor modulators, diuretics, thiazolidinediones, insulin, and androgen/testosterone replacement therapy. [g]For objectives 1, 2, and 4: results are from models adjusted for age on index date, baseline Quan-Charlson Comorbidity Index, smoking, ischemic heart disease/CAD, T2DM, and hypertension. For objective 3: results are from models adjusted for the same covariates as objectives 1 and 2 and additionally adjusted for months between erectile dysfunction diagnosis and index date, antiplatelets including acetylsalicylic acid, high- and moderate-low-intensity statins, angiotensin receptor blockers, beta-blockers, calcium channel blockers, aldosterone receptor modulators, and diuretics.

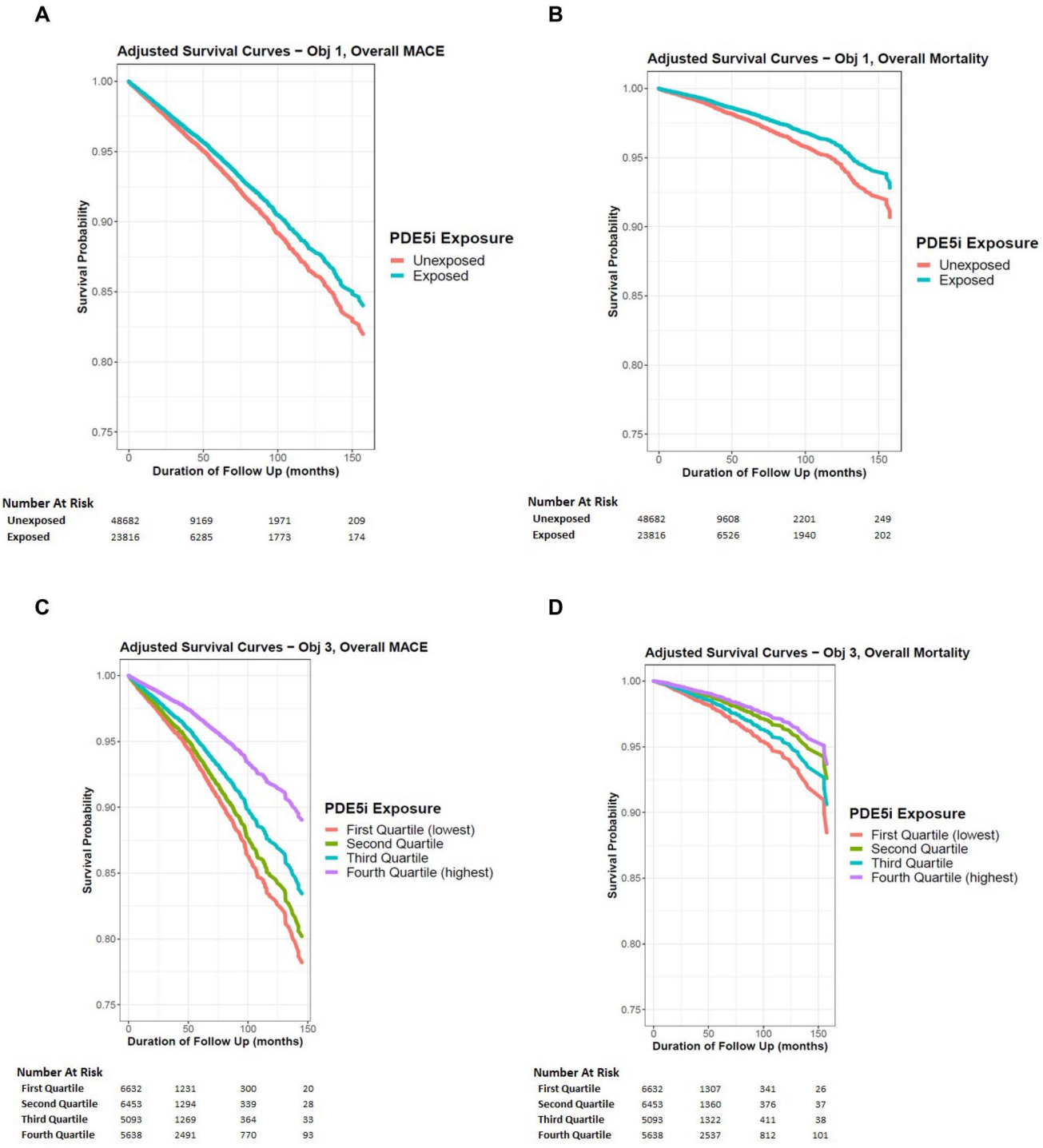


Figure 2. Key Kaplan-Meier plots from matched plus multivariable adjusted analyses. Note that the first 2 adjusted survival curves for MACE (A) and overall mortality (B) show that exposed group had improved survival and that the lines continued to separate over time in favor of exposure extending to 150 months. C and D show a suggested dose response effect with improved survival for both MACE and overall mortality improved in the highest exposure quartile. MACE, major adverse cardiovascular events.

a nationwide cohort study in Denmark that also observed improved cardiac outcomes in men prescribed medicine for ED, although in that study the benefits persisted only for the first 3 years.[28] Our findings expand the previous observations by showing that PDE-5is were associated with reduced MACE and mortality in a large general US population of men with ED, as well as men without overt CAD but with 1 or more CV risk factors, and that these associations persisted long term. In fact, Kaplan Meier curves (Figure 2) suggest wider separation in outcomes between exposed and unexposed groups over time. The results also show that within this general population of men with ED that the highest exposure levels of PDE-5is were associated with the largest magnitude of associations. A similar finding was observed in a previous study of men with known CAD treated with either PDE-5is or alprostadil.[13] This dose-response observation can now be extended to a much broader population of men with ED in the US. Our findings are consistent with recent studies demonstrating safety of

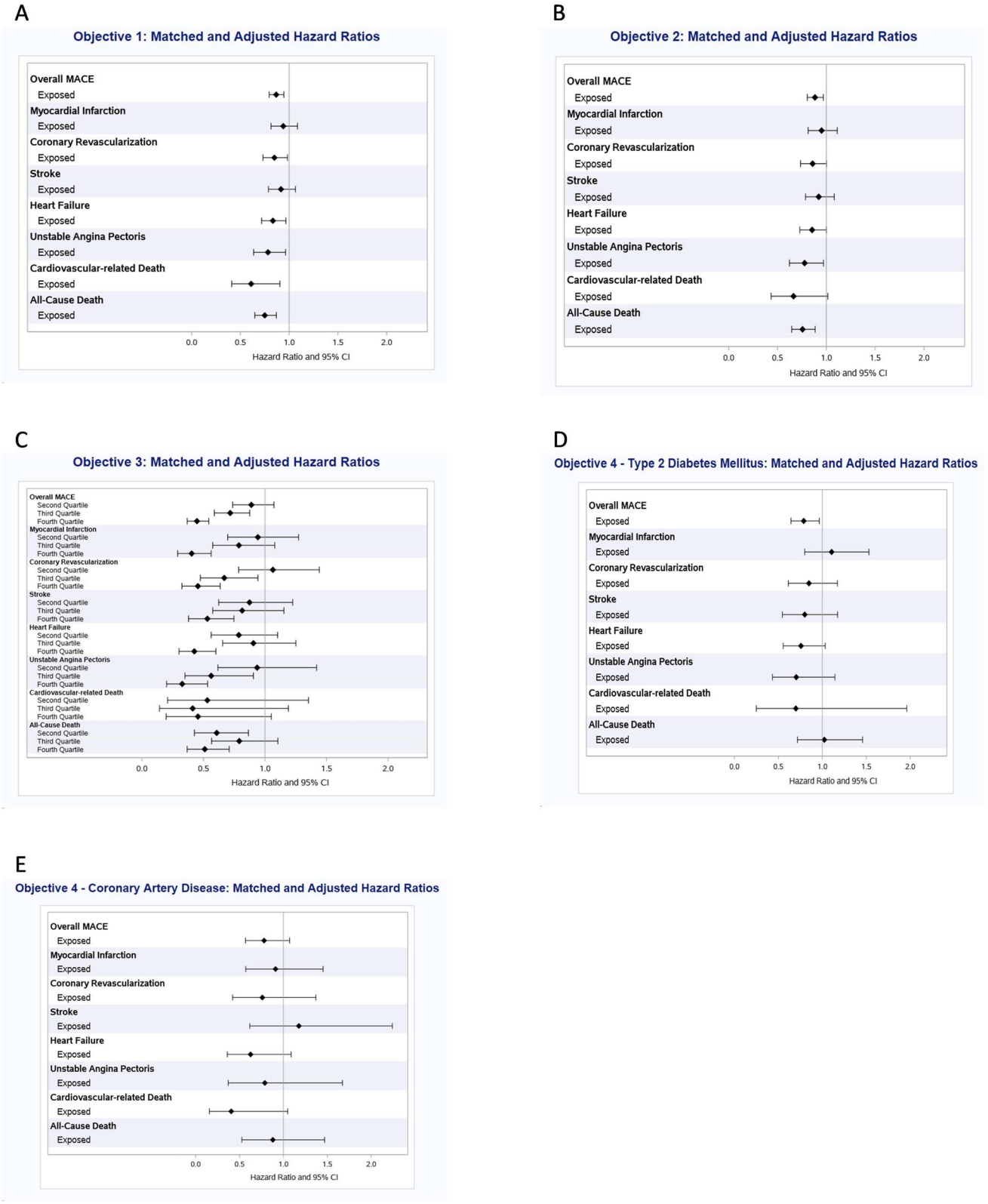


Figure 3. Key Forest plots from matched plus multivariable adjusted analyses. Hazard ratios for objective 1 (A) and 2 (B) were similar and in favor of PDE-5i exposure for MACE and all cause death. Results for objective 3 (C) suggest that the hazard ratios for MACE and most of its components were lower at higher levels of exposure. For objective 4, overall MACE had a lower hazard ratio in the exposed group, but not the individual components of MACE in the diabetic cohort (D). In those with known coronary artery disease, hazard ratios were not significantly improved by exposure (E). MACE, major adverse cardiovascular events.

PDE-5is when combined with antihypertensive medicines[29] and notably, no increase in CV events when patients received both PDE-5is and nitrates.[30] Our findings in diabetic patients are consistent with recent reports that chronic tadalafil therapy improved cardiac function in men with diabetic cardiomyopathy.[31]

Future perspectives

Taken together, these recent studies on the effects of PDE-5is in diverse populations of men with ED have provided consistent signals that PDE-5is are not only safe but may have important cardioprotective properties, findings that suggest an urgent need for an adequately powered, prospective randomized placebo-controlled trial. In addition, studies might be designed to examine the effect of PDE-5is on a general population of men with CV risk factors but not necessarily those with ED, to determine if PDE-5is have beneficial effects in that population.

Limitations of the current study

Our study has the limitations of it being a retrospective observational study with the potential for residual confounding by unaccounted-for variables. While we observed a clinically significant association between exposure to PDE-5i and reductions in MACE and mortality, we cannot establish causation. It may be postulated that men who have ED and are capable of taking PDE-5is and engaging in sexual activity may be healthier to begin with, and that unmeasured baseline differences may contribute to the effects observed. A second study limitation is the absence of an independent measure of sexual activity in these men, so it is not clear whether increased sexual activity may have contributed to the benefits seen that were independent of pharmacological effects of PDE-5i exposure. However, we attempted to address this issue in our study design by matching our control population for relevant risk factors and comorbidities; in addition, we conducted a preplanned, multivariable analysis that took into account other risk factors, concomitant illnesses, and differences in CV and other drug usage. Our observation of a "dose-response" effect with varying levels of PDE-5i exposure, estimated by the number of tablets dispensed, lends further support to this hypothesis. Patients in the highest quartile of PDE-5i exposure had noticeably greater reductions in MACE and mortality, compared to patients in the lowest quartile, in addition to significant reductions in myocardial infarction and stroke rates. These reductions in CV rates were consistent and clinically meaningful.

A major limitation of our study is that PDE-5i exposure was necessarily estimated from the number of tablets dispensed via the patient health plan. In addition, for the dose response analysis, the number of PDE-5i tablets dispensed was used as a proxy measure for drug exposure.

These measures do not take into account tablets that patients may have obtained from another source (e.g. internet, friends) or tablets dispensed, but not actually consumed, in the context of sexual activity. Since we anticipated a drug class effect, and to maintain adequate sample sizes for our subgroup analyses we did not differentiate effects of individual PDE-5is or actual dosages prescribed. We plan to investigate these differences in addition to the effects of PDE-5i treatment dropout or failure, and other subgroups of interest (any history of previous MACE) in future studies. Finally, we also have no measure of the frequency of sexual activity in either the PDE-5i–exposed or –unexposed groups.

Potential mechanisms

If PDE-5is have CV protective effects as this and other studies suggest, what are the potential mechanisms? While the purpose of our study was not to investigate mechanisms by which PDE-5is may have CV-protective effects, there are existing data and hypotheses in the literature on this topic. In a study by Rosano et al,[7] men with ED and CV risk factors were randomized to placebo vs 4 weeks of tadalafil and were then evaluated for brachial artery flow-mediated vasodilation. Tadalafil improved flow-mediated dilation compared to placebo and also increased nitrite/nitrate levels and decreased endothelin levels. The authors concluded that tadalafil significantly improved endothelial function in treated patients. In previous preclinical studies, our laboratory (RAK) observed that sildenafil in a rabbit model of coronary artery ischemia/reperfusion reduced specific vascular resistance during reperfusion within the risk region of the heart,[32] which also suggested possible improvement in endothelial function. In addition, sildenafil reduced left ventricular end diastolic pressure during ischemia, suggesting an improvement in diastolic function of the heart. In a rodent model in our laboratory, tadalafil reduced the size of experimental myocardial infarction; it was also associated with lower blood pressure in this model. The reduction in cell death could have been due in part to reduced afterload and therefore less oxygen demand of the heart.[33] Others have suggested that benefits of PDE-5is may involve reduced arterial stiffness, reduced systolic velocity, and reduced inflammation.[13] An additional mechanism whereby PDE-5is may have a beneficial effect on the CV system is by a potential antiplatelet effect.[34]

In conclusion, our study found that in a general population of men with ED, exposure to PDE-5is was associated with a 13% lower rate of MACE, 25% lower rate of mortality, and 39% lower rate of CV mortality than nonexposure. The highest exposure levels were associated with the greatest reductions in MACE and death and were also associated with significant reductions in myocardial infarction and stroke. This study adds to our knowledge base of the potential for PDE-5is to provide CV protection and provides impetus for future randomized, controlled trials.

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Conflict of interest: Dr. Kloner is a paid consultant to Sanofi but did not receive consulting fees for this project. Dr. Rosen received a consulting fee from HMRI. Dr. Bradsher is an employee of HMRI. Dr. Stanek and Singhal; Mr. Crowe, and Ms. Pepe are employees of Healthcore, which received a subaward from HMRI for the current study.

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