SEXUAL MEDICINE REVIEWS REVIEW

Cardiovascular Safety of Phosphodiesterase Type 5 Inhibitors After Nearly 2 Decades on the Market

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ABSTRACT

Background: The phosphodiesterase-5 (PDE5) inhibitors that have been available for nearly 20 years are highly effective in treating erectile dysfunction and have been consistently shown to be safe when used according to package insert instructions.

Aim: To review the cardiovascular (CV) safety of PDE5 inhibitors used to treat erectile dysfunction.

Methods: PubMed, the Derwent Drug File, and Embase were searched to identify papers published from 1990–2016 presenting CV safety data for PDE5 inhibitors.

Outcomes: This narrative review focuses mainly on papers published in the last 10 years with CV safety data for sildenafil, tadalafil, or vardenafil.

Results: Similar to earlier studies, newer studies demonstrate that PDE5 inhibitors do not show an increased incidence of serious CV adverse events such as cardiac death or myocardial infarction. There are drug–drug interactions with PDE5 inhibitors that for the most part are now commonly known, and PDE5 inhibitors are generally safe to use with other commonly used drugs including antihypertensive agents.

Conclusion: PDE5 inhibitors are a class of drugs that when used appropriately demonstrate a favorable CV safety profile and present some encouraging signals for new CV indications, which will require additional study. **Kloner RA, Goldstein I, Kirby MG, et al. Cardiovascular Safety of Phosphodiesterase Type 5 Inhibitors After Nearly 2 Decades on the Market. Sex Med Rev 2018;XX:XXX–XXX.**

Key Words: Cardiovascular System; Phosphodiesterase Inhibitors; Erectile Dysfunction; Safety

INTRODUCTION

Mechanism of Action of Phosphodiesterase-5 Inhibitors

For a penile erection to occur, vasodilation of the blood vessels with accompanying increased blood flow and storage in the penis is necessary.[1] Cases of erectile dysfunction (ED) are commonly due to inadequate vasodilation and reduced blood flow within the penile blood vessels. A major mechanism for increasing blood flow and storage in the corpora cavernosa of the penis involves nitric oxide.[2] Sexual stimulation normally releases nitric oxide from neurons in the penis as well as from the endothelial cells that line the penile arteries. Within smooth muscle cells, nitric oxide results in the production of cyclic guanosine monophosphate (cGMP), a second messenger that ultimately causes relaxation of the smooth muscles in the penile vasculature and vasodilation of penile blood vessels (including the sinusoids of the corpus cavernosa) that fill with blood and cause an erection. cGMP is inactivated by the enzyme phosphodiesterase-5 (PDE5), which is normally released during the relaxation phase following ejaculation. PDE5 inhibitors, such as sildenafil, vardenafil, and tadalafil, improve erectile function by reducing the breakdown of cGMP, thereby allowing better and longer vasodilation and increased engorgement.[3] PDE5 is found in high concentrations in the blood vessels of the corpora cavernosa of

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the penis as well as the pulmonary vasculature, but it is also present at lower concentrations in the systemic vasculature, where it performs a comparable function.[4,5]

POTENTIAL CARDIOVASCULAR CONCERNS DURING TREATMENT WITH PDE5 INHIBITORS

PDE5 inhibitors have revolutionized the treatment of ED and are also commonly used to treat pulmonary hypertension.[6] While PDE5 inhibitors are generally efficacious and well tolerated, there were some cardiovascular (CV) safety concerns in the early days of their use regarding the possibility that PDE5 inhibitors could precipitate adverse CV events (Table 1). However, the results of large-scale data analyses have demonstrated that there is no increase in adverse CV events (including death) in men taking PDE5 inhibitors compared with control groups. Nitrates remain a contra-indication for the use of PDE5 inhibitors (within 24 hours of taking sildenafil and vardenafil and within 48 hours of taking tadalafil), because when nitrates are administered with these agents, potentially significant hypotension develops in a small number of individuals.[7] A more recently licensed drug used to treat pulmonary hypertension, riociguat, which increases the synthesis of cGMP, is also contra-indicated for use with PDE5 inhibitors due to concerns over additive vasodilation.[8] A warning also exists regarding the use of PDE5 inhibitors with alpha-blockers because of the possibility of orthostatic hypotension.[7] When PDE5 inhibitors are added to most anti-hypertensive drugs, small and clinically insignificant additional decreases in blood pressure occur.[7] Because PDE5 inhibitors are vasodilators, they should be avoided in patients with obstruction in the left ventricular outflow track or aortic valve and pre-existing hypotension, because they have the potential to precipitate hypotension. Because no data are available on the use of PDE5 inhibitors in patients with very recent myocardial infarction (MI) or stroke, these drugs should be avoided in these patient populations.

Over the past 10 years, there have been few updated reports regarding the CV safety of PDE5 inhibitors. The purpose of this article is to review papers that have been published primarily during the 10 years from 2006–2016 that provide an update on the CV safety of PDE5 inhibitors. This article will focus on the 3 major PDE5 inhibitors used in the United States: sildenafil, tadalafil, and vardenafil. The efficacy and general safety of these PDE5 inhibitors in patients with ED are essentially equal, although some differences exist, particularly with regard to duration of action.[9]

Table 1. Potential cardiovascular safety concerns during treatment with phosphodiesterase-5 inhibitors

Physiologic change during PDE5 inhibitor therapy/concomitant medication	Potential concern
Release of NO, production of cGMP	Smooth muscle relaxation, increased blood flow
Vasodilation	Hypotension
Concomitant medication	
Nitrates	Hypotension
Riociguat	Additive vasodilation
Alpha-blockers	Orthostatic hypotension

cGMP = cyclic guanosine monophosphate; NO = nitric oxide; PDE5 = phosphodiesterase-5.

LITERATURE SEARCH

In this narrative review, a search of the published literature (ie, PubMed, the Derwent Drug File, and Embase) on the CV safety of the PDE5 inhibitors sildenafil, tadalafil, and vardenafil was conducted on April 4, 2016, using the following search terms: (phosphodiesterase type 5 inhibitor OR sildenafil OR Viagra OR Revatio OR tadalafil OR Cialis OR Adcirca OR vardenafil OR Levitra OR Staxyn OR Vivanza) AND (cardiovascular OR myocardial OR infarct OR cardiac OR heart OR ventricular OR fibrillation OR cardiomyopathy) AND (nitrate OR nitroglycerin). The search was limited to English language, published from January 1, 1990, to April 1, 2016, humans (valid for PubMed and Embase only), and containing an abstract (valid for PubMed and Embase only). An evaluation of the identified articles was conducted by 2 independent reviewers. Of the articles retrieved, articles with CV safety data for sildenafil, tadalafil, or vardenafil that were predominantly published from 2006–2016 were retained and summarized qualitatively.

LARGE CV SAFETY STUDIES

Findings from publications of large CV safety studies are summarized in Table 2.[10–16]

Review of Double-Blind, Placebo-Controlled Trials and Post-Marketing Safety Database of Sildenafil

Giuliano et al[10] published an important article on the CV safety of sildenafil in 2010. Data from 67 double-blind, placebo-controlled, sildenafil trials were evaluated, together with the post-marketing safety database, in men who received 50- or 100-mg doses of sildenafil for the treatment of ED. This analysis included >14,000 men from clinical studies and >39,000 patients from the manufacturer's post-marketing safety database. The men in the clinical trials were a mean age of 55 years; most had a history of ED for 4.5 years, and most cases of ED were organic in nature. Concomitant CV risk factors and/or CV disease were common in these men (ie, diabetes mellitus, hypertension, coronary artery disease, angina, MI, stroke); those with severe cardiac failure, unstable angina, or a recent stroke or MI event were excluded. Headache and facial flushing were the most common adverse events, which is consistent with the known pharmacology of PDE5 inhibitors as vasodilators and consistent with the product labeling (Supplementary Table 1[10]). Of note these events diminished substantially after continued use of sildenafil for 8–16 weeks

Table 2. Incidence of death or serious cardiovascular adverse events during treatment with phosphodiesterase-5 inhibitors

			Incidence	
Reference	PDE5 inhibitor	Death or serious CV adverse event	PDE5 inhibitor	Placebo
Giuliano et al[10]	Sildenafil	All-cause mortality	0.13% (11/8,691)	0.11% (7/6,602)
		CV death	36% (4/11)*	43% (3/7)
		Acute MI	4.1%	4.5%
		Chest pain	3.0%	2.3%
		Coronary artery disease	2.7%	5.3%
		Stroke	2.5%	2.3%
Mittleman et al[11]	Sildenafil	All-cause mortality	0.4/100 patient-y	
		MI	0.6/100 patient-y	
		Stroke	0.1/100 patient-y	
Mittleman et al[12]	Sildenafil	All MIs	0.80/100 patient-y	0.84/100 patient-y
		CV death	0.23/100 patient-y	0.19/100 patient-y
		MI or CV death	0.91/100 patient-y	0.84/100 patient-y
Kloner et al[13]	Tadalafil	CV death, MI, cerebrovascular death	0.40/100 patient-y	0.43/100 patient-y
Hazell et al[14]	Tadalafil	MI	15/6,266	
		Ischemic heart disease	11/6,266	
Isidori et al[15]	Vardenafil	Serious adverse events	0/604	
Van Ahlen et al[16]	Vardenafil	Serious adverse events	0.06%	

CV = cardiovascular; MI = myocardial infarction; PDE5 = phosphodiesterase-5.
*4 of 11 deaths in sildenafil users were cardiovascular in nature; none were considered related to sildenafil.

(Figure 1[10]). The frequency of deaths in the double-blind, placebo-controlled database was 0.13% (11/8,691) for sildenafil-treated patients and 0.11% (7/6,602) for patients receiving placebo. Most deaths occurred in men aged ≥50 years, with none considered by the investigators to be drug related. In the double-blind, placebo-controlled database, the overall CV death rate was 3 of 7 deaths (43%) in the placebo group and 4 of 11 deaths (36%) in the sildenafil group. The incidence of acute MI was similar in the placebo (4.5%) and sildenafil (4.1%) groups. The incidence of chest pain (2.3% vs 3.0%), coronary artery disease (5.3% vs 2.7%), and stroke (2.3% vs 2.5%) was similar between placebo and sildenafil treatment groups, respectively. Of note, none of the serious adverse CV events was thought to be related to sildenafil. The authors noted that post-marketing studies also did not indicate an increased rate of serious CV events in patients receiving sildenafil.

Regarding drug—drug interactions, it is noteworthy that only a few patients (16/8,691 patients) included in the study of Giuliano et al[10] took nitrates with sildenafil. Of the patients who took this combination, there were no reports of hypotension or adverse events. In the review of the double-blind, placebo-controlled studies, the concomitant use of alpha-blockers with sildenafil was uncommon (4.2%). Dyspepsia, flushing, and headache were the most common adverse events reported with this combination, and the incidence of either decreased blood pressure or orthostatic hypotension was low. After reviewing the pooled data, Giuliano et al[10] concluded that there was no causal link between sildenafil and adverse CV events, which is in agreement with older systematic analyses, including an earlier review of the CV safety of sildenafil.[17]

CV Outcomes From a Prospective Observational Study of Sildenafil (International Men's Health Study)

In 2008, Mittleman et al[11] published data from the International Men's Health Study, which was a prospective, observational cohort study of men with ED who took sildenafil. Baseline, follow-up, and post-event questionnaires were completed by patients

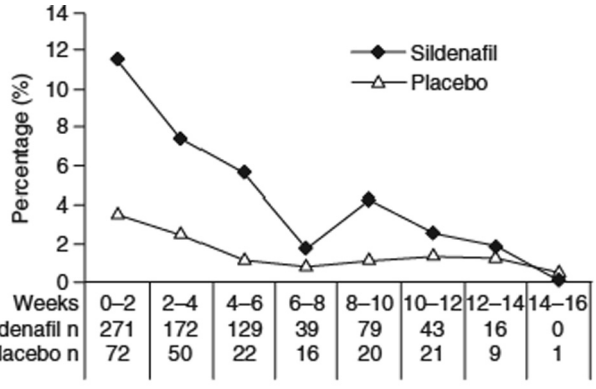

Figure 1. Rate of treatment-related adverse events over time collated from 17 randomized, double-blind, placebo-controlled, flexible-dose trials (sildenafil 25—100 mg, n = 2,362; placebo, n = 1,986). Treatment periods of ≤4 months were divided into 2-week intervals; the number of patients who experienced any adverse event was recorded for each interval and divided by the total number of patients who received treatment during that interval. (Reproduced with permission from Giuliano et al.[10])

Table 3. Incidence rates of myocardial infarction and death (per 100 person-years) in clinical studies of sildenafil conducted from 1993–2002

	Double-blind treatment		Open-label	
Variable	Sildenafil	Placebo	Sildenafil	*P* value*
Patients, n	7,462	5,753		–
Total person-y	1,758	1,066	11,540	–
All MIs, mean (95% CI)	0.80 (0.44–1.34)	0.84 (0.39–1.60)	0.53 (0.40–0.68)	.88
CV death, mean (95% CI)	0.23 (0.06–0.58)	0.19 (0.02–0.68)	0.16 (0.09–0.25)	.86
MI or CV death, mean (95% CI)	0.91 (0.52–1.48)	0.84 (0.39–1.60)	0.56 (0.44–0.72)	.87

CV = cardiovascular; MI = myocardial infarction.
*Double-blind sildenafil vs placebo; mean represents the rate per 100 person-y and Poisson exact 95% CIs.
Adapted with permission from Mittleman et al.[12]

following non-fatal CV events. The men were a mean age of 57 years and had a mean duration of ED of 3 years. The proportion of patients who had risk factors for CV disease included 36% with hypertension, 26% with hyper-cholesterolemia, and 25% who smoked; 21% had >2 CV risk factors. 30 of 3,813 patients had 35 fatal and non-fatal CV events. The incidence of all-cause mortality was 0.4, MI was 0.6, and stroke was 0.1 per 100 patient-years. These rates were low and similar to those reported in other clinical trials and epidemiologic studies of men in this demographic.[18–20] Of the 6 men who reported using sildenafil in the month before a non-fatal CV event, only 2 reported using sildenafil within 24 hours of the CV event. The authors did note that ED and CV disease share common risk factors and, therefore, men with ED are at greater risk of having a CV event compared with those who do not have ED.

Pooled Clinical Trial Data on the CV Safety of Sildenafil and Tadalafil

2 earlier studies by Mittleman et al[12,21] had also provided valuable information on the CV safety of sildenafil. Based on pooled data from more than 120 clinical trials of sildenafil, there was no increase in the risk of MI or cardiac death in patients receiving sildenafil compared with placebo (Table 3[12]). In placebo-controlled trials, the rate of MI or CV death was 0.84 (95% CI, 0.39–1.60) per 100 patient-years in the placebo group and 0.91 (95% CI, 0.52–1.48) per 100 patient-years for sildenafil-treated patients. No increase was reported in the relative risk of MI or CV death with sildenafil compared with placebo (1.08; 95% CI, 0.45–2.77; $P = .87$) (Table 4[12]). In open-label studies with sildenafil, the rate of MI or CV death was also low (0.56 per 100 patient-years).[12] The authors noted that these data provide further evidence of the low rate of CV adverse events among sildenafil users and that the data are consistent with previous reports. A second article focused on the timing of MI in relation to the use of sildenafil.[21] Using data from 80 clinical trials of sildenafil conducted from 1993–2000, the onset of MI was evaluated during 2 hazard periods: within 24 hours and within 6 hours of sildenafil treatment. 69 MIs occurred during more than 11,000 person-years of exposure to the drug. Importantly, the mean time from the last dose of sildenafil to the MI event was 14 days, and the relative risk of MI was 0.80 within 24 hours after taking sildenafil (Table 5[21]) and 0.79 within 6 hours of taking sildenafil. The authors concluded that sildenafil was not associated with a short-term risk of MI.

Similar findings were observed in a retrospective study of data from 36 placebo-controlled and open-label clinical studies of tadalafil, in which administration of tadalafil was administered as needed, 3 times a week, or once daily.[13] Serious CV treatment-emergent adverse events were evaluated based on these 36 clinical trials of tadalafil, involving 12,487 men with ED receiving

Table 4. Relative risk and absolute rate difference of myocardial infarction and cardiovascular death in randomized, double-blind, placebo-controlled trials conducted from 1993–2002

Variable	Relative risk (95% CI)*	Absolute rate difference† (95% CI)*
All MIs	0.94 (0.38–2.47)	−0.05 (0.44–0.64)
CV death	1.21 (0.17–13.41)	0.04 (−0.30 to 0.38)
MI or CV death	1.08 (0.45–2.77)	0.07 (−0.64 to 0.78)

CV = cardiovascular; MI = myocardial infarction.
*Compared with placebo.
†Per 100 person-y.
Adapted with permission from Mittleman et al.[12]

Table 5. Risk for developing myocardial infarction <24 hours after sildenafil use*

Variable	<24 h After sildenafil use	>24 h After sildenafil use	Total
MI cases	22	47	69
Person-d at risk	5,258	10,957	16,215
Absolute risk	0.42%/d	0.43%/d	
Crude relative risk		0.97	
Case-crossover relative risk (95% CI)		0.80 (0.52–1.26)	

MI = myocardial infarction.
*No association was observed between the day of sildenafil use and the day of MI in 69 men in a cohort of 9,317 men aged ≥50 y who were followed up for 11,000 person-y.
Adapted with permission from Mittleman et al.[21]

tadalafil and 2,047 men receiving placebo. The serious CV treatment-emergent adverse events included MI, CV death, and cerebrovascular death. The incidence rates of these serious CV treatment-emergent adverse events were 0.43 per 100 patient-years in the placebo group and 0.40 per 100 patient-years in tadalafil-treated patients. Therefore, in men with ED, tadalafil treatment was not associated with an increase in serious CV or cerebrovascular adverse events.

Large Observational Studies and Other Clinical Trials on the CV Safety of Tadalafil and Sildenafil

Hazell et al[14] reported an observational cohort study of patients receiving tadalafil, prescribed by their general practitioners in England in 2003. Of 6,266 patients, 15 had MI (6 fatal), and 11 had ischemic heart disease (5 fatal). A standardized mortality ratio was 0.91 when comparing deaths from MI or ischemic heart disease in the men taking tadalafil vs those due to ischemic heart disease in the general English population of men. These results suggest that there was a similar incidence of death due to MI and ischemic heart disease between those taking the PDE5 inhibitor and the English population of men, confirming the concept that PDE5 inhibitors are not increasing cardiac adverse events. 2 separate studies from Asia, one an analysis of pooled data from three 12-week, randomized, double-blind, placebo-controlled studies in men (N = 1,199) with lower urinary tract symptoms secondary to benign hyperplasia and the other an 8-week, prospective, multicenter study in men with ED (N = 127 completers), also found that there was no increase in CV adverse events in men who took once-daily tadalafil (5 mg) for ED.[22,23] In addition, Finkle et al[24] reported the rate ratio for MI before and after a first prescription for sildenafil or tadalafil (N = 162,279) using data from a U.S. health care insurance claims database. The MI rate ratio adjusted for age and pre-existing medical conditions and medication use associated with MI or MI risk factors was 1.08 (95% CI, 0.93−1.24), consistent with a lack of association between PDE5 inhibitor use and MI risk.

6-Month Clinical Trial and Large, Open-Label (REALISE) Study on the CV Safety of Vardenafil

The Italian Society of Andrology and Sexual Medicine published a multicenter study of 604 men with ED who were treated with vardenafil for 6 months.[15] Like many studies of men (median age, 55 years) with ED, metabolic syndrome and CV risk factors were common. No severe adverse events occurred in the men treated with vardenafil. Headache (4.1%) and flushing (3.6%) were the most common adverse events. There were no reports of serious adverse events. The Real-Life Safety and Efficacy of Vardenafil (REALISE) study assessed the efficacy and safety of vardenafil in a large international, open-label, prospective, non-comparative study of nearly 74,000 men with ED plus underlying conditions.[16] Hypertension, diabetes, lipid disorders, and CV disease were common at baseline. Efficacy was high, with 97% of men stating that they were satisfied with vardenafil treatment. The most common adverse events were headache (≤2%) and flushing, erythema, and nasal congestion (all <1%), which were generally mild and transient. Serious adverse events were very rare (0.06%), as were serious drug reactions (0.04%). Eardley et al[25] pointed out in a review of clinical trials and post-marketing surveillance studies of vardenafil that the use of the drug in patients on antihypertensive medicines or medicines for hyper-cholesterolemia was not associated with an increase in adverse events. Specifically, no increase was seen in CV adverse events in men with underlying CV risk factors (diabetes, hypertension, and/or dyslipidemia) who received the drug. Thus, like the other PDE5 inhibitors, there was no signal for an increase in CV adverse events.

10-Year Analysis of Adverse Event Reports to the U.S. Food and Drug Administration for PDE5 Inhibitors

Lowe and Costabile[26] reported a non-industry−sponsored analysis of U.S. Food and Drug Administration (FDA)-reported CV events and mortality over a 10-year period for the PDE5 inhibitors. The data were derived from spontaneous reports of adverse events to the FDA, so it is not clear what the denominator was for such events (ie, the total number of patients taking the drug). Nevertheless, the authors suggested that using an estimate of about 5 million men taking PDE5 inhibitors for ED per year, a conservative estimate of the risk of a man having any adverse event over 10 years is only 0.0005% (26,451 total adverse events reported over 10 years). Of the total adverse events, using an estimated rate of CV adverse events of 12%, the risk of experiencing a CV adverse event over this time is only 0.00006% among users of PDE5 inhibitors.

Comprehensive Review of the Incidence of MI and Cardiac Death During Sildenafil Treatment

In a review of the safety of sildenafil and other PDE5 inhibitors, Kontaras et al[27] summarized many of the articles published between 1994 and 2007 that assessed the incidence of MI and cardiac death in men using sildenafil for the treatment of ED. Because the purpose of our article is to consider articles published during the last 10 years, we did not review most of the papers covered by Kontaras et al.[27] They concluded that the vast majority of the studies describe no association of sildenafil with an increase in acute MI or sudden cardiac deaths; in fact, some analyses suggested a lower number of deaths from MI in patients on sildenafil than otherwise would have been expected. Some intriguing recent reports exist of men with diabetes and ED that also support a possible cardio-protective effect of PDE5 inhibitors, as described in the section on patients with diabetes below.

CASE REPORTS

Within the last 10 years, a few case reports were published about patients having CV events, including MI, after taking

sildenafil but before sexual activity and not involving nitrates.[28–30] Because these are case reports with no controls, and some patients had other CV risk factors, it is difficult to determine their significance as bias may have confounded results. Although these CV events occurred before actual sexual intercourse, anxiety before sexual intercourse, which has the potential to increase oxygen demand, may play a role. It is also possible that these events were simply coincidental. There was also a case report of a 49-year-old man who developed epigastric pain and vomiting 4 hours after a fatty meal and about 3 hours after taking sildenafil and having sexual activity.[31] On admission to hospital, this man had electrocardiogram evidence of an inferoposterior MI and experienced cardiac arrest associated with torsade de pointes rhythm. He was successfully resuscitated and defibrillated. In this case, it is likely that the ventricular dysrhythmia was due to the acute MI, which may have been precipitated by the increased oxygen demand associated with sexual activity. Although sildenafil enabled sexual activity, there is no direct evidence that sildenafil per se directly precipitated the MI or torsade de pointes. There also was a case report about a patient who had a cardiac arrest after using an over-the-counter sexual enhancement medicine that apparently contained tadalafil plus a substance containing alkyl nitrites, one form of poppers.[32]

This case points out several important lessons. Over-the-counter drugs that are advertised as sexual enhancement remedies may actually contain active ingredients, but are often not labeled as such.[33] Poppers are commonly used in the gay community to induce sphincter relaxation and for their psycho-active effects.[34] They are inhaled substances that are nitrate or nitrite donors[34] and can exacerbate the hypotension observed when nitric oxide breakdown is inhibited, as occurs with a PDE5 inhibitor.[35] When poppers and PDE5 inhibitors are used together, hypotension may occur. Therefore, it is important that the public be warned that over-the-counter sexual enhancement preparations sometimes contain PDE5 inhibitors or products that cause the same physiologic response as PDE5 inhibitors and should not be taken with nitrates, including poppers.

SAFETY OF PDE5 INHIBITORS IN PATIENTS UNDERGOING CARDIAC SURGERY

Safety of Vardenafil in Adults Undergoing Coronary Artery Bypass Graft Surgery

Studies from a group at the Virginia Commonwealth University in Richmond, VA, suggest that PDE5 inhibitors may reduce myocardial ischemia/reperfusion injury in experimental MI models.[36] If this is the case, PDE5 inhibitors administered as pre-treatment in a controlled setting, such as coronary artery bypass graft (CABG) surgery, might better preserve the heart during cardio-pulmonary bypass. Ali et al[37] studied the safety of a single dose of vardenafil before CABG surgery in 10 patients and compared this to outcomes in 47 patients who did not receive vardenafil and who underwent CABG surgery. No perioperative deaths or episodes of hypotension occurred in the patients receiving vardenafil. In addition, no difference was observed in the composite of freedom from death/re-operation or re-intubation between patients receiving and not receiving vardenafil. Postoperative serum troponin levels were similar between the study groups. However, given the small sample size, no firm conclusions regarding the safety or efficacy of tadalafil can be made in the setting of CABG surgery. Of note, a recent multicenter clinical trial studying the effect of sildenafil on MI size did not observe that sildenafil reduced infarct size.[38]

Safety of Sildenafil in Children Undergoing Cardiac Surgery

In contrast to adults, there was a report in the pediatric cardiac surgery literature suggesting that sildenafil given on the day before cardiac surgery for repair of ventricular septal defect may be associated with a decrease in cardiac function.[39] This occurred in a very different patient population (children with congenital heart disease receiving a PDE5 inhibitor for pulmonary hypertension) and not in older patients with coronary artery disease who might receive sildenafil for ED. However, other reports suggest that PDE5 inhibitors are well tolerated in children with pulmonary hypertension who are undergoing cardiac surgery to correct cardiac congenital defects.[40,41]

SAFETY OF PDE5 INHIBITORS WITH CONCOMITANT CV MEDICATIONS

Safety of PDE5 Inhibitors With Anti-angina Agents Other Than Nitrates

Currently, the use of nitrates remains an absolute contraindication with PDE5 inhibitors because of the potential for the development of significant hypotension in a small number of individuals.[7] For example, among 50 subjects receiving nitroglycerin 0.4 mg and a single dose of tadalafil 5 mg, 26% of patients had standing systolic blood pressure <85 mm Hg, and 12% had standing diastolic blood pressure <45 mm Hg on day 1 of administration.[42] However, other anti-anginal agents appear to be safe to use with PDE5 inhibitors. In a study in which patients were taking beta-blockers, calcium-channel blockers, diuretics, or angiotensin-converting enzyme inhibitors for hypertension, administration of sildenafil (25–200 mg) resulted in additional modest mean reductions in systolic and diastolic blood pressure (−3.6/−1.9 mm Hg) that occurred without an increase in adverse events.[43] Neither beta-blockers nor calcium-channel blockers, some of which are also used as anti-anginal agents, are contra-indicated with the use of PDE5 inhibitors. For example, 1 study used a sublingual application of liquid nitrendipine (a calcium-channel blocker) as a potential substitute for nitroglycerin in healthy volunteers to determine if this approach would cause hypotension in individuals taking tadalafil.[44] 8 healthy male volunteers were pre-treated with 20 mg of tadalafil, 5 mg of sublingual nitrendipine, or 20 mg tadalafil plus 5 mg of nitrendipine (2 hours after tadalafil). Tadalafil alone did not significantly affect blood pressure. Nitrendipine alone

reduced blood pressure by 1.91 mm Hg ($P = .008$). 20 mg of tadalafil plus 5 mg of nitrendipine reduced blood pressure by only 2.86 mm Hg from baseline ($P < .0001$). No patients developed significant hypotension (systolic blood pressure <85 mm Hg) with the combination. The authors postulated that sublingual nitrendipine might be an appropriate alternative to nitrates in patients taking PDE5 inhibitors, but this hypothesis would need to be tested specifically in patients with ED taking a PDE5 inhibitor.

Kloner and Henderson[3] reviewed the anti-anginal agents that are not contra-indicated with PDE5 inhibitors. In the United States, these include beta-blockers, calcium-channel blockers, and the late inward sodium current blocker ranolazine. In other countries, this may include additional pharmacologic agents, such as the I_f channel blocker ivabradine that slows heart rate[45] and the metabolic agent trimetazidine that enhances glucose oxidation and inhibits fatty acid oxidation.[46] Current guidelines stress the use of beta-blockers as first-line therapy for stable angina pectoris.[47] However, beta-blockers such as propranolol, celiprolol, carvedilol, and atenolol may actually worsen ED.[48] There are exceptions. Nebivolol is a beta-blocker that also has direct vasodilating properties and may be less likely to cause ED. However, nebivolol is currently approved for the treatment of hypertension but not angina. Ranolazine, a late sodium current inhibitor, is an approved pharmacologic therapy in the United States for the treatment of angina. Ranolazine was shown to improve exercise tolerance in patients with angina, reduce episodes of angina, and reduce the use of nitroglycerin without effects on heart rate or blood pressure.[49,50] 1 pre-clinical study showed that ranolazine did not alter sildenafil-induced changes in blood pressure.[51]

Are There Situations in Which a PDE5 Inhibitor and a Nitrate May Be Used Together?

Despite the fact that the use of PDE5 inhibitors is contra-indicated in patients taking nitrates, reports in the literature suggest that under very specific conditions, the concomitant use of these drugs may be considered. Parker et al[52] studied 34 men (aged 47−80 years) with angina who received sildenafil (100 mg) or placebo followed by increasing doses of intravenous nitroglycerin ≤160 μg/min, while carefully monitoring blood pressure and heart rate. The infusion of nitroglycerin was stopped if there was a reduction in systolic blood pressure of >35 mm Hg from the pre-nitroglycerin baseline in 1 measurement, a reduction to <100 mm Hg for 1 minute, an increase in heart rate of >25 beats/min, a heart rate of >100 beats/min that persisted for 1 minute, or symptomatic hypotension. After sildenafil treatment but before nitroglycerin infusion, the decrease in systolic/diastolic blood pressure was 12/8 mm Hg compared with 5/4 mm Hg with placebo, consistent with previous studies. The median maximum tolerated dose of nitroglycerin was 80 μg/min when patients were treated with sildenafil vs 160 μg/min with placebo ($P < .001$). Sildenafil was associated with only a slightly greater maximum blood pressure decrease (4−6 mm Hg) and heart rate increase (≤1 beats/min) at nitroglycerin doses of ≤80 μg/min compared with placebo. Adverse events were mostly mild to moderate and were often associated with nitroglycerin alone; these included headache, hypotension, and dizziness. Most of the pre-specified decreases in blood pressure on nitroglycerin were asymptomatic. Only 3 of the discontinuations of nitroglycerin infusion were associated with symptomatic hypotension (2 in the sildenafil group and 1 in the placebo group). The authors concluded that patients who have taken sildenafil may tolerate intravenous nitroglycerin at low starting doses and gradual upward titration and with careful monitoring of blood pressure and heart rate.

Oliver et al[53] described the use of isosorbide mononitrate combined with sildenafil as a therapy for patients with treatment-resistant systemic arterial hypertension. They evaluated 6 patients with treatment-resistant hypertension who remained on their usual anti-hypertensive medicines but then received a single dose of sildenafil 50 mg alone, isosorbide mononitrate 10 mg alone, or the combination of the 2 medications. Sildenafil alone or isosorbide mononitrate alone acutely reduced supine brachial and central aortic blood pressures vs placebo; the combination of the 2 medications produced the greatest maximum reduction in brachial blood pressure (−26/−18 mm Hg) compared with placebo, with only minor adverse events. The combination caused a greater reduction in supine systolic blood pressure than either drug alone and a greater reduction in diastolic and mean arterial blood pressure than sildenafil alone. An additional maximum reduction in blood pressure with single-dose sildenafil (approximately −13/−10 mm Hg vs placebo) or single-dose isosorbide mononitrate (approximately −18/−14 mm Hg vs placebo) was observed in this patient population. The authors concluded that for patients with treatment-resistant hypertension, the combination of a PDE5 inhibitor with a nitrate may represent a promising treatment, but cautioned that long-term studies with larger patient samples would be needed.

Reports in the literature also suggest that the combination of PDE5 inhibitors with nitrates may be useful for the treatment of pulmonary hypertension. PDE5 inhibitors alone are now commonly used for the treatment of pulmonary hypertension.[8] These agents cause smooth muscle relaxation with some degree of selectivity for the pulmonary vessels where PDE5 is concentrated. However, even with PDE5 inhibitors and other vasodilators, the reduction in pulmonary resistance may not be adequate or may be accompanied by reductions in systemic blood pressure—characteristics that diminish clinical utility. Stehlik and Movsesian[54] described 3 patients with heart failure, pulmonary hypertension, and low systemic arterial pressure, respectively, who were taking sildenafil, in whom nitrates were added to try to further lower pulmonary hypertension. The addition of isosorbide dinitrate decreased pulmonary artery pressure by 11 mm Hg, whereas mean systemic arterial pressure fell only 4 mm Hg. The ratio of pulmonary vascular resistance to

systemic arterial resistance was decreased by 45% with the addition of the nitrate to sildenafil. The combination of sildenafil with isosorbide dinitrate was continued for several months with no episodes of marked systemic hypotension, syncope, or feeling of light-headedness. The authors concluded that the addition of nitrates to a PDE5 inhibitor can potentiate vasodilation that is relatively selective for the pulmonary circulation. Although this report was based on a small number of patients, it nevertheless suggests that in certain situations the combination of PDE5 inhibition with nitrates may have a therapeutic role.

POTENTIAL BENEFICIAL EFFECTS OF PDE5 INHIBITORS IN PATIENTS WITH DIABETES OR CARDIAC DISEASE

Do PDE5 Inhibitors Improve Survival in Patients With Diabetes?

At least 4 recent publications suggest that PDE5 inhibitors may be beneficial in patients with diabetes; however, as these publications do not report data from randomized controlled studies, findings should be interpreted with caution. Hackett et al[55] described mortality rates in men with type 2 diabetes who participated in a prospective study to determine the long-term effects of testosterone replacement therapy with testosterone undecanoate on clinical symptoms and metabolic factors. A total of 857 men in 5 primary care practices were studied over a 2-year period: 320 with normal testosterone levels were untreated; 362 with low testosterone levels were untreated; and 175 with low testosterone levels received testosterone therapy (of note, the CV safety of testosterone replacement therapy has not been adequately studied[56,57]). Of the 857 men, 175 were taking a PDE5 inhibitor, and 682 were not. Mortality rates were 11.3% in men with normal testosterone levels who were not taking testosterone therapy, 16.9% in men with low testosterone levels who were untreated, and 3.4% in men with low testosterone levels who were treated. Normal testosterone levels (hazard ratio = 0.62 [95% CI, 0.41−0.94]) or testosterone replacement therapy (hazard ratio = 0.38 [95% CI, 0.16−0.90]) were significantly associated with reduced mortality in men with diabetes. Retrospectively assessed mortality rates were 14.7% in men with diabetes not taking a PDE5 inhibitor and 1.7% in those taking a PDE5 inhibitor. Taking a PDE5 inhibitor was associated with a significant reduction in mortality in men with diabetes (hazard ratio = 0.21 [95% CI, 0.066−0.68]). Further analysis suggested that testosterone and PDE5 inhibitor use had independent benefits on mortality in men with diabetes. The authors speculated that perhaps the benefits of a PDE5 inhibitor on mortality were related to its benefits on endothelial function. They noted that PDE5 inhibitors have been shown to improve brachial artery flow−mediated dilation. In a study by Rosano et al,[58] this benefit was observed even 2 weeks after cessation of tadalafil treatment, suggesting that even intermittent exposure to a PDE5 inhibitor might have some sustained benefit on endothelial function.

Gazzaruso et al[59] studied 317 consecutive men with diabetes and angiographically documented coronary artery disease that was silent (asymptomatic but positive stress test). The presence of ED was determined by the International Index of Erectile Function-5 questionnaire. The main end point was major adverse cardiac events (MACE), with the patients followed up for a mean of 47 months. There were 49 patients who had MACE, and the prevalence of ED was greater in those with MACE (61%) than in those without MACE (36%; $P = .001$). The use of a statin and the use of a PDE5 inhibitor were associated with a lower rate of MACE. The association between use of a PDE5 inhibitor and a lower rate of MACE was statistically significant by Kaplan-Meier and univariate analyses and was of borderline significance in a multi-variate analysis. The authors discussed the concept that PDE5 inhibitors may have cardio-protective effects (Supplementary Table 2[59−64]) (see also the "Possible Cardio-Protective Effects of PDE5 Inhibitors" section below). Recently, the improvement in CV outcomes with PDE5 inhibitors in patients with known CV risk factors, especially diabetes, was reviewed by Hackett et al.[65]

Anderson et al[66] described the results of an observational study of 5,956 men with diabetes in which they assessed the association between on-demand use of a PDE5 inhibitor and mortality over a mean follow-up period of 7.5 years. Of this total, 1,359 (22.8%) men took a PDE5 inhibitor a median of 16 times. All-cause mortality rates were lower in the group that received a PDE5 inhibitor (25.2 per 1000 person-years) than in those who did not (34.0; $P < .0001$). Men on a PDE5 inhibitor had a 31% lower risk of all-cause mortality vs those not on a PDE5 inhibitor (hazard ratio = 0.69; $P < .001$). This lower risk of death in those patients taking a PDE5 inhibitor was maintained after adjusting for a number of confounding variables, including age; smoking history; history of CV disease; CV risk factors; and the use of statins, aspirin, beta-blockers, metformin, and other drugs. The rate of incident MI was lower in PDE5 inhibitor users (incident rate ratio = 0.62; $P < .0001$) and associated with a lower mortality rate in this subgroup vs PDE5 inhibitor non-users.

Finally, in a retrospective cohort study, Hackett et al[67] found that among 857 men with diabetes, treatment with PDE5 inhibitors alone or combined with statins or testosterone significantly reduced age-related mortality.

Safety of PDE5 Inhibitors in Patients With MI or Heart Failure

Evidence exists that PDE5 inhibitors may have a role in the treatment of congestive heart failure.[62] A meta-analysis by Giannetta et al[63] described 1,622 patients in 24 randomized, controlled trials of PDE5 inhibitors given in a chronic fashion to patients with heart disease, including patients with heart failure and left ventricular hypertrophy. PDE5 inhibition reduced cardiac mass in those patients with left ventricular hypertrophy and improved cardiac index and ejection fraction (Figure 2[63]). In patients with severe left ventricular hypertrophy, PDE5

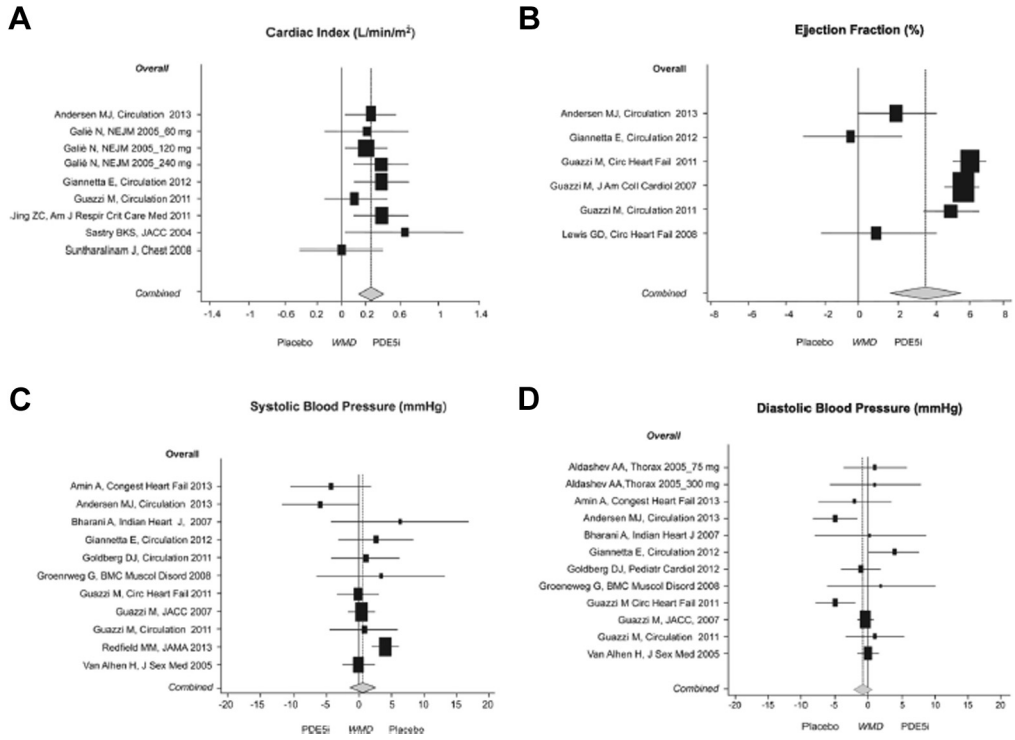

Figure 2. Effects of phosphodiesterase-5 inhibitors (PDE5i) over placebo on cardiac performance and blood pressure. Main analysis on: cardiac index (L/min/m^2) (A), ejection fraction (%) (B), systolic blood pressure (mm Hg) (C), and diastolic blood pressure (mm Hg) (D). Diamonds indicate the overall summary estimate for the analysis (width of the diamond represents 95% CI); boxes indicate the weight of individual studies in the pooled analysis. WMD = weighted mean difference. (Reproduced with permission from Giannetta et al.[63])

inhibition decreased the biomarker for heart failure, N-terminal-pro brain natriuretic peptide. In addition, PDE5 inhibition improved flow-mediated vasodilation. Importantly, the most common adverse effects were flushing, headache, epistaxis, and gastric symptoms, with no signal of increased MACE related to the PDE5 inhibitors, even though this was a sicker and older group of patients than usually described in ED studies. An article by Guazzi et al[64] studied patients with stable congestive heart failure randomized to placebo vs sildenafil over the course of 6 months, with assessment of endothelial function and exercise performance parameters. Patients receiving sildenafil demonstrated an improved exercise ventilation and aerobic efficiency, which correlated with an improvement in flow-mediated vasodilation (endothelial function). No major CV adverse events due to sildenafil and no deaths in either treatment group were reported; 2 hospitalizations occurred in the placebo group. A few patients experienced flushing. Therefore, even in the ill cardiac patient, sildenafil was well tolerated. Recently, in a Swedish nationwide observational study of 43,145 men with a first MI, among 3,068 men treated with at least 1 PDE5 inhibitor, the risk of death was 33% lower and the risk of hospitalization for heart failure was 40% lower compared with men without treatment for ED.[68]

Of note, the phase III Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) study[69] of the efficacy and safety of sildenafil vs placebo was recently completed. Safety data from this study should provide additional information on the CV safety of sildenafil in patients with heart failure.

POSSIBLE CARDIO-PROTECTIVE EFFECTS OF PDE5 INHIBITORS

In the aforementioned study by Anderson et al,[66] the authors postulated that the reduction in all-cause mortality during PDE inhibitor treatment may result from the so-called cardio-protective effect of these agents (Supplementary Table 2) and referred to animal models of MI in which the PDE5 inhibitor reduced MI size. However, in animal models of MI and reperfusion, sildenafil given at the time of reperfusion failed to reduce infarct size.[38] Another suggestion is that this benefit is due to the preservation of endothelial function by the PDE5 inhibitor.[60] In a previous study in a rabbit model of coronary artery occlusion, sildenafil did not reduce MI size, but did improve post-reperfusion coronary artery resistance, again consistent with the hypothesis that PDE5 inhibitors improve endothelial dysfunction.[61]

CONCLUSION

A review of the literature on the CV safety of PDE5 inhibitors over the last 10 years suggests that this class of drugs is safe when administered per the product label. Large placebo-controlled studies and observational studies did not show statistically

significant or clinically significant increases in major adverse cardiovascular events with the use of these agents. Rare case reports exist that describe cardiac events occurring near the time of ingestion of a PDE5 inhibitor. However, given that ED shares the same risk factors as coronary artery disease and is common in the patients with coronary artery disease, and that sexual activity increases oxygen demand and is associated with a small increase in the absolute risk of triggering MI, such case reports are not unexpected. Although nitrates remain a contra-indication with PDE5 inhibitor use, there are situations emerging where the combination of a nitrate plus a PDE5 inhibitor are being explored (eg, refractory systemic and pulmonary hypertension).

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SUPPLEMENTARY DATA

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