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Association of Phosphodiesterase-5 Inhibitors Versus Alprostadil With Survival in Men With Coronary Artery Disease

Daniel P. Andersson, MD, PhD,[a] Laura Landucci, MD,[b] Ylva Trolle Lagerros, MD, PhD,[c,d] Alessandra Grotta, PhD,[e] Rino Bellocco, ScD,[e,f] Mikael Lehtihet, MD, PhD,[a] Martin J. Holzmann, MD, PhD[c,g]

ABSTRACT

BACKGROUND Phosphodiesterase 5 inhibitor (PDE5i) treatment is associated with reduced mortality compared with no treatment for erectile dysfunction after myocardial infarction (MI).

OBJECTIVES This study sought to investigate the association between treatment with PDE5i or alprostadil and outcomes in men with stable coronary artery disease.

METHODS All Swedish men with a prior MI or revascularization who received PDE5i or alprostadil during 2006 through 2013 at >6 months after the event were included, using the Swedish Patient Register and the Swedish Prescribed Drug Register. Cox regression was used to estimate adjusted hazard ratios with 95% confidence intervals for all-cause mortality, MI, heart failure, cardiovascular mortality, noncardiovascular mortality, cardiac revascularization, peripheral arterial disease, and stroke in men treated with PDE5i versus alprostadil.

RESULTS This study included 16,548 men treated with PDE5i and 1,994 treated with alprostadil. The mean follow-up was 5.8 years, with 2,261 deaths (14%) in the PDE5i group and 521 (26%) in the alprostadil group. PDE5i compared with alprostadil treatment was associated with lower mortality (hazard ratio: 0.88; 95% confidence interval: 0.79 to 0.98) and with similar associations for MI, heart failure, cardiovascular mortality, and revascularization. When quintiles (q) of filled PDE5i prescriptions were compared using q1 as reference, patients in q3, q4, and q5 had lower all-cause mortality. Among alprostadil users, those in q5 had a lower all-cause mortality compared to q1.

CONCLUSIONS In men with stable coronary artery disease, treatment with PDE5i is associated with lower risks of death, MI, heart failure, and revascularization compared with alprostadil treatment. Although the decrease in all-cause mortality was PDE5i dose dependent, the data do not permit the inference of causality or any clinical benefits of PDE5i because of the observational study design. (J Am Coll Cardiol 2021;77:1535–50) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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From the [a]Department of Medicine Huddinge H7, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [b]Functional Area of Emergency Medicine, Karolinska University Hospital, Huddinge, Stockholm, Sweden; [c]Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital, Stockholm, Sweden; [d]Center for Obesity, Academic Specialist Center, Stockholm Health Services, Stockholm, Sweden; [e]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [f]Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy; and the [g]Department of Emergency and Reparative Medicine, Karolinska University Hospital, Stockholm, Sweden.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensinogen receptor blocker

CABG = coronary artery bypass surgery

CAD = coronary artery disease

CCB = calcium-channel blocker

ED = erectile dysfunction

MACE = major adverse cardiac events

MI = myocardial infarction

PAD = peripheral arterial disease

PCI = percutaneous coronary intervention

PDE5i = phosphodiesterase-5 inhibitor

q = quintile

Erectile dysfunction (ED) is a multifactorial and common condition affecting more than 40% of men older than 70 years (1). It is associated with an increased risk of cardiovascular events and mortality in the general population and among individuals with established cardiovascular disease (1–4).

Vasculogenic ED has been proposed to be an early manifestation of atherosclerosis and to precede presentation of coronary artery disease (2,5). Men with ED have been identified as a high-risk population for incident cardiovascular disease. Conversely, treatment for ED is associated with a lower risk of death and development of cardiovascular disease (6–8). In a previous nationwide Swedish cohort study including men with a first myocardial infarction (MI), treatment for ED with PDE5i was associated with a lower risk of death and cardiovascular events (8). These findings may have been associated with the positive effects of PDE5i on endothelial function and especially vasodilatation, thrombosis, and inflammation (9). However, the main limitation with these studies was that the reference group comprised men who were not receiving treatment for ED, which may have introduced confounding by indication. Therefore, we conducted a nationwide study of men with stable coronary artery disease (CAD) who were treated with either PDE5i or alprostadil, which is an alternative for PDE5i for treatment of ED. To limit the risk of confounding by indication, we compared the 2 treatments for the outcomes all-cause mortality, MI, heart failure, cardiovascular mortality, non-cardiovascular mortality, cardiac revascularization, peripheral arterial disease, and stroke.

SEE PAGE 1551

METHODS

DATA SOURCES. The study population was identified from the National Swedish Patient Register kept by the Swedish Board of Health and Welfare, in which all hospital stays across the country have been registered since 1987 (10). Additionally, this register contains information about surgeries, including cardiac revascularization with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). The dataset included all patients with an MI or cardiac revascularization from 1997 to 2013 in Sweden (N = 387,712). Information about outcomes was available until December 31, 2017, from the same register.

All residents in Sweden have a unique personal identity number, which enabled us to link information from several other national registers to the study population. From the Swedish Prescribed Drug Register, which includes information on dispensed medication, dosages, number of packages, and number of tablets, we obtained information on all dispensed medication from pharmacies in Sweden from July 1, 2005, when the registry was started until December 31, 2018. Every time a prescription is dispensed in any pharmacy in the country, the information about this is automatically transferred to the National Board of Health and Welfare, which is responsible for this registry (11).

The socioeconomic variables marital status and length of education were collected from the LISA registry (Longitudinal Integration Database for Health Insurance and Labor Market Studies) at Statistics Sweden. Furthermore, we used the Cause of Death register to ascertain the date and primary cause of death. We had information from this register from January 1, 1997, until December 31, 2016.

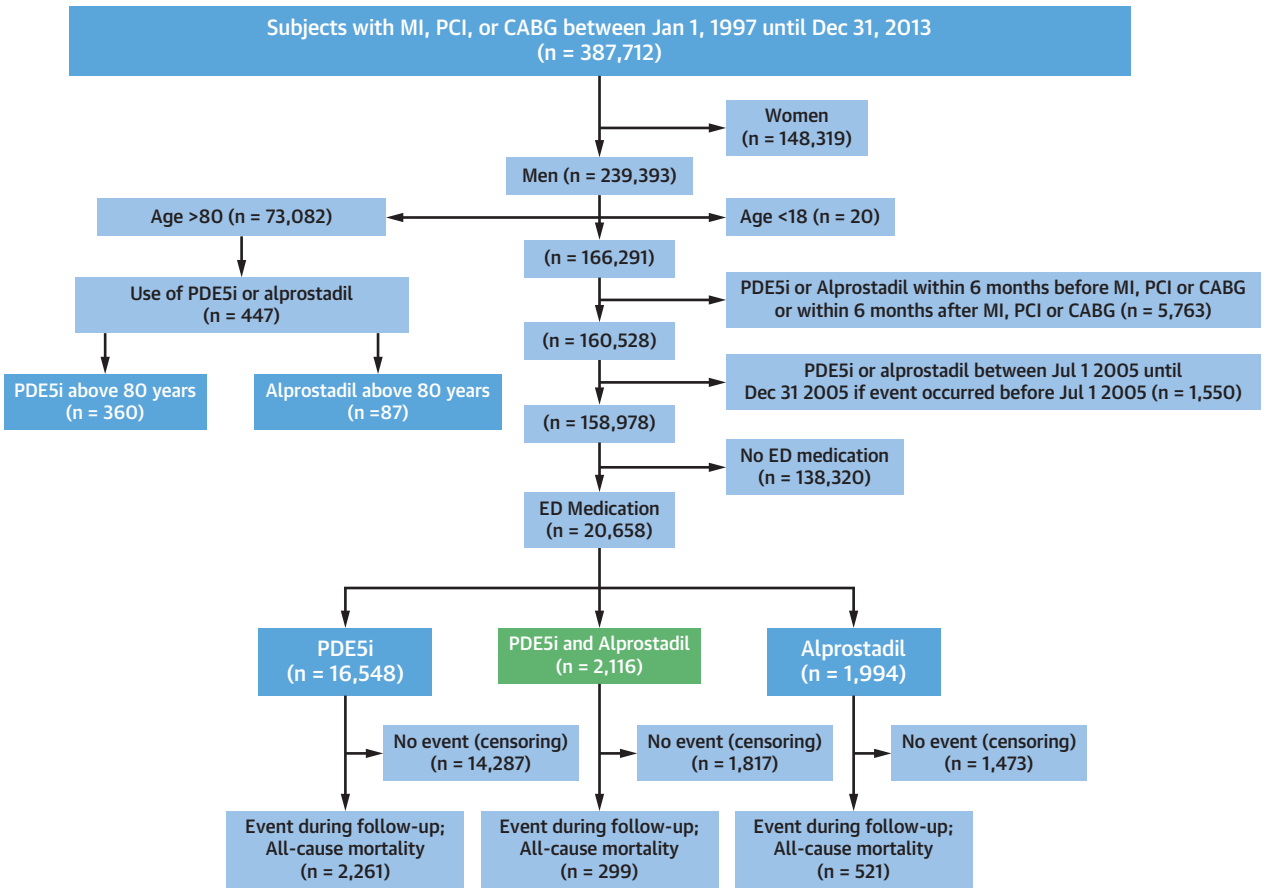
The study was approved by the Stockholm regional ethics review board (ethics permit number: 2015/1180-31/4) and complied with the Helsinki Declaration.

EXPOSURE. We defined the exposure as at least 1 filled prescription of any phosphodiesterase-5 inhibitor (PDE5i) using the following Anatomical Therapeutic Chemical codes: sildenafil (G04BE03), tadalafil (G04BE08), and vardenafil (G04BE09). Patients who were treated with alprostadil (G04BE01) were considered unexposed and thus represented the reference group.

SELECTION OF THE STUDY POPULATION. All Swedish men who had an MI or underwent CABG or PCI any time between January 1, 1997, and December 31, 2013, were eligible for inclusion (n = 239,393). Men ages >80 years (n = 73,082) and <18 years (n = 20) were excluded. To ensure that only ED-medication-naive men were included, we excluded those who were treated 6 months before or after the cardiac event with PDE5i or alprostadil (n = 5,763). Participants were included only if they used either alprostadil or PDE5i during the study period, and 2,116 were excluded because they had been treated with both alprostadil and PDE5i. This led to a final study population of 16,548 men who were treated with PDE5i and 1,994 men who were treated with alprostadil (Figure 1).

DEFINITIONS. The index date was the date when the patient had his first PDE5i or alprostadil prescription filled. Ongoing medication was defined as a minimum of 1 filled prescription during the 6 months preceding

FIGURE 1 Flowchart Showing the Selection of the Study Population



The study population included men with stable coronary artery disease who were treated either with phosphodiesterase-5-inhibitors (PDE5i) or alprostadil. CABG = coronary artery bypass grafting; ED = erectile dysfunction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PDE5i = phosphodiesterase 5 inhibitors.

the index date. We collected information from the Prescribed Drug Register about the following drugs: statins, platelet inhibitors, calcium-channel blockers (CCB), beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), thiazides, opioids, selective serotonin reuptake inhibitors, and neuroleptic drugs. (See Supplemental Table 1 for the Anatomical Therapeutic Chemical Classification codes.)

Baseline comorbidities were defined according to primary discharge diagnoses in the Swedish Patient Register in the years preceding the index date (except cancer, which was regarded as active if there was a diagnosis within 2 years preceding the index date). Information regarding the following diseases was collected: MI, heart failure, cardiac revascularization (PCI or CABG), peripheral arterial disease (PAD), stroke, chronic obstructive pulmonary disease, diabetes, atrial fibrillation and active cancer. (See Supplemental Table 2 for International Classification of Disease-10 codes.)

RISK CATEGORIES. We categorized patients into 6 risk categories from 0 to 5, depending on the number of cardiovascular risk factors according to Bohula et al. (12): age of >75 years, diabetes, prior stroke, prior CABG and/or PAD, heart failure, and estimated hazard ratios (HRs) for the risk of adverse outcome in each risk category. There were few patients with >2 risk factors; therefore, we decided to analyze data in 2 categories: <3 and >2.

OUTCOMES AND FOLLOW-UP. The primary outcome was all-cause mortality. Secondary outcomes included MI, heart failure, cardiovascular mortality,

TABLE 1 Baseline Characteristics of 18,542 Men With Coronary Artery Disease and Erectile Dysfunction Treated With PDE5i or Alprostadil

	PDE5i (n = 16,548)	Alprostadil (n = 1,994)	p Value
Age, yrs	62 ± 8.5	64 ± 8.4	
Heart failure	665 (4.0)	166 (8.3)	<0.0001
Diabetes	3,422 (21.0)	636 (32.0)	<0.0001
COPD	190 (1.2)	49 (2.5)	<0.0001
Stroke	840 (5.1)	172 (8.6)	<0.0001
PAD	281 (1.7)	69 (3.5)	<0.0001
Active cancer	445 (2.7)	197 (9.9)	<0.0001
Atrial fibrillation	1,014 (6.1)	188 (9.4)	<0.0001
Medication			
Beta blockers	12,224 (74.0)	1,597 (80.0)	<0.0001
Statins	13,348 (81.0)	1,638 (82.0)	0.11
ACE inhibitors/ARBs	10,910 (66.0)	1,367 (69.0)	0.02
Thiazides	4,280 (26.0)	711 (36.0)	<0.0001
Platelet inhibitors	13,966 (84.0)	1,691 (85.0)	0.64
Opioids	1,752 (11.0)	364 (18.0)	<0.0001
SSRIs	907 (5.5)	172 (8.6)	<0.0001
Neuroleptics	123 (0.7)	21 (1.1)	0.14
Calcium-channel blockers	3,841 (23.0)	592 (30.0)	<0.0001
Nitrates	1,126 (6.8)	619 (31.0)	<0.0001
Length of education, yrs			<0.0001
<10	4,710 (28.0)	670 (34.0)	
10–12	6,094 (37.0)	794 (40.0)	
>12	3,417 (21.0)	342 (17.0)	
Unknown	2,327 (14.0)	188 (9.0)	
Marital status			<0.0001
Divorced	3,095 (19.0)	428 (21.0)	
Married	8,629 (52.0)	1,093 (55.0)	
Single	1,448 (9.0)	155 (8.0)	
Widowed	1,122 (7.0)	140 (7.0)	
Unknown	2,254 (14.0)	178 (9.0)	

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensinogen receptor blockers; COPD = chronic obstructive pulmonary disease; PAD = peripheral artery disease; PDE5i = phosphodiesterase 5 inhibitor; SSRI = selective serotonin reuptake inhibitor.

noncardiovascular mortality, cardiac revascularization, PAD, and stroke. Cardiovascular death was defined according to the definition of the European Society of Cardiology. Only diagnoses in the primary position were used for outcomes.

For patients with an event—that is, MI or cardiac revascularization—after July 1, 2005—the index date could be no earlier than 6 months after the event had occurred for the patient to be regarded as clinically stable following the cardiac event. For patients who had their event before July 1, 2005, the index date could be no earlier than January 1, 2006, because there was no information about medication before July 1, 2005. Follow-up ended: 1) for all-cause, cardiovascular, or noncardiovascular mortality at the time of death or December 31, 2016, whichever occurred first; 2) MI; 3) heart failure; 4) PAD; and 5) stroke when the patient was admitted to hospital for these outcomes, at the time of death, or December 31, 2017, whichever occurred first.

STATISTICAL METHODS. Summary statistics were computed both for the whole sample and for alprostadil and PDE5i users separately. For continuous variables, mean ± SD are reported, whereas for categorical variables, percentages are provided. The Student's *t*-test and chi-square test were used to compare continuous and categorical variables between alprostadil and PDE5i users.

Cox proportional hazards regression models were used to study the association between PDE5i medication and: 1) all-cause mortality; 2) MI; 3) heart failure; 4) cardiovascular mortality; 5) noncardiovascular mortality; 6) revascularization; 7) PAD; and 8) stroke. Alprostadil users were used as the reference category.

We estimated HRs with 95% confidence intervals (CIs) for unadjusted models, age-adjusted models, and multivariable-adjusted models in which we included dichotomous variables for medications (Supplemental Table 1), comorbidities (**Table 1**), and socioeconomic variables (**Table 1**) assessed around the index date.

We also included a variable to track if the individual had an MI and/or underwent CABG or PCI as an inclusion diagnosis as well as the time from this event to the index date. Follow-up started at the index date for both alprostadil and PDE5i users.

Alprostadil and PDE5i users were defined as those patients who were prescribed alprostadil or PDE5i medication, respectively, at least once and who did not use both types of medications during the follow-up period.

Finally, we also ran Cox proportional hazards regression models using quintiles of ED medication as the main exposure to investigate the dose-response association between the amount of medication dispensed and: 1) all-cause mortality; 2) MI; 3) heart failure; 4) cardiovascular mortality; 5) noncardiovascular mortality; and 6) revascularization. Models were adjusted for medications (**Table 1**), comorbidities (**Table 1**), and socioeconomic variables (**Table 1**) and were run separately for alprostadil and PDE5i users. This analysis accounted for the time each individual spent in each quintile; thus, our exposure was treated as time varying.

To assess the robustness of our results, we performed a propensity score matching analysis. The propensity score, that is, the probability that a patient received alprostadil instead of PDE5i, was estimated by using a multivariable probit regression model that

included age and baseline comorbidities and dispensed drugs. Using the estimated propensity score, we matched each individual treated with alprostadil with up to 3 individuals treated with PDE5i. In detail, we chose a nearest neighbor matching algorithm with replacement, with a caliper equal to 0.20 of the SD of the logit of the estimated propensity score according to the literature guidelines (13). Balance in baseline covariates between PDE5i and alprostadil users was assessed both before and after performing matching by using absolute standardized differences (13). Unconditional Cox regression models including only the treatment indicator were run on the propensity score-matched cohorts, and unbalanced covariates, if any, were added in the model as extra independent variables. We defined a covariate as unbalanced if the absolute standardized difference was higher than 0.10. Because the goal of the propensity score model is to balance covariates among treatment groups and not to predict treatment assignment, the C-statistic—which is an index assessing the performance of predictive models—was not reported as a part of the propensity score analysis (13,14). Propensity score estimation and matching were repeated on the whole sample for each outcome separately.

A formal testing procedure with Schoenfeld residuals was used to assess the assumption of Cox regression.

We considered p values of <0.05 statistically significant. All the statistical analyses were performed with Stata 15 (Stata Corp, College Station, Texas).

RESULTS

STUDY POPULATION. The baseline characteristics of the study population are shown in Table 1. Alprostadil users were more likely to have prior stroke, diabetes, active cancer, heart failure, chronic obstructive pulmonary disease, atrial fibrillation, and PAD compared with the PDE5i users. Moreover, they were more likely to use beta-blockers, ACE inhibitors/ARBs, thiazides, opioids, selective serotonin reuptake inhibitors, CCBs, and nitrates. Patients who were treated with PDE5i were more likely to have a postgraduate education and were slightly younger.

ALL-CAUSE MORTALITY, MI, AND HEART FAILURE. During a mean follow-up of 5.8 years, there were 521 deaths (26%) in men treated with alprostadil and 2,261 (14%) in men treated with PDE5i (Table 2). The annual death rates were 4.3% and 2.4% in patients treated with alprostadil and PDE5i, respectively. Patients treated with PDE5i had a 12% lower risk for death than men treated with alprostadil (adjusted HR: 0.88; 95% CI: 0.79 to 0.98). Survival free of death is shown in Figure 2A.

TABLE 2 HRs With 95% CIs for All-Cause Mortality, Heart Failure, and MI

	PDE5i	Alprostadil
All-cause mortality	16,548	1,994
Deaths	2,261 (13.7)	521 (26.1)
Incidence rate, cases/100 person-years	2.39 (2.30-2.49)	4.26 (3.91-4.64)
Unadjusted HR	0.58 (0.52-0.63)	Referent
Adjusted for age	0.67 (0.61-0.74)	Referent
Multivariable adjusted*	0.88 (0.79-0.98)	Referent
MI	15,700	1,885
MI	1,478 (9.4)	276 (14.6)
Incidence rate, cases/100 person-years	1.72 (1.64-1.81)	2.54 (2.26-2.86)
Unadjusted HR	0.68 (0.60-0.77)	Referent
Adjusted for age	0.68 (0.60-0.77)	Referent
Multivariable adjusted*	0.81 (0.70-0.93)	Referent
Heart failure	16,235	1,938
Events	899 (5.5)	238 (12.2)
Incidence rate, cases/100 person-years	0.99 (0.93-1.06)	2.09 (1.84-2.37)
Unadjusted HR	0.48 (0.41-0.55)	Referent
Adjusted for age	0.55 (0.47-0.63)	Referent
Multivariable adjusted*	0.75 (0.64-0.88)	Referent

Values are n, n (%), hazard ratio (HR) (95% confidence interval [CI]), or incidence rate (95% CI), unless otherwise indicated. *Adjusted for all variables in Table 1.

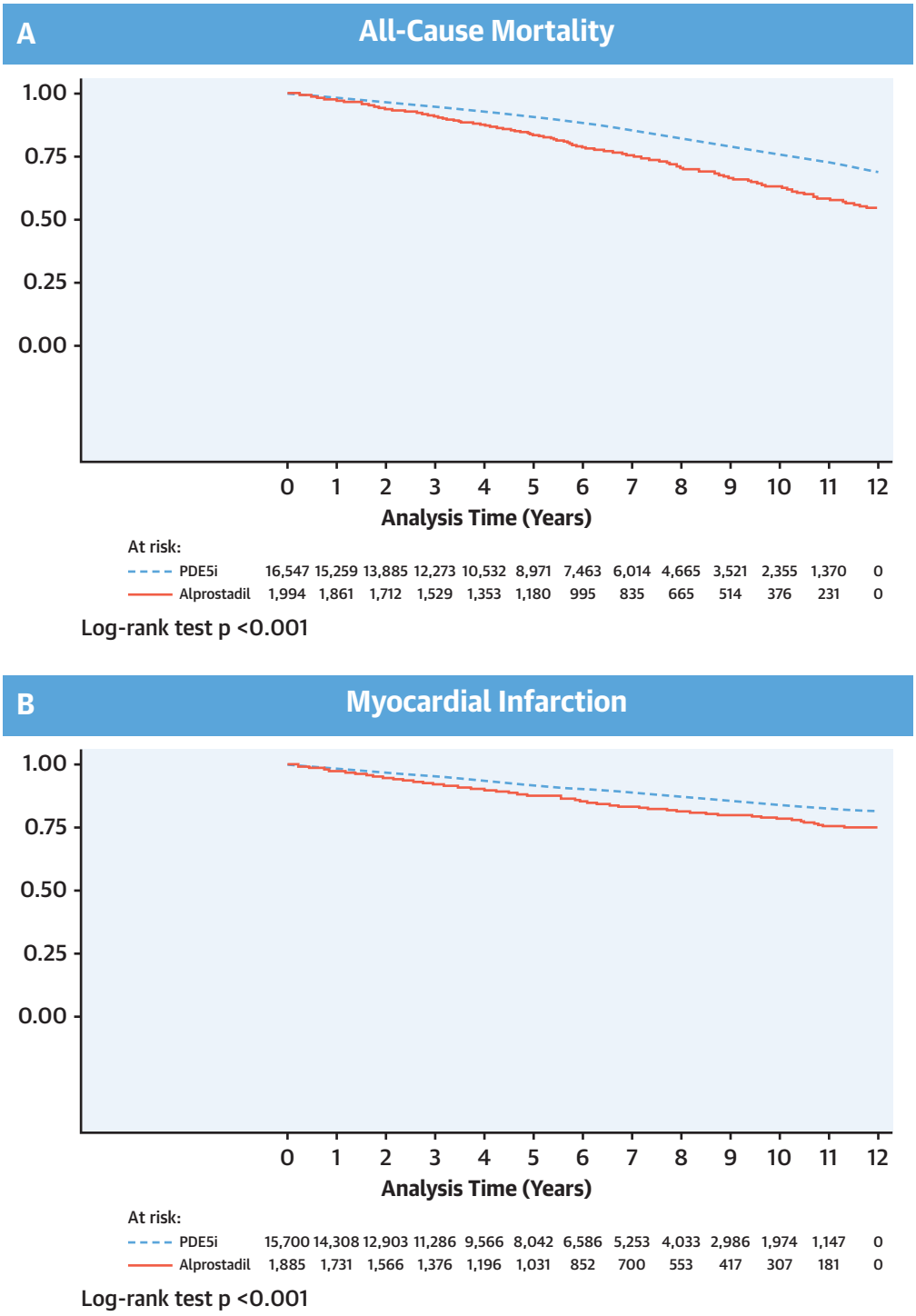
CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PDE5i = phosphodiesterase 5 inhibitor.

During a mean follow-up of 5.5 years, there were 276 (15%) and 1,478 (9.4%) MIs, with average annual rates of 2.5% and 1.7% in men treated with alprostadil and PDE5i, respectively. Treatment with PDE5i was associated with a 19% lower risk for MI compared with treatment with alprostadil (adjusted HR: 0.81; 95% CI: 0.70 to 0.93). Survival free of MI is shown in Figure 2B.

There were 238 (12%) hospitalizations for heart failure, with an annual rate of 2.1% in men treated with alprostadil. In the PDE5i group there were 899 heart failure cases (5.5%), with an annual rate of 1.0%. Treatment with PDE5i was associated with a 25% lower risk of hospitalizations for heart failure than treatment with alprostadil (adjusted HR: 0.75; 95% CI: 0.64 to 0.88) (Table 2). Survival free of hospital stay for heart failure is shown in Figure 2C.

CARDIOVASCULAR MORTALITY, NONCARDIOVASCULAR MORTALITY, REVASCULARIZATION, STROKE, AND PAD. The proportions of cardiovascular deaths were 40% (209 of 521) and 35% (790 of 2,261) in men treated with alprostadil and PDE5i, respectively. We found an association between treatment with PDE5i compared with treatment with alprostadil and a lower risk of cardiovascular (adjusted HR: 0.83; 95% CI: 0.70 to 0.98) but not with noncardiovascular death (adjusted HR: 0.92; 95% CI: 0.79 to 1.07). Survival free

FIGURE 2 Kaplan-Meier Estimates for Different Outcomes Comparing Men Using PDE5i With Men Who Were Using Alprostadil



(A) Estimates for overall survival. **(B)** Survival free of myocardial infarction. **(C)** Survival free of heart failure hospitalization. **(D)** Survival free of cardiovascular (CVD) mortality. **(E)** Survival free of noncardiovascular (non-CVD) mortality. **(F)** Survival free of revascularization. **(G)** Survival free of peripheral arterial disease. **(H)** Survival free of stroke. Men who were using PDE5i had a lower risk for all outcomes except for peripheral arterial disease and stroke over men who were using alprostadil where no difference was found between the 2 treatments.

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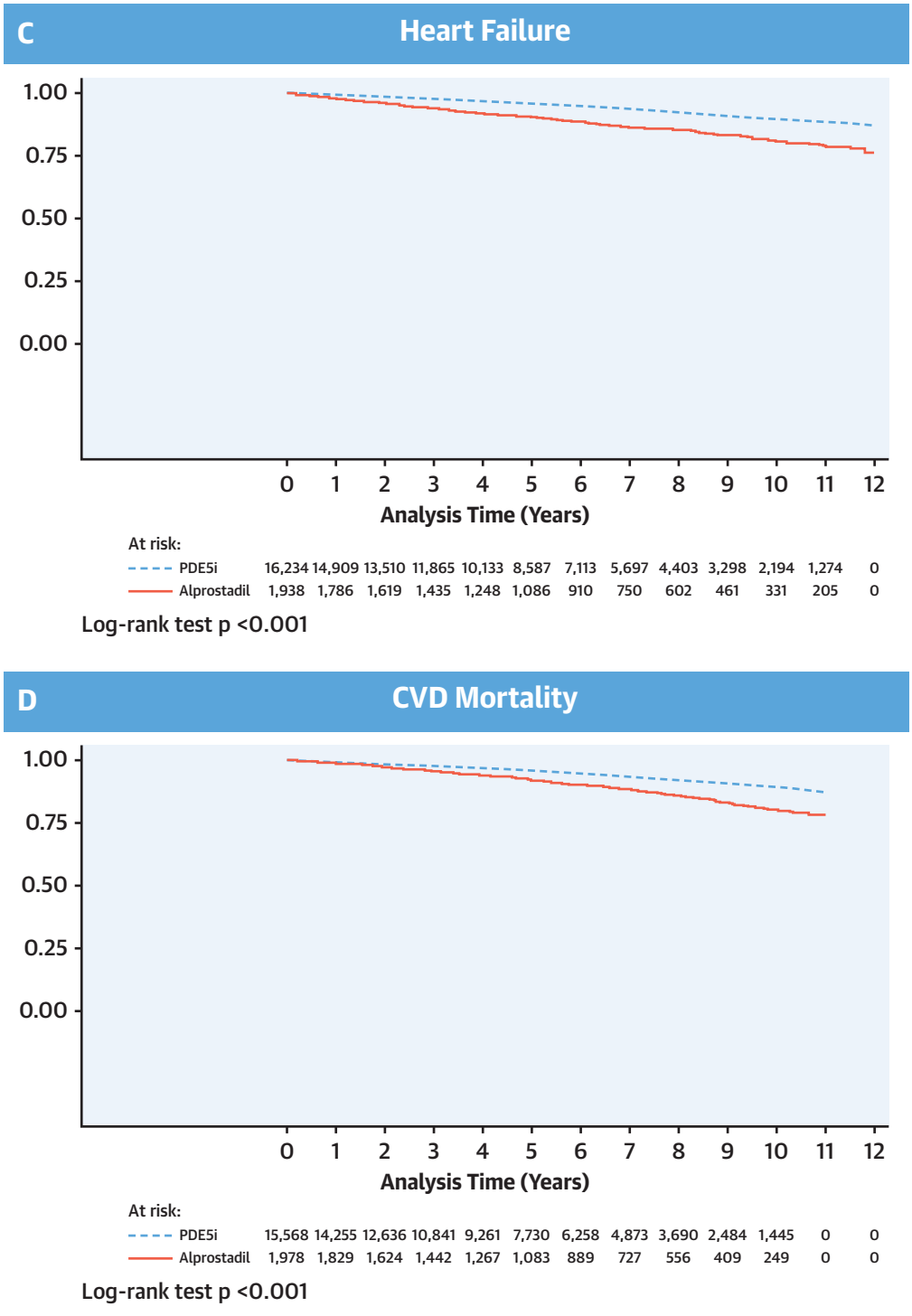
FIGURE 2 Continued



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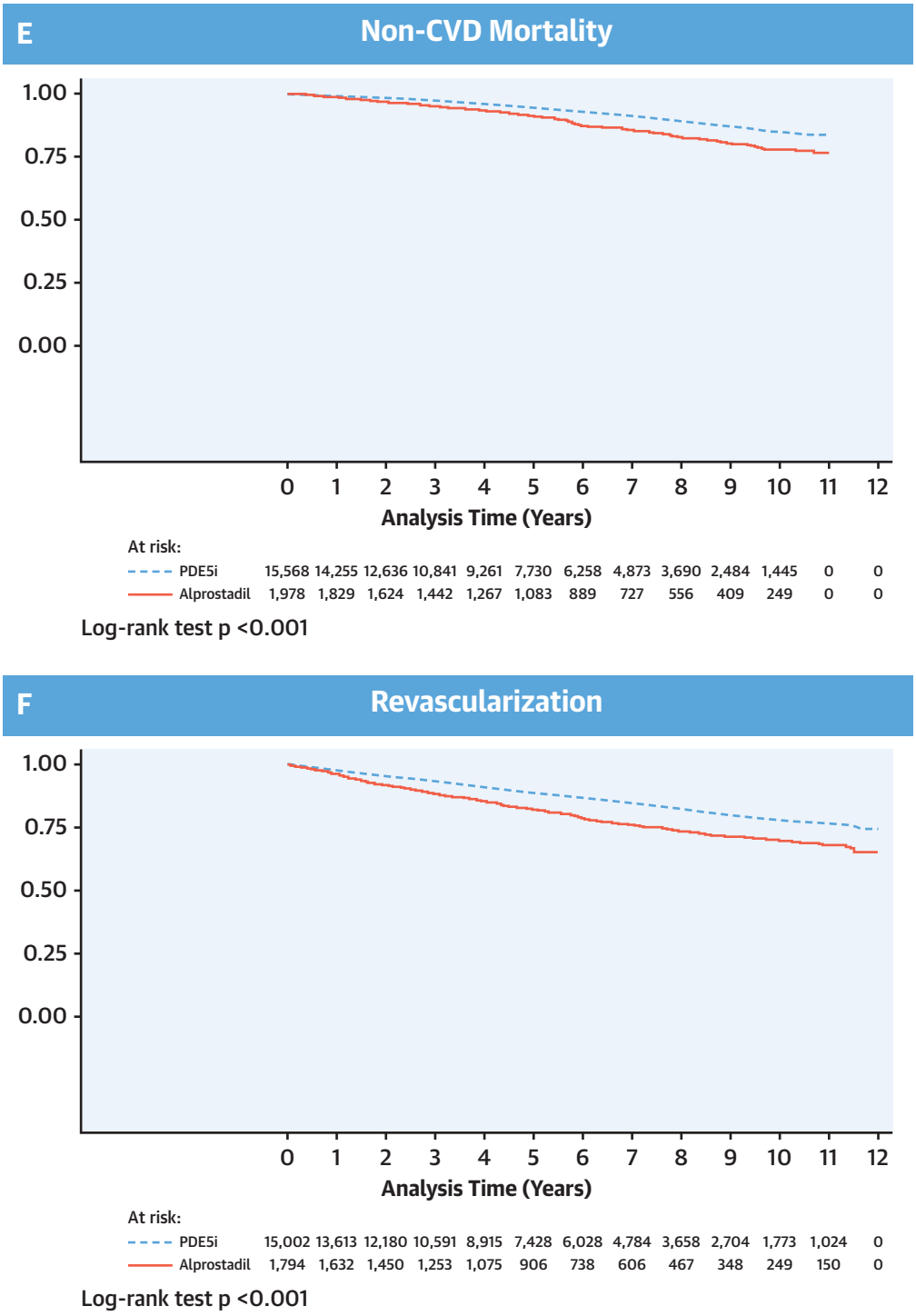

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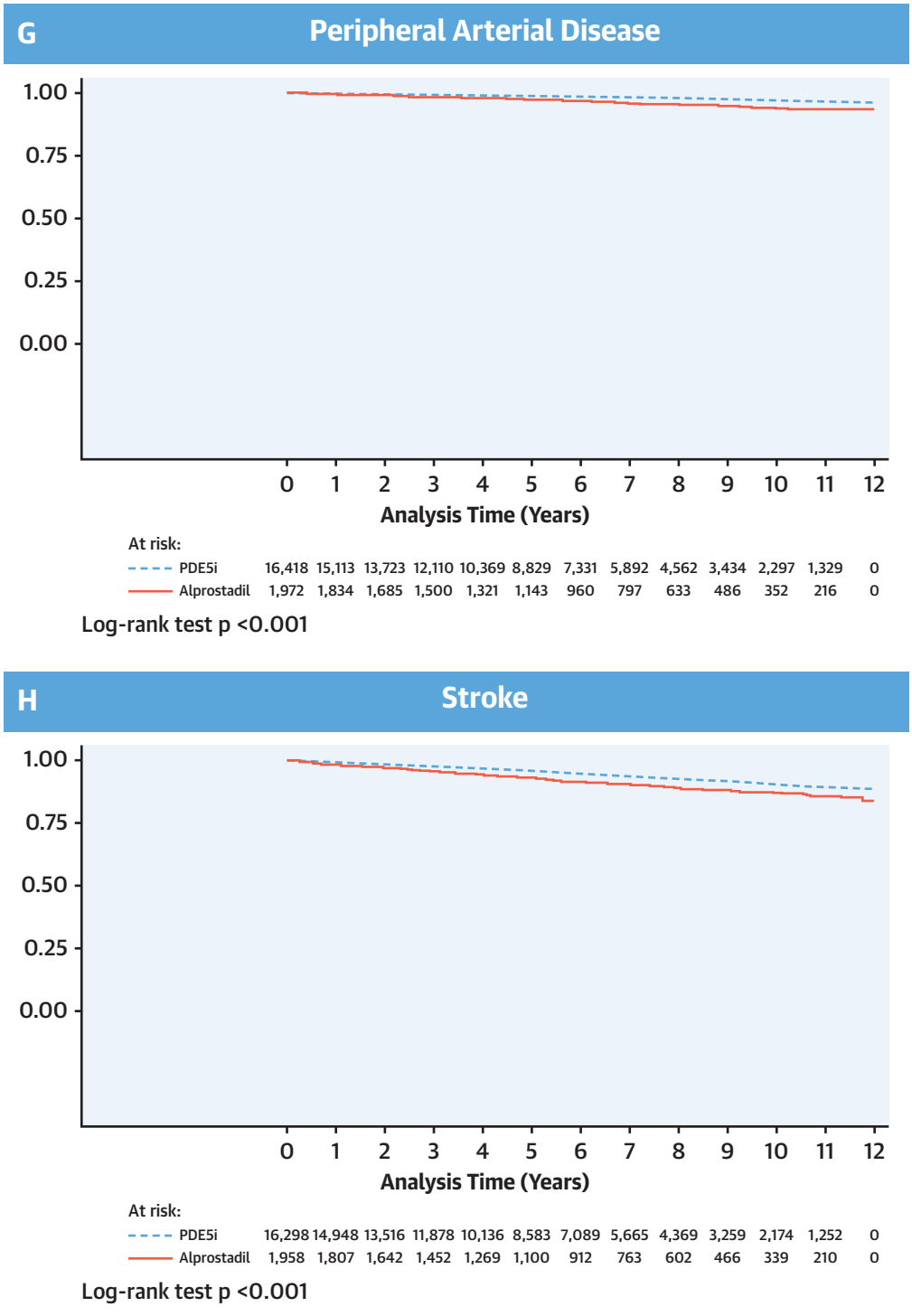


TABLE 3 HRs With 95% CIs for Cardiovascular and Noncardiovascular Mortality, Revascularization, Peripheral Arterial Disease, and Stroke in Men Treated With PDE5i Compared With Men Treated With Alprostadil

	PDE5i	Alprostadil
Cardiovascular mortality	15,568	1,978
Deaths	790 (5.1)	209 (10.6)
Incidence rate, cases/100 person-years	0.97 (0.91-1.04)	1.89 (1.65-2.16)
Unadjusted HR	0.53 (0.45-0.61)	Referent
Adjusted for age	0.61 (0.52-0.71)	Referent
Multivariable adjusted*	0.83 (0.70-0.98)	Referent
Noncardiovascular death	15,568	1,978
Deaths	1,073 (6.9)	242 (12.2)
Incidence rate, cases/100 person-years	1.32 (1.24-1.40)	2.19 (1.93-2.48)
Unadjusted HR	0.62 (0.54-0.71)	Referent
Adjusted for age	0.72 (0.62-0.82)	Referent
Multivariable adjusted*	0.92 (0.79-1.07)	Referent
Revascularization	15,002	1,794
Events	1,971 (13.1)	374 (20.8)
Incidence rate, cases/100 person-years	2.46 (2.35-2.57)	3.82 (3.46-4.23)
Unadjusted HR	0.64 (0.58-0.72)	Referent
Adjusted for age	0.61 (0.55-0.68)	Referent
Multivariable adjusted*	0.69 (0.62-0.78)	Referent
Peripheral arterial disease	16,418	1,972
Events	272 (1.7)	69 (3.4)
Incidence rate, cases/100 person-years	0.29 (0.26-0.33)	0.58 (0.46-0.73)
Unadjusted HR	0.51 (0.39-0.67)	Referent
Adjusted for age	0.53 (0.41-0.69)	Referent
Multivariable adjusted*	0.77 (0.58-1.02)	Referent
Stroke	16,298	1,958
Events	852 (5.2)	166 (8.5)
Incidence rate, cases/100 person-years	0.94 (0.88-1.00)	1.44 (1.24-1.68)
Unadjusted HR	0.66 (0.56-0.77)	Referent
Adjusted for age	0.75 (0.63-0.89)	Referent
Multivariable adjusted*	0.86 (0.72-1.03)	Referent

Values are n, n (%), hazard ratio (HR) (95% confidence interval [CI]), or incidence rate (95% CI), unless otherwise indicated. *Adjusted for all variables in Table 1.

Abbreviations as in Table 2.

of cardiovascular and noncardiovascular death is shown in Figures 2D and 2E.

During a mean follow-up of 5.4 years, 374 (21%) and 1,971 (13.1%) men underwent revascularization in the alprostadil and PDE5i groups, respectively. Men in the PDE5i group had a 31% lower risk of undergoing revascularization during follow-up compared with men in the alprostadil group (HR: 0.69; 95% CI: 0.62 to 0.78). Survival free of revascularization is shown in Figure 2F.

The risks for PAD and stroke were not lower in men using PDE5i compared with alprostadil (Table 3). Survival free of PAD and stroke is shown in Figures 2G and 2H, respectively.

In the Central Illustration, a forest plot illustrates HRs with 95% CIs comparing PDE5i with alprostadil.

ASSOCIATION BETWEEN THE NUMBER OF FILLED PRESCRIPTIONS AND ALL-CAUSE MORTALITY, NONCARDIOVASCULAR MORTALITY, CARDIOVASCULAR MORTALITY, MI, HEART FAILURE, AND REVASCULARIZATION. When quintiles (q) of filled PDE5i prescriptions were compared using q1, which had the fewest filled prescriptions, as reference, men in q3, q4, and q5 had a 16%, 25%, and 27% lower adjusted risk for death, respectively, compared with men in q1 (adjusted HR: 0.84 [95% CI: 0.74 to 0.96]; adjusted HR: 0.75 [95% CI: 0.66 to 0.85]; and adjusted HR: 0.73 [95% CI: 0.63 to 0.84], respectively). Similarly, men using alprostadil had a lower risk of death in q5 compared to q1. PDE5i users had lower risks for noncardiovascular mortality in q4 and q5 compared to q1. Cardiovascular mortality was associated only with category q4 among PDE5i users and q5 among alprostadil users. There was no association with quintiles of use of either medicine for the outcome MI and heart failure. Men using PDE5i in q2 had lower risks for undergoing revascularization during follow-up compared with men in q1 (Table 4).

AGE-STRATIFIED ANALYSES. Men ages 60 to 69 years and treated with PDE5i had a lower mortality compared with men of similar ages treated with alprostadil (adjusted HR: 0.81; 95% CI: 0.69 to 0.95). This was not seen for men >70 years of age (Supplemental Table 3).

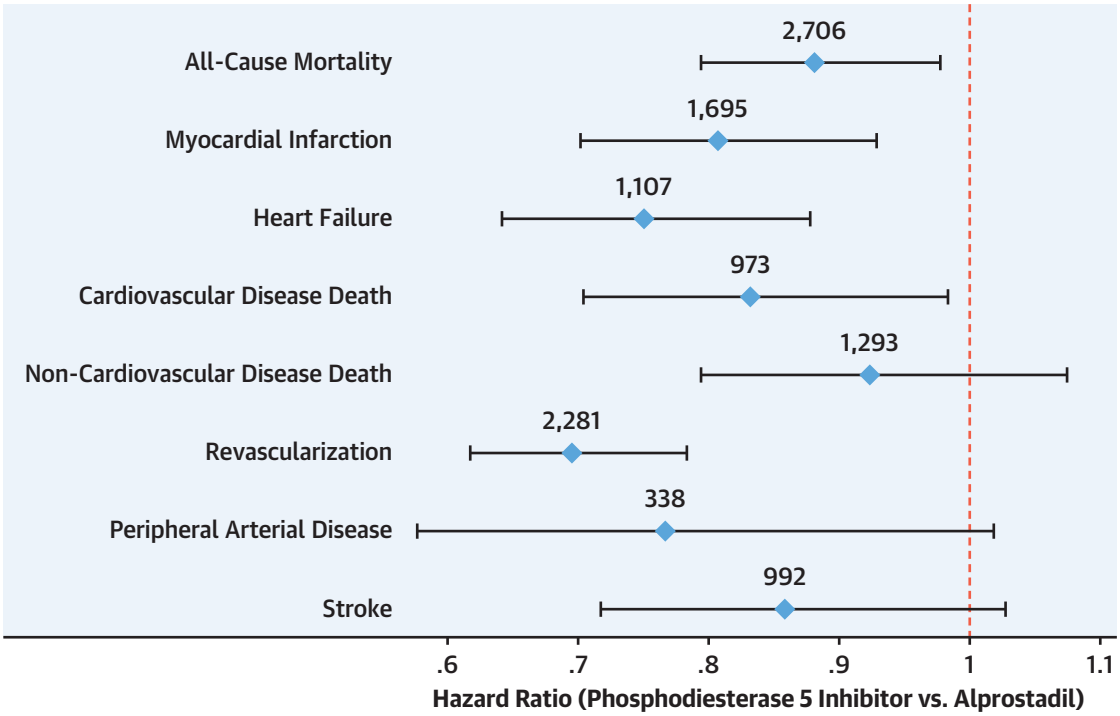
Only men between the ages of 60 and 69 years as well as 70 to 80 years were found to benefit from PDE5i and risk of hospitalization for heart failure during follow-up, with HRs (95% CIs) of 0.74 (0.58 to 0.94) and 0.78 (0.61 to 0.99), respectively. Only men >70 years of age had a significantly lower risk of MI (adjusted HR: 0.61; 95% CI: 0.48 to 0.78) if they were treated with PDE5i compared with alprostadil (Supplemental Table 3).

The lower mortality was found to be significant only for noncardiovascular deaths in men between 60 and 69 years (adjusted HR: 0.77; 95% CI: 0.62 to 0.97) (Supplemental Table 4).

There were 447 men older than 80 years, of whom 87 used alprostadil and 360 used PDE5i. There was no association between PDE5i and mortality in this age group. The adjusted HR for all-cause mortality among men using PDE5i versus alprostadil was 1.11 (95% CI: 0.80 to 1.54).

RISK IN DIFFERENT RISK CATEGORIES. There were few patients in the risk categories >2 (n = 489). Therefore, we decided to analyze data in 2 subgroups: those with a score of 0 to 2 and those with a score of >2. The adjusted HR for all-cause mortality was 0.83

CENTRAL ILLUSTRATION **Summary of the Study Results**



Andersson, D.P. et al. J Am Coll Cardiol. 2021;77(12):1535–50.

Forest plot showing multiple adjusted hazard ratios with 95% confidence intervals and number of events comparing phosphodiesterase 5 inhibitor treatment with alprostadil in men with stable coronary artery disease for the outcomes all-cause mortality, myocardial infarction, heart failure, cardiovascular disease mortality, noncardiovascular mortality, revascularization, peripheral arterial disease, and stroke. Hazard ratio below 1.0 indicates a benefit for phosphodiesterase 5 inhibitor treatment over alprostadil. Number of events refers to the multivariable-adjusted models.

(95% CI: 0.69 to 1.00) among men with 0 to 2 risk factors who were using PDE5i compared to alprostadil users.

INTERACTIONS. We found a significant ($p = 0.038$) interaction between ED medication and beta blockers in the all-cause mortality analysis and between ED medication and ACE inhibitors in the MI analysis ($p = 0.008$), with a significant ED medication effect only among men who were using beta-blockers or ACE inhibitors. Moreover, we found a significant ($p = 0.036$) interaction between ED medication and ACE inhibitors in the noncardiovascular disease mortality analysis as well as a significant interaction between ED medication and both the use of nitrates and of CCB ($p = 0.007$ and 0.011, respectively) in the PAD analysis, with a significant ED medication effect only among men who were not medication users. When analyzing the subgroup of individuals free of nitrates or CCB, we found a significant inverse association (adjusted HR: 0.53; 95% CI: 0.37 to 0.75) between PDE5i treatment and PAD. By contrast, in individuals taking both nitrates and CCB, the use of PDE5i was associated with an increased HR (adjusted HR: 7.85; 95% CI: 1.55 to 39.80). However, there were only 17 cases out of 459 individuals in this subgroup, which is reflected in the wide confidence interval. A marginally statistically significant ($p = 0.045$) interaction was found between the use of ED medication and the use of nitrates in the heart failure analysis.

PERSISTENCE IN USE OF COMEDICATION AND CHANGE OF PDE5i AND ALPROSTADIL USE OVER TIME. One year after the index date, 96% of beta-blocker users, 96% of statin users, 97% of ACE inhibitor/ARB users, 93% of thiazide users, 94% of CCB users, 97% of platelet users, 61% of opioid users, 83% of selective serotonin reuptake inhibitors users, 72% of neuroleptics users, and 42% of nitrate users were still prescribed the medicine they had been prescribed at the index date. The percentage and

TABLE 4 Outcomes in Relation to Frequency of Use of PDE5i and Alprostadil

	Quintiles				
	1	2	3	4	5
Number of daily doses PDE5i	4 ± 1	10 ± 2	21 ± 5	58 ± 20	340 ± 425
Number of daily doses alprostadil	3 ± 2	10 ± 3	24 ± 4	57 ± 16	319 ± 419
All-cause mortality					
PDE5i					
Number of cases	623	546	391	396	305
Incidence rate, cases/100 PY	3.66 (3.38-3.96)	3.21 (2.96-3.50)	2.44 (2.21-2.70)	1.89 (1.71-2.09)	1.30 (1.16-1.45)
Adjusted* HR (95% CI)	Referent	0.97 (0.87-1.10)	0.84 (0.74-0.96)	0.75 (0.66-0.85)	0.73 (0.63-0.84)
Alprostadil					
Number of cases	86	142	104	101	88
Incidence rate, cases/100 PY	5.37 (4.35-6.63)	5.16 (4.38-6.08)	4.86 (4.01-5.89)	3.94 (3.24-4.79)	2.76 (2.24-3.40)
Adjusted* HR (95% CI)	Referent	0.98 (0.74-1.29)	0.94 (0.70-1.27)	0.76 (0.56-1.02)	0.67 (0.49-0.91)
Noncardiovascular mortality					
PDE5i					
Number of cases	250	197	298	181	147
Incidence rate, cases/100 PY	1.89 (1.67-2.13)	1.88 (1.63-2.16)	1.51 (1.35-1.69)	1.06 (0.92-1.23)	0.71 (0.61-0.84)
Adjusted* HR (95% CI)	Referent	1.06 (0.88-1.28)	0.95 (0.80-1.13)	0.81 (0.67-0.99)	0.74 (0.60-0.92)
Alprostadil					
Number of cases	39	68	51	40	44
Incidence rate, cases/100 PY	2.71 (1.98-3.70)	2.87 (2.26-3.64)	2.46 (1.87-3.24)	1.72 (1.26-2.34)	1.54 (1.15-2.07)
Adjusted* HR (95% CI)	Referent	1.08 (0.72-1.62)	0.92 (0.60-1.42)	0.67 (0.43-1.06)	0.75 (0.48-1.17)
Cardiovascular mortality					
PDE5i					
Number of cases	204	138	202	127	119
Incidence rate, cases/100 PY	1.54 (1.34-1.77)	1.32 (1.11-1.56)	1.02 (0.89-1.17)	0.75 (0.63-0.89)	0.58 (0.48-0.69)
Adjusted* HR (95% CI)	Referent	0.92 (0.74-1.15)	0.88 (0.72-1.07)	0.79 (0.63-0.99)	0.83 (0.65-1.05)
Alprostadil					
Number of cases	34	49	54	41	31
Incidence rate, cases/100 PY	2.36 (1.69-3.30)	2.07 (1.56-2.73)	2.61 (2.00-3.41)	1.76 (1.30-2.39)	1.09 (0.76-1.55)
Adjusted* HR (95% CI)	Referent	0.87 (0.55-1.37)	1.12 (0.72-1.76)	0.78 (0.49-1.25)	0.56 (0.33-0.93)
MI					
PDE5i					
Number of MIs	316	221	428	295	218
Incidence rate, cases/100 PY	2.31 (2.06-2.58)	2.04 (1.79-2.32)	2.05 (1.86-2.25)	1.58 (1.41-1.77)	1.00 (0.88-1.15)
Adjusted* HR (95% CI)	Referent	0.89 (0.75-1.07)	0.96 (0.83-1.11)	0.96 (0.75-1.05)	0.90 (0.75-1.08)
Alprostadil					
Number of MIs	49	69	52	55	51
Incidence rate, cases/100 PY	3.36 (2.54-4.46)	2.91 (2.30-3.69)	2.62 (2.00-3.44)	2.44 (1.87-3.18)	1.83 (1.39-2.41)
Adjusted* HR (95% CI)	Referent	0.96 (0.66-1.40)	0.82 (0.55-1.23)	0.88 (0.59-1.32)	0.99 (0.65-1.50)

Continued on the next page

number of filled prescriptions of PDE5i and alprostadil for each year are depicted in Supplemental Table 5.

PROPENSITY SCORE MATCHING ANALYSIS. To assess the robustness of our findings, we performed a propensity score matching analysis. For each outcome specific analysis, we were able to match more than 80% of the alprostadil individuals with at least 1 individual treated with PDE5i. Propensity score models performed well in balancing baseline characteristics among alprostadil and PDE5i users. Indeed, when repeating the analysis for each outcome, standardized differences showed residual unbalances only for nitrates usage and cancer prevalence (see Supplemental Table 6 for all-cause mortality analysis); therefore, we further adjusted only for these 2 variables in the Cox model run on the new cohorts. The results were similar to those in the main analyses (Supplemental Table 7).

DISCUSSION

In a nationwide observational cohort study, we included 18,542 men with stable CAD who were treated with either PDE5i or alprostadil and compared the 2 treatments for long-term outcomes. Men with PDE5i treatment had lower long-term risk of all-cause and cardiovascular mortality, MI, heart failure, and

TABLE 4 Continued

	Quintiles				
	1	2	3	4	5
Heart failure					
PDE5i					
Number of cases	249	202	142	176	130
Incidence rate, cases/100 PY	1.54 (1.36–1.74)	1.24 (1.08–1,43)	0.92 (0.78–1.08)	0.89 (0.7–1.03)	0.56 (0.47–0.66)
Adjusted* HR (95% CI)	Referent	0.96 (0.79–1.16)	0.81 (0.65–1.00)	0.95 (0.77–1.16)	0.93 (0.74–1.17)
Alprostadil					
Number of cases	39	67	43	46	43
Incidence rate, cases/100 PY	2.64 (1.93–3.61)	2.64 (2.08–3.36)–	2.14 (1.59–2.89)	1.92 (1.43–2.56)	1.45 (1.07–1.95)
Adjusted* HR (95% CI)	Referent	0.92 (0.51–1.38)	0.81 (0.51–1.27)	0.87 (0.56–1.36)	0.93 (0.58–1.47)
Revascularization					
PDE5i					
Number of revascularizations	413	259	579	407	313
Incidence rate, cases/100 PY	3.23 (2.93–3.55)	2.60 (2.30–2.94)	2.98 (2.75–3.23)	2.30 (2.08–2.53)	1.55 (1.39–1.73)
Adjusted* HR (95% CI)	Referent	0.80 (0.68–0.94)	0.96 (0.84–1.09)	0.87 (0.76–1.01)	0.95 (0.81–1.11)
Alprostadil					
Number of revascularizations	48	95	78	74	79
Incidence rate, cases/100 PY	3.42 (2.58–4.54)	4.61 (3.77–5.64)	4.25 (4.30–5.31)	3.69 (2.94–4.63)	3.19 (2.56–3.98)
Adjusted* HR (95% CI)	Referent	1.41 (0.99–2.01)	1.23 (0.85–1.78)	1.28 (0.88–1.86)	1.65 (1.13–2.40)

Values are mean ± SD or incidence rate (95% CI), unless otherwise indicated. *Adjusted for all variables in Table 1.
MI = myocardial infarction; PY = person-years; other abbreviations as in Table 2.

cardiac revascularization after adjustment for potential confounders, including marital status and length of education. To our knowledge, this is the largest study investigating the association between the use of ED medication and long-term outcomes.

In 2 previous studies, 1 in men with type 2 diabetes (7) and 1 in men with a first MI (8), those who were treated with PDE5i were compared with men who were not treated with PDE5i for long-term outcomes. Both studies found lower mortality risk in men with PDE5i treatment. One study (8) also found a lower risk of heart failure in men with PDE5i treatment. The main limitation of these studies was that men treated with PDE5i were compared with men who were not treated with ED medication at all. This may have introduced confounding by indication, meaning that there may have been reasons unknown to the investigators for not treating the untreated men. In another study of men with type 2 diabetes and established CAD, among whom 41% had ED, patients who experienced major adverse cardiac events (MACE) during follow-up were less likely to be treated, not only with PDE5i, but also with statins (15). Thus, the lower risk of MACE in men with PDE5i may well have been associated with a more frequent use of statins rather than the potential positive cardiovascular effects of PDE5i. Additionally, none of these studies considered socioeconomic status, which is associated with PDE5i use, life expectancy, and risk of cardiovascular events (16,17).

Contrary to our previous study (8), we now included only men who were treated with ED medication to minimize the risk of bias. We compared 2 treatments for ED: PDE5i, which is taken orally, and alprostadil, which is used locally. To be able to understand which drug was responsible for the effect, patients were included only if they used either PDE5i or alprostadil. Thus, there was no mixed group. Additionally, we enriched our dataset with information from Statistics Sweden about length of education and marital status. After adjustment for various potential confounders, associations between PDE5i use and all outcomes were significant with a 12% lower risk of death, 19% lower risk of MI, and 25% lower risk of heart failure. Interestingly, the strongest association was found for revascularization, with a 31% lower risk for men using PDE5i, an association that was not found in our previous study (8). This may be explained by differences in the study populations because all individuals in our previous study were included at the time of their first MI.

ED is an established predictor for future cardiovascular events among healthy men (18). However, a recent nationwide Danish study found that men who were treated with PDE5i had a lower risk of cardiovascular events than the general male population (6). Interestingly, in a Dutch study, the higher incidence of CAD in men with ED was no longer significant 2 years after the introduction of sildenafil (19). In the same study, the prevalence of CAD in men with ED

who sought medical help after the introduction of sildenafil was lower, whereas the number of men consulting general practitioners for ED doubled.

The beneficial effects of PDE5i on the cardiovascular system are also supported by numerous animal and human studies showing a sustained improvement of hemodynamical parameters including arterial stiffness, flow-mediated dilation, and peak systolic velocity, even after discontinuation (20–23). Moreover, individuals treated with PDE5i tend to have lower inflammatory markers, including C-reactive protein and interleukin 6 and more endothelial progenitor cells, which is associated with a reduced risk of MACE. It has also been suggested that the effects of PDE5i may be due to a reduction in arterial stiffness that, in turn, leads to a decrease in vascular aging (24). Additionally, patients with diabetes who are treated with PDE5i have lower mean levels of microalbuminuria (25).

STUDY STRENGTHS. The main strength of our study was the large number of men included, which allowed us to perform analyses in relevant subgroups. Furthermore, by using nationwide health care registers and information from Statistics Sweden, we could characterize patients on a detailed level, which allowed us to adjust for differences between the 2 groups. Information about exposure and outcomes was collected from nationwide registers that are complete for the whole country, so there was no loss to follow-up. Furthermore, we believe that the external validity of our findings is high and may be generalized to other countries and health care systems similar to the Swedish one.

STUDY LIMITATIONS. Our cohort was a high-risk cohort for cardiovascular events. Therefore, our results should not be extrapolated to the general population. The main limitation was the risk of confounding by indication, which may have led to a more pronounced association between treatment with PDE5i versus alprostadil and risk of cardiovascular events. Indeed, men in the alprostadil group were slightly older and, more importantly, had more comorbidities. Moreover, we lacked information about some risk factors that are associated with ED and cardiovascular disease, like body mass index, smoking, physical activity, and fitness. However, we had information on proxies, such as length of education and marital status, which are related to lifestyle factors including physical activity, body mass index, and smoking status.

Because PDE5i and alprostadil are used on demand, we did not know the exact amount patients were taking on a weekly basis or how they were using the ED medication. Therefore, we were not able to calculate risks in relation to exact dosage. However, when PDE5i use was analyzed in quintiles, there was an association between the frequency of how often a patient had a PDE5i dispensed and the risk for death, heart failure, and revascularization. The highest quintile of alprostadil use was also associated with a lower risk for all-cause and cardiovascular mortality compared to the lowest quintile. The associations found both for the use of alprostadil and PDE5i indicate that there may be other factors than the ED medications that are responsible for the lower risk found. It may indicate that sexual activity, or ability, or willingness to perform sex is beneficial—or simply that men who have an active sex life are healthier, more active, and more health conscious and more often have a partner to share their life with, all factors that may promote longevity.

Additionally, we did not adjust for changes in medication during follow-up, which may have been associated with outcome and choice of ED medication. However, because we included only men with stable CAD and none with an acute event, it is likely that medication was stable between baseline and follow-up. Indeed, we found virtually no change in medication use at 1 year of follow-up.

Residual confounding is an inherent problem in every observational cohort study, but it is unlikely that any single confounder or group of confounders would nullify the associations we found. Associations found in observational studies should always be interpreted cautiously and never as causal. However, 2 findings in our study increase the likelihood of a causal association between PDE5i treatment and a lower risk of cardiovascular events. First, the association was dose dependent. Second, the strongest effect for PDE5i treatment on mortality seemed to be in younger men, the age group that is most commonly affected by atherosclerosis-associated ED, which is in line with previous studies (25).

We had no information on sexual activity. Therefore, we are not able to separate the effect of PDE5i and alprostadil from that of frequent sexual activity for the inverse association with cardiovascular disease and death. There were only 26 patients with pulmonary hypertension in the cohort, all of them in the PDE5i group. We did not exclude them because it was unlikely that this small number of patients would bias our results. Furthermore, we had no information on the side effects of alprostadil or PDE5i treatment, which may have affected how these medications were used.

CONCLUSIONS

In a cohort of 18,542 men with stable CAD who were treated with either PDE5i or alprostadil, men using PDE5i had a lower long-term risk of death, MI, heart failure, and revascularization compared with men using alprostadil. The lower risk of death was dose dependent and stronger among younger than older men. PDE5i use is associated with a better prognosis in men with stable CAD. Randomized controlled trials are needed to determine if this is a causal effect because of the pharmacodynamic effects of PDE5i or merely a marker for better socioeconomic status and compliance, younger age, fewer comorbidities, and a healthier lifestyle.

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ADDRESS FOR CORRESPONDENCE: Dr. Martin J. Holzmann, Department of Emergency Medicine, Karolinska University Hospital, Huddinge, Stockholm, Sweden, Sweden. E-mail: martin.holzmann@sll.se. Twitter: @karolinskainst.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: Phosphodiesterase-5 inhibitors are associated with reduced mortality in patients with stable ischemic heart disease as well as those with recent myocardial infarction.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to clarify the effect of phosphodiesterase-5 inhibitors on the risks of death and recurrent cardiovascular events in patients with stable coronary artery disease.

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KEY WORDS cardiovascular disease, coronary artery disease, phosphodiesterase 5 inhibitors, mortality, risk

APPENDIX For supplemental tables, please see the online version of this paper.