Long-term Effects of Phosphodiesterase-5 Inhibitors on Cardiovascular Outcomes and Death: A Systematic Review and Meta-analysis

Stergios Soulaidopoulos*[1], Dimitrios Terentes-Printzios*[1], Nikolaos Ioakeimidis[1], Konstantinos P. Tsioufis[1], Charalambos Vlachopoulos[1]

*Shared first authorship

Affiliations:

[1]First Cardiology Department, Hippokration Hospital, Athens Medical School, National and Kapodistrian University of Athens, Greece

Address for Correspondence:

Charalambos Vlachopoulos
First Department of Cardiology,
Hippokration Hospital, Medical School,
National and Kapodistrian University of Athens,
Profiti Elia 24, Athens 14575, Greece
Tel.: +30 6932528561, Fax.: +30 2132088676
E-mail address: cvlachop@otenet.gr

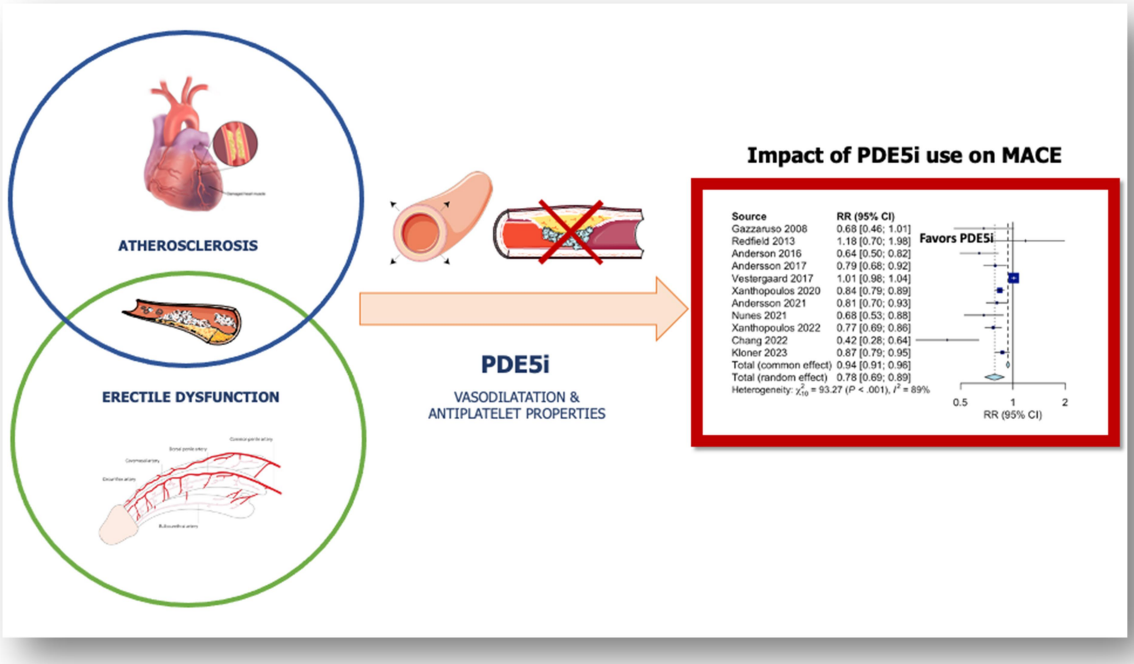
Abstract

Background and Aims: Phosphodiesterase 5 inhibitors (PDE-5i), which are widely used for the treatment of erectile dysfunction (ED), have been found to exhibit systemic vascular benefits by improving endothelial function. In this context, we sought to evaluate the effects of PDE5i on long-term cardiovascular outcomes and mortality. **Methods:** A comprehensive search of electronic databases was conducted up to May 30, 2023. Cohort studies comparing PDE5i treatment at any dose with other ED treatment, placebo or no treatment and minimum follow-up duration of 6 months were considered eligible. The primary endpoints were: (1) major adverse cardiovascular events (MACE) and (2) all-cause mortality. Pooled risk ratios (RR) with 95% confidence intervals (CI) were calculated. **Results:** Sixteen studies were included (1,257,759 subjects – 10.5% treated with PDE5i). The majority of patients (99.4%) were men[median age 61.5 years (range 30 – 72.8)]. The median follow-up duration was 4.3 years (range 6 months – 7.5 years). PDE5i use was associated with a significant reduction in the composite of MACE (RR 0.78, 95% CI 0.69-0.89). Moreover, the analysis of pooled data from 13 studies, demonstrated that the use of PDE5i was associated with a significantly lower risk of all-cause mortality (RR 0.70, 95% CI 0.56-0.87). **Conclusions:** The use of PDE5i primarily in men with or without known coronary artery disease was associated with a lower risk for cardiovascular events and overall mortality. This information underlines that PDE5i could provide clinical benefit beyond ED treatment and could instigate the conduction of further, large-scale randomized clinical trials.

Keywords

Erectile dysfunction, phosphodiesterase 5 inhibitors, coronary artery disease, cardiovascular disease, mortality, sildenafil

Structured Graphical Abstract



Key Question

What are the effects of phosphodisesterase-5 inhibitors (PDE5i) on hard cardiovascular endpoints and overall mortality?

Key Finding

Over a median follow-up period of 4.3 years, this pooled analysis of 16 studies demonstrated that the risk of major adverse cardiovascular events and all-cause mortality was reduced by 22% and 30%, respectively, in patients exposed to PDEi compared to controls.

Take-home Message

The use of PDE5i provides important clinical benefits that extend beyond erectile dysfunction and include cardioprotective effects and improved AMI, acute myocardial infarction; survival.

Impact of phosphodiesterase 5 inhibitors on major adverse cardiovascular events. PDE, phosphodisesterase-5 inhibitors; MACE, major adverse cardiovascular events.

Introduction

Phosphodiesterase 5 inhibitors (PDE5i) constitute a milestone in the treatment of erectile dysfunction (ED). In fact, these drugs were originally developed in the late of 1980s for the relief of angina pectoris, with early trials eventually revealing their positive effect on penile erection[1]. Following the revolution they brought on the field, signaled by the introduction of sildenafil on the market in 1998, the administration of PDE5i was limited for many years to men suffering from ED. Nevertheless, the increasing experience from PDE5i use in ED along with a deeper understanding of cyclic guanosine monophosphate (cGMP)-regulated mechanisms, gradually stimulated the scientific interest for further potential applications of these therapeutic agents. In respect to their mechanism of action, PDE5i work by selectively inhibiting the degradation of cGMP signaling in vascular smooth muscle cells, thereby enhancing nitric-oxide (NO) availability which promotes vascular dilatation[2]. Apart from their recognized effectiveness in treating ED, PDE5i were found to ameliorate pulmonary vascular resistance and improve several clinical variables in large clinical studies by augmenting NO-mediated vasodilation in the lungs, a finding that led in 2005 to the approval of sildenafil for the treatment of pulmonary arterial hypertension[3].

Over the last two decades, initial safety concerns have given their place to a growing impression that the use of PDE5i may exhibit several cardiovascular benefits[45]. Starting from animal experimental models, PDE5i were found to attenuate ischemia - reperfusion myocardial injury and reduce arrhythmia burden, supporting a cardioprotective potential of PDE5i [6–8]. In human studies, through a combination of direct actions on myocardial tissue and favorable effects on both systemic and pulmonary hemodynamics, PDE5i seem to

substantially improve myocardial contractility and clinical variables in patients with systolic heart failure[9,1011]. In the same direction, PDE5i of patients have been shown to reduce pro-inflammatory mediators and improve markers of vascular aging in patients with ED[1213]. Recently, though, attention has shifted to the effect of PDE5i on hard cardiovascular endpoints. In particular, accumulating epidemiological data suggest that PDE5i use are probably associated with a lower long-term risk of death and cardiovascular events. These data gain more interest by the fact that they mainly concern patients with ED, which is an established predictor for the development of cardiovascular disease [1415]. Nevertheless, not all studies on this field yielded consistent results, while significant diversities in study designs, comparators, drug dosages and populations exist. Thus, the absolute effect of PDE5i administration on cardiovascular outcomes and death remains still unclear.

Within this framework, the present systematic review and meta-analysis was conducted with the intention to provide an overview of relevant studies and to examine whether and to which extent treatment with PDE5i is associated with a reduction in cardiovascular events and mortality.

Methods

This systematic review and meta-analysis study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[16]. The research protocol for this meta-analysis was prospectively registered in the PROSPERO international database (ID: 322288).

Outcomes

The primary outcomes of interest of this meta-analysis were the following: (i) total number of major adverse cardiovascular events, including cardiovascular death and nonfatal

cardiovascular events (myocardial infarction, ischemic stroke, revascularization, hospitalization for heart failure, pump thrombosis); and (ii) all-cause mortality. Secondary outcomes were incidence of i) myocardial infarction and ii) heart failure.

Search strategy and selection criteria

A literature search took place in 2 major databases (PubMed/MEDLINE, Embase) from inception to May 30, 2023 and was restricted to articles published in English. A basic search string using a combination of free text terms and relevant Medical Subject Headings (MeSH) was developed for PubMed and modified accordingly for the other search engines (Supplementary Material 1). Randomized controlled trials or case-control observational studies evaluating the impact of treatment with PDE5i on hard cardiovascular endpoints and all-cause mortality over a minimum follow-up period of 6 months were considered eligible. Reference lists of the retrieved articles were also screened in order to detect other potentially missed relevant literature. Abstract books of relevant international meetings available online were searched, as well as ClinicalTrials.gov for ongoing relevant studies. We excluded cohort studies not using control groups, studies with a follow-up duration less than 6 months and those assessing the effect of PDE5i on different outcomes from those defined in our protocol.

Study Selection and Data Extraction

All retrieved studies were imported into a reference manager software for duplicate removal. Papers were screened by two independent authors (SS, DTP) for the fulfillment of the inclusion criteria, initially at a title and an abstract level and subsequently by full-text screening of potentially relevant articles. The required data from eligible studies were extracted into a data extraction form, designed according to the Cochrane checklist of items (PICO - Patients, Interventions, Comparisons, Results). All disagreements were resolved by

consensus. Numerical data appearing in the selected articles were used. For each of the outcomes of the meta-analysis, adjusted and unadjusted estimates of treatment effects with the 95% Confidence Intervals (95% CI) as reported in the eligible studies were obtained.

Study quality assessment

The quality of the included observational studies was evaluated with the Newcastle-Ottawa assessment Scale (NOS) for cohort studies[17]. The NOS rating system is based on the evaluation of eight quality parameters, which are categorized into three main domains: 1) selection of study groups, 2) comparability of groups and 3) outcome measurements. The maximum score for each study is 9, with studies scoring less than 5, being considered to exhibit a high risk of bias. The results of the quality assessment of the included studies, except for the RELAX trial which was the only randomized controlled trial, are presented in Table 2.

Statistical analysis

The summary effects of PDE5i treatment on the endpoints were estimated. The risk ratios (RRs) with 95% CI were initially calculated for individual studies and pooled according to the inverse variance model in order to estimate study weights. A random-effects metanalytic model was selected to obtain pooled estimates of treatment effect with the 95% CIs on each of the following outcomes: 1) major cardiovascular events; 2) all-cause mortality; 3) myocardial infarction; 4) heart failure. A separate analysis using the multi-adjusted RRs for each outcome, where applicable, was accordingly performed. Risk estimates reported as hazard ratios, were treated as RRs. A prespecified subgroup analysis was performed for patients with a history of coronary artery disease (CAD). To quantify heterogeneity across studies, the statistical inconsistency test I^2 was calculated. The RRs and

95% CIs of individual studies were illustrated with forest plots. The existence of potential publication bias was graphically investigated by funnel plots. A two-tailed p value of < 0.05 was considered significant. All analyses were performed using the "meta" and "metaphor" packages in the R Project for Statistical Computing (version 3.6.3).

Results

Study selection

The combined search of two large databases yielded 1391 unique publications. The preliminary review performed at a title/abstract level identified 36 potentially relevant articles, which were further screened at full-text for eligibility. Of these, 1346 articles were excluded because of absence of a control group (n=1)[18], duration of follow-up less than 6 months and assessment of endpoints other than cardiovascular events or death, including the effect of PDE5i on surrogate markers of endothelial dysfunction (n=19). Between 2 publications reporting results for the same cohort at different time points, we selected the one with the longest follow-up period. A recent study by Lagerros et al.[19], showing greater overall risk of all-cause mortality (HR: 1.39) as well as higher risk of MACE (HR: 1.70) in patients receiving both nitrate and PDE5i medications, was not included in our analysis since this was published after the end of our literature search and it would be anyhow rejected since the population used overlapped with 2 other relevant studies already included in our analysis[20, 21]. Owing to a short follow-up period, a study conducted by Holt et al. concluding that there is neither harm nor benefit from the concomitant use of nitrates and PDE5i, was also deemed ineligible for our analysis[22]. Sixteen studies evaluating the long-term effects of PDE5i treatment on either cardiovascular outcomes and/or cumulative mortality were ultimately included in the systematic review and in quantitative analysis [19-34]. Given that only studies with hard cardiovascular endpoints, particularly all-cause mortality, were considered eligible,

we did not include pulmonary hypertension trials in this analysis. The PRISMA flow diagram of study selection is depicted in Supplemental Figure 1 of the Supplementary Material 1. The indication for PDE5i use across the studies included in the analysis is demonstrated in Supplemental Table 1.

Characteristics of the included studies

The 16 studies that were selected for the quantitative analysis included a total of 1,257,759 subjects, of whom 132,805 (10.5%) received PDE5i. Regarding their design, twelve of these studies were retrospective studies utilizing health record data to identify patients being prescribed PDE5i [20-22, 24–27, 30-34], while one study retrospectively evaluated follow-up data from 857 diabetic patients that had previously been included in a randomized clinical trial [32]. Among the eligible studies, there were two prospective observational studies: one aiming to identify predictors of cardiovascular events among 291 diabetic patients with silent coronary artery disease[23] and another examining the association between PDE5i use and outcomes in patients with contemporary centrifugal flow LVADs [36]. The RELAX trial, a randomized controlled study evaluating the effect of sildenafil administration for 24 weeks on functional markers of patients with heart failure and preserved ejection fraction, also reported cardiovascular outcomes and was, thus, deemed eligible for our analysis[25]. The majority (99.4%) of patients included in these studies were men, with a median of age 61.5 years (range 30 – 72.8), most of them receiving PDE5i for ED. Apart from ED, two studies exclusively included patients with known diabetes, whereas two other included patients with a history of myocardial infarction or coronary revascularization. The presence of both silent CAD and diabetes mellitus was used as a criterion for patient selection in the unique prospective study[23]. In another study, patients using nitrates with or without PDE5i for ED were selected. Of note, one study investigated the association of PDE5i with the risk of

metastasis and all-cause mortality in patients with colorectal cancer[33] while, in accordance, another one assessed the effect of PDE5i on relapse-free period and overall survival in patients with prostate cancer treated with prostatectomy[27]. In the same spirit, another study investigated whether the use of PDE5i for ED after robot assisted radical prostatectomy provides a survival benefit in patients with prostate cancer[30].

Furthermore, 3 studies reported survival outcomes in patients with LVAD treated with PDE5i[26,35,36]. Most of the studies were based on prescription drug data to identify patients using PDE5i, but none of the articles provided specific information about the dose and type of the prescribed PDE5i. The follow-up duration ranged between 6 months and 7.5 years across studies. The basic characteristics of the eligible studies that were included in the final analysis are summarized in Table 1.

Major adverse cardiovascular events

Eleven of the included studies evaluated the impact of PDE5i used for the treatment of ED on MACE. The multivariable adjusted RR were pooled for the analysis when provided. Except for the study conducted by Gazzaruso et al. [23] that dates from 2008, all studies were published between 2013 and 2023 and the mean follow-up ranged from 6 months [34] to 7.5 years [37] (median 4.3 years).

The risk of MACE was significantly lower in PDE5i users compared to controls (RR 0.78, 95% CI 0.69-0.89). (Figure 1). The p value for heterogeneity was < 0.001, I^2=89%. Even after excluding 2 studies reporting outcomes of PDE5i administration on patients supported by LVADs[27, 28], the risk of MACE remained significantly lower in patients that received PDE5i compared to controls (RR 0.77, 95% CI 0.65-0.91, I^2=87% - Supplemental Figure 2).

Focusing on patients that used PDE5i for ED, including those with a prescpription for PDE5i in the large epidemiological registries, the pooled RR for MACE for PDE5i users derived from 7 studies was 0.81 (95% CI 0.72-0.91) compared to controls (Supplemental Figure 3).

All-cause mortality

The outcome of all-cause mortality was evaluated in 12 cohorts. One of these studies evaluated the impact of postoperative administration of PDE5i on cumulative mortality in patients with colorectal cancer and another one in patients with operated prostatic cancer[27,33]. Three studies included patients on PDE5i for erectile dysfunction[20,21,24], while the patients studied by Nunes et al. were taking nitrates with or without PDE5i for erectile dysfunction[34]. Patients hemodynamically supported by left ventricular assist devices (LVADs) from three different cohort studies were also included in this analysis[26,35,36].

In the analysis of pooled data from these 12 studies, the use of PDE5i was associated with a lower risk for all-cause mortality (RR 0.70, 95% CI 0.56-0.87) (Figure 2). A sub-analysis focusing on patients with a history of coronary artery disease, demonstrated that PDE5i reduce the risk of all-cause mortality by 25% (RR 0.75, 95% CI 0.53 – 1.06), but this finding was not statistically significant (Figure 3).

An additional subgroup analysis based on the indication for PDE5i use was performed. Particularly, studies including patients who received PDE5i for ED were selected. Large epidemiological studies including male patients with a prescription for PDE5i were considered appropriate for this sub-analysis, assuming that the vast majority of these men used PDE5i for erectile dysfunction. The pooled RR for all cause mortality for patients using PDE5i for ED, derived from a total of 9 studies, was 0.63 (95% CI 0.49-0.81) (Supplemental Figure 4).

Myocardial infarction and heart failure

Regarding the secondary outcomes, 5 studies reported results regarding the effect of PDE5 inhibition on the incidence of myocardial infarction and the analysis of the multivariable adjusted RRs showed a trend towards a statistically significant association between PDE5i treatment and a lower incidence of myocardial infarction (RR 0.78, 95% CI 0.60-1.02) (Supplemental Figure 5)[20,21,28,29,31]. Five studies reported results on heart failure and the pooling of results showed that the treatment with PDE5i shows a trend towards reduction of the risk of heart failure (RR 0.84, 95% CI 0.66 -1.06)(Supplemental Figure 6) [20,21,25,29,31].

Discussion

This is the first meta-analysis to fully assess the long-term effects of PDE5i on hard cardiovascular endpoints. The major finding of our analysis is that the use of PDE5i is associated with a reduction of 22% in MACE and 30% in all-cause mortality primarily in middle-aged men with a rather elevated baseline risk for cardiovascular events. Interestingly, this beneficial seems to be maintained in patients with known, stable coronary artery disease. Indeed, ED represents an independent risk factor for the development of future clinical cardiovascular events[15]. It is now well established that ED and CAD share mutual vascular risk factors along with common pathogenic features, dominated by vascular endothelial dysfunction[3839]. PDE5i restore endothelial function predominantly through the enhancement of nitric oxide viability, inducing the appropriate endothelial-dependent vasorelaxation that is necessary to obtain an erection. Theoretically, owing to their mechanism of action, PDE5i could optimally be suitable for the treatment of cardiovascular disorders. As a matter of fact,

prolonged administration of PDE5i in diabetic patients with or without erectile dysfunction has been shown to improve surrogate markers of endothelial dysfunction, such as flow mediated dilatation, and reduce serum indices of vascular inflammation[404112]. At a clinical level, a generalized improvement of endothelial function promoted by PDE5 inhibition in patients with an elevated cardiovascular risk may be responsible for the substantial decrease in MACE that was observed in our analysis.

Beyond ED, strong evidence demonstrates that PDE5i drastically reduce vascular resistance and improve functional measurements in patients with pulmonary arterial hypertension[4243]. Therefore, the treatment of pulmonary arterial hypertension represents for the moment the only established cardiovascular use of PDE5i. In the short term, PDE5i improve survival in patients with pulmonary arterial hypertension, whereas data regarding their impact on cardiovascular events or long-term survival are still lacking[44].

A number of beneficial effects of PDE5i on heart failure with preserved ejection fraction, have also been reported. These include improvements in pulmonary hemodynamics and left ventricular diastolic function following regression of left ventricular hypertrophy[45]. In addition, the RELAX trial found that the administration of sildenafil for 6 months in heart failure patients with preserved ejection fraction resulted in a significant improvement in functional capacity and clinical status compared with placebo[46].

With respect to patients with impaired left ventricular ejection fraction, we identified three studies evaluating the effects of PDE5i administration in patients hemodynamically supported with LVAD. The INTERMACS study recruited more than 7,000 patients supported with LVAD, of whom about 2,200 received PDE5i after LVAD implantation. PDE5i was associated with lower mortality (adjusted HR: 0.75; 95% CI: 0.65-0.86; p< 0.0001) and ischemic stroke rates (HR: 0.71; 95% CI: 0.56-0.89; p<0.01) at 12 months of follow-up[36]. In line with these data, the analysis of 13,772 patients with continuous flow

LVADs participating in a national registry found a significant association of the postimplant PDE5i administration with a lower risk for thrombotic events (HR, 0.82; 95% CI, 0.74–0.90; p<0.001) and cumulative mortality (HR, 0.86; 95% CI, 0.79–0.93; p<0.001) at 48 months post LVAD implantation[47]. Although these studies focused on patients with advanced heart failure, who significantly differed from patients with ED that were recruited in most of the eligible cohort studies we decided to include them in our final analysis. These data provide support to the hypothesis that PDE5i may exert antithrombotic effects by potentiating nitric oxide–mediated inhibition of platelet adhesion and aggregation following blockade of cGMP degradation[4849]. They also confirm the ability of PDE5i to improve hemodynamics in patients with LVAD, more likely through augmentation of right ventricular function, decrease in pulmonary vascular resistance and improvement of left ventricular filling[50].

It is noteworthy that the therapeutic potential of PDE5i in colorectal cancer was evaluated in a Swedish cohort included in our analysis[33]. There is now mounting experimental evidence that inhibition of PDE5 might act against tumor progression and reduce the incidence of metastases among patients with colorectal cancer[51–53]. While several theories have been proposed, including the induction of apoptosis and effective immune restoration, the potential mechanisms underlying the antitumor effect of PDE5i remain largely unclear[54]. After all, the association of post-diagnostic, postoperative use of PDE5i with a reduced risk of colorectal-specific mortality that was demonstrated in this retrospective study, sets challenging therapeutic targets that worth to bae further investigated in randomized clinical trials. This favorable effect of PDE5i on non-cardiovascular mortality could also justify the greater benefit form PDE5 inhibition on all-cause mortality compared to that on MACE that was demonstrated in our analysis.

Study Limitations

We acknowledge that our analysis is not free from certain limitations. First of all, the results of this meta-analysis should be interpreted with caution, taking into consideration that we did not deal with methodological issues of the original studies because they are mainly based on epidemiological data. Differences regarding the primary endpoint, the features of each cohort and the follow-up periods may also account for a certain degree of heterogeneity that was observed across the included studies. Our analysis is further limited by the fact that no dose-response assessment of PDE5i use could be performed, given that such information was not provided or was not available in detail in the eligible publications. Thus, although our analysis indicates a favorable effect of PDE5i on cardiovascular outcomes, the dose of PDE5i that is required to produce a particular effect of interest could not be specified. Another reasonable assumption is that PDE5i use could reflect existing sexual ability, willingness for sexual activity, increased sociability and overall better quality of life, all factors that to some extent may promote increased longevity. Last but not least, all the eligible cohorts consisted primarily of men, denoting that our results cannot be extrapolated to women.

Eight out of the ten studies that were included in our analysis recruited patients at high cardiovascular risk or with already known cardiovascular disease. Paradoxically, given that ED was the most common reason for PDE5i use, our analysis demonstrated higher survival rates among patients with ED compared to controls, who were not on PDE5i and thus did not suffer theoretically from ED. The absence of PDE5i use in the control group, on the other hand, does not necessarily exclude the presence of ED, considering that many men with erectile dysfunction do not seek treatment, while none of the included studies evaluated the socioeconomic status, which also seems to be associated with PDE5i use and life

expectancy[55]. It is also possible that PDE5i are protective against cardiovascular disease and, thus, reverse the worse prognosis associated with ED.

Conclusion

The use of PDE5i for the treartment of ED in male patients at high risk for cardiovascular disease is associated with a substantial reduction in cardiovascular events and rates of overall mortality. The results of this meta-analysis emphatically demonstrate that treatment with PDE5i could provide considerable clinical benefit for specific patient populations beyond the treatment of erectile dysfunction. Whether our findings are potentially applicable to clinical practice is a question that remains to be further elucidated in well-designed, randomized clinical trials.

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Disclosures

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Table 1. Main characteristics of the included studies

Study	Study Design	Population characteristics	Patients on PDE5i (N)	Controls (n)	Mean/Median Age	Outcomes	Follow-up (years)
Gazzaruso 2008	Cohort study	Men with silent CAD and Diabetes	44	74	54.8±7.3	MACE	47±22 months
Redfield 2013	Randomized Controlled Study	Patients with Preserved Heart Failure	113	103	68 (62-77)	6MWT, HF decompensation, death	24 weeks
Anderson 2016	Cohort study	Patients with DM type II and elevated CVD risk	1359	4597	71.3 (70.6–71.7)	Death - Myocardial infarction	7.5 years
Andersson 2017	Cohort study	Patients without prior MI or revascularization	3068	40077	61±9	All cause and CV death - MI- revascularization - prostatectomy - surgery for rectal cancer	3.3 years
Hackett 2017	Cohort study	Patients with DM type II	175	682	62.7±10	All-cause death	3.8 years
Vestergaard 2017	Cohort study	Danish men 40-80 years old	71710	992017	60.7±8.4	cardiovascular disease, stroke, AMI, ischemic heart disease, heart failure	3 years
Huang 2020	Cohort study	Male patients with colorectal cancer	1136	11329	-	Death due to CRC, metastasis	4.25 years
Xanthopoulos 2020	Cohort study	Patients with LVAD	4950	8822	57±13	Stroke, LVAD thrombosis, all-cause mortality	48 months
Andersson 2021	Cohort study	Men with a prior MI or revascularization who received PDE5i or alprostadil (naïve)	16548	1994	62±8.5	All cause and CV death, HF, MI, PAD, stroke	5.8 years
Nunes 2021	Cohort study	Patients with erectile dysfunction	3648	3648	-	Cardiovascular outcomes, death	12 months
Danley 2021	Cohort study	Patients with prostate cancer	1372	1728	60.7	All-cause mortality	10 years
Xanthopoulos 2022	Cohort study	Patients with LVAD	2173	5056	57.2±13	Stroke, LVAD thrombosis, all-cause mortality	12± 8 months
Chang 2022	Cohort study	Patients with Pulmonary Hypertension	763	3032	54	AMI, Ischemic stroke	7 years
Grandin 2022	Cohort study	Patients with LVAD	1600	1600	56.1±12.8	Heart Failure, all-cause mortality	3 years
Kloner 2023	Cohort study	Patients with ED without MACE within 1 year	23816	48682	51.7±10.4	All-cause mortality MACE MI Heart Failure	37 months
Lee 2023	Retrospective	Patients undergoing robot assisted radical prostatectomy	1298	545	64 (59-68)	All-cause mortality	47 months

CAD, coronary artery disease; CVD, cardiovascular disease; MI, myocardial infarction; PDE5i, phosphodiesterase inhibitors; LVAD, left ventricular assist device; ED, erectile dysfunction; MACE, major adverse cardiovascular events; 6MWT, 6-minute walking test; CV, cardiovascular; AMI, acute myocardial infarction; CRC, colorectal cancer; HF, heart failure; PAD, peripheral arterial disease.

Table 2. Newcastle-Ottawa Quality assessment scale for observational Studies

Case-Control Studies									
Studies	Selection				Comparability	Exposure			Quality Score
	Is the case definition adequate	Representativenesof the cases	Selection of Controls	Definition of Controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Gazzaruso 2008	*	*	*	*	*	*	*		**7**
Cohort Studies									
Studies	Selection				Comparability	Exposure			Quality Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	based on the design or analysis	Assessment of outcome	follow-up long enough	Adequacy of follow up of cohorts	
Anderson 2016	*	*	*		*	*	*	*	**7**
Andersson 2017	*	*	*		*	*	*	*	**7**
Hackett 2017	*	*	*		**	*	*	*	**8**
Vestergaard 2017	*	*	*		*	*	*	*	**8**
Huang 2020		*	*		*	*	*		**5**
Xanthopoulos 2020		*	*		**	*	*	*	**7**
Andersson 2021	*	*	*		*	*	*	*	**7**
Nunes 2021	*	*	*		**	*	*	*	**8**
Xanthopoulos 2021		*	*		**	*	*	*	7

Danley 2021	*	*	*		**	*	*	*	8
Grandin 2022	*	*	*		**	*	*	*	8
Chang 2022	*	*	*	*	*	*	*	*	8
Kloner 2023	*	*	*	*	*	*	*	*	8
Lee 2023	*	*	*		*	*	*	*	7

Figure 1. Forest plot of multivariable adjusted RRs of MACE associated with PDE5i use

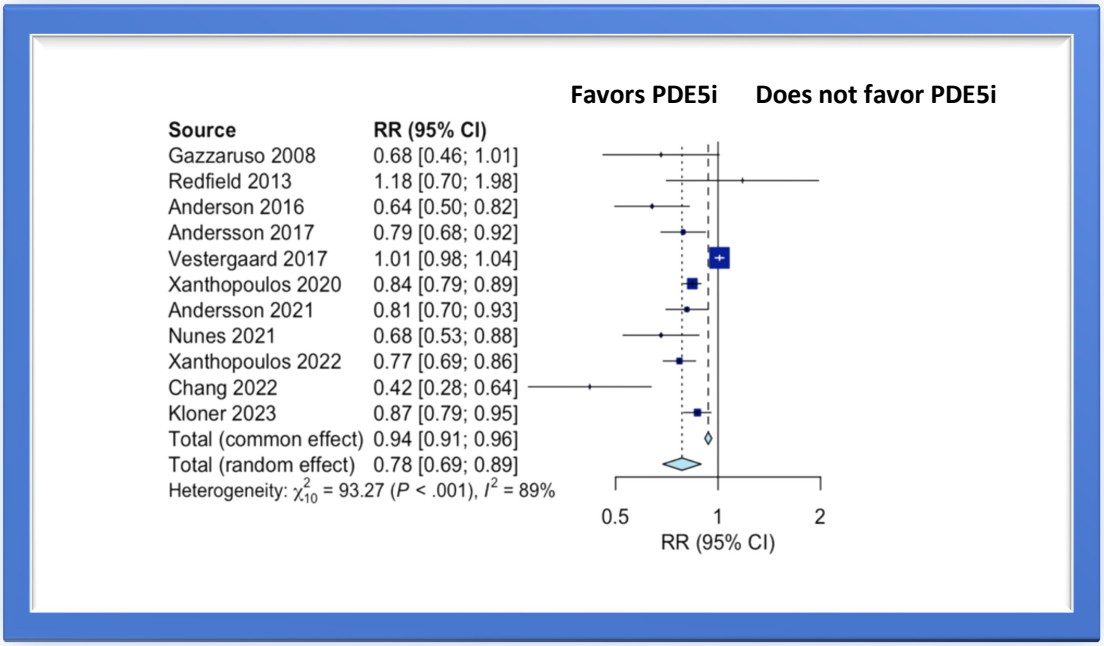

Figure 2. Forest plot of multivariable adjusted RRs of all-cause mortality associated with PDE5i use

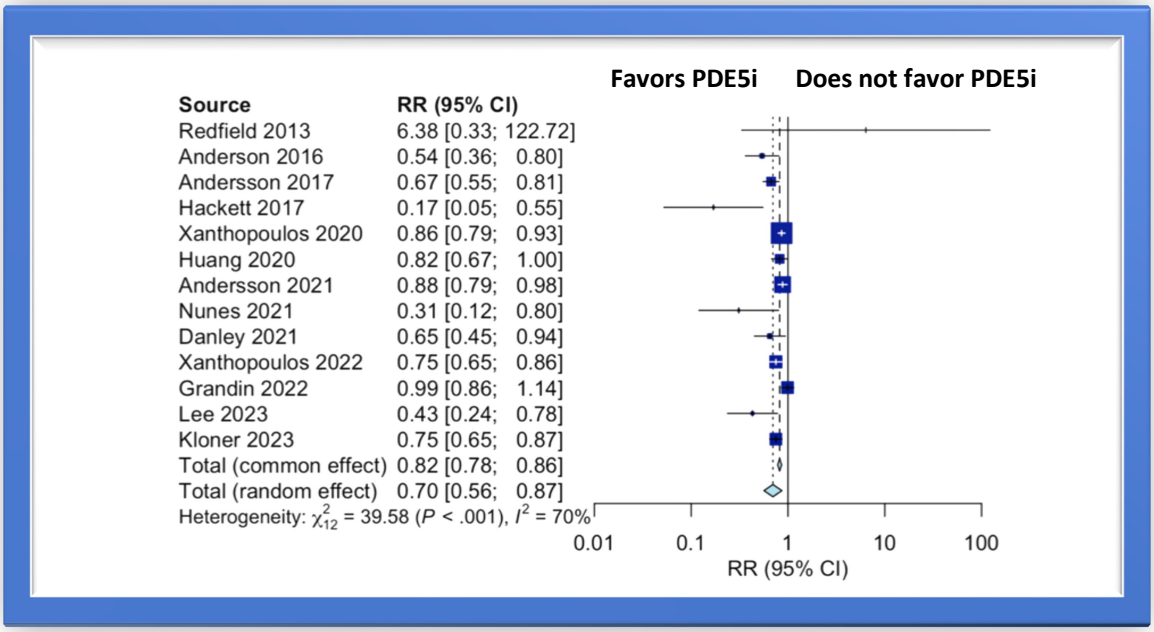

Figure 3. Forest plot of multivariable adjusted RRs of all-cause mortality associated with PDE5i use in patients with a history of coronary artery disease