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Effectiveness and Safety of Phosphodiesterase 5 Inhibitors in Patients with Cardiovascular Disease and Hypertension

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Abstract Phosphodiesterase 5 (PDE 5) inhibitors are selective inhibitors of the enzyme PDE 5, which catalyzes the hydrolysis of cyclic guanosine monophosphate (cGMP), a potent vasodilator and nitric oxide (NO) donor, to its corresponding metabolites (monophosphates). The enzyme PDE 5 is widely distributed in the body, including the heart and blood vessels. Because of its distribution, it was hypothesized that its inhibition could lead to significant coronary vasodilation, which would benefit patients with coronary artery disease (CAD). This hypothesis led to the development of PDE 5 inhibitors with the first being sildenafil citrate. Subsequent studies with sildenafil in patients with CAD demonstrated a modest cardiovascular effect, but a potent action on penile erection in men, resulting in sildenafil becoming a first-line therapy of erectile dysfunction (ED). Subsequently, two more PDE 5 inhibitors (vardenafil and tadalafil) were developed and approved by the Food and Drug Administration (FDA) for the treatment of ED. Recent studies have shown several pleiotropic beneficial effects of PDE 5 inhibitors in patients with CAD, hypertension, heart failure, pulmonary arterial hypertension, diabetes mellitus and Raynaud's phenomenon. Side effects and interactions of PDE 5 inhibitors with other drugs have been minimal, with the exception of their coadministration with nitrates, which could lead to severe vasodilation and hypotension and therefore, their coadministration is prohibited. All these pleiotropic cardiovascular effects of PDE 5 inhibitors and their drug interactions will be discussed in this concise review in the context of the American College of Cardiology / American Heart Association guidelines and the recent developments in this field.

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Introduction

The posphodiesterases (PDEs) are a superfamily of enzymes that catalyze the hydrolysis of the nucleotide monophosphates cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) into their corresponding 5' monophosphates [1]. Several of the PDEs have, already, been identified and characterized including, PDE 5, PDE 7, PDE 8, PDE 9, PDE 10, and PDE 11, to name a few [2–7]. However, of all these PDEs the major research interest has been focused on PDE 5, because of its specificity in catalyzing the hydrolysis of cGMP [1, 8, 9]. PDE 5 is widely expressed in body tissues, including the corpora cavernosa of penis, systemic arteries and veins, the pulmonary arteries, the myocardium, the skeletal muscles, and the platelets [10, 11]. The hydrolysis of cGMP, a potent vasodilator and nitric oxide (NO) donor by PDE 5, shifted the emphasis of the research in discovering inhibitors of the action of PDE 5. The hope was to prevent the degradation of cGMP, increase its vascular tissue levels, and prolong the duration of its action with the expectation to use them for the treatment of CAD. This led to the discovery of sildenafil citrate in 1989, the first highly selective PDE 5 blocker. Subsequent studies with sildenafil in patients with CAD showed a modest effect, but a "surprising beneficial side effect" of sildenafil in male subjects by enhancing penile erection. These observations led to further studies with sildenafil in subjects with documented erectile dysfunction (ED), which resulted in 1998 in the approval of sildenafil by the Food and Drug Administration (FDA) for the treatment of ED. After the approval of sildenafil, two more PDE 5 inhibitors (vardenafil, and tadalafil) were developed and approved by FDA for the treatment of ED and their chemical structure is

depicted in Fig. 1. These three PDE 5 inhibitors represent the current mainstay of treatment of ED [12–14]. It is now well recognized that ED is a vascular disease and is age- and disease-dependent. The most common conditions associated with ED are CAD, pulmonary arterial hypertension (PAH), systemic arterial hypertension (SAH), heart failure (HF), diabetes mellitus (DM), and peripheral arterial disease (PAD). The association of ED with these comorbidities, presents important functional and safety implications related to the interactions of PDE 5 inhibitors with the drugs that these patients might be taking. Recent studies have also shown that PDE 5 inhibitors possess several other beneficial cardiovascular effects besides their action on ED. For these reasons, the treatment of ED has now been shifted from the realm of urologists to the realm of general practitioners and cardiologists. All these actions and interactions of PDE 5 inhibitors will be discussed in this review in the context of the American College of Cardiology / American Heart Association guidelines [15] and the recent developments in this field.

Cardiovascular Disease

Cardiovascular disease (CVD) remains a source of considerable morbidity and mortality despite significant advances in the prevention, diagnosis, and treatment. At present, CAD and cerebrovascular disease are the most common causes of morbidity and mortality globally and they are projected to remain the same till the year 2030 [16]. Also, a growing evidence indicates that ED frequently coexists with CAD and may precede its onset as has been demonstrated by clinical trials and retrospective analyses [17, 18]. In addition, in clinical and experimental studies PDE 5 inhibitors have shown beneficial cardiovascular effects. In men with ED, PDE 5 inhibitors lowered BP and improved cardiac hemodynamic function [19]. In experimental animal studies sildenafil provided a cardioprotective effect given immediately [20], 30 minutes [21], 24 hours [22, 23], and 4 weeks before coronary artery occlusion [24], or reperfusion [25]. Likewise, vardenafil [26], and tadalafil [27•] reduced infarct size, when given 30 to 120 minutes before coronary artery occlusion in animal models. In addition, PDE 5 inhibitors increase the endothelial and inducible NO synthase, reduce cardiac hypertrophy and apoptosis, preserve myocardial fractional shortening, and improve survival [28]. In clinical trials in male subjects with ED and stable CAD, administration of a single dose of sildenafil 50 to 100 mg [29], or vardenafil 10 mg [30], while the patients were off nitrates, were well tolerated and improved cardiac function and ED significantly more than placebo. These patients were previously exercised on a Bruce protocol to symptom limited exercise and ST depression ≥1 mm, and to a level of exercise equivalent to the effort produced by sexual activity. Compared to placebo, vardenafil did not alter the exercise time ($p=0.39$), or the time to awareness of angina (p=0.59), but significantly prolonged the time to ischemic threshold ($p=0.0004$) as depicted in Fig. 2. In addition, at peak exercise vardenafil did not significantly affect the BP, heart rate (HR), or the rate pressure product compared to placebo. The drugs were well tolerated and the most common side effects were facial flushing and headache which were of mild to moderate severity and were short-lived. Similar findings have also been reported by other investigators [31, 32]. In a study of 31 patients with stable CAD and ED [33], the hemodynamic effects of a single dose of sildenafil 100 mg (n=10), or isosorbide mononitrate (ISMN) 40 mg (n=11), were compared to placebo (n=10). The hemodynamic effects of sildenafil -placebo subtracted are listed in Table 1. Compared with baseline, sildenafil produced greater reductions in systolic blood pressure (SBP) at 2 hours, pulmonary arterial pressure (PAP) at 4 hours and systemic and pulmonary vascular resistance at 1 and 4 hours, respectively, and increased slightly the cardiac index at 1 hour. The other parameters were not different than placebo (Table 1). With

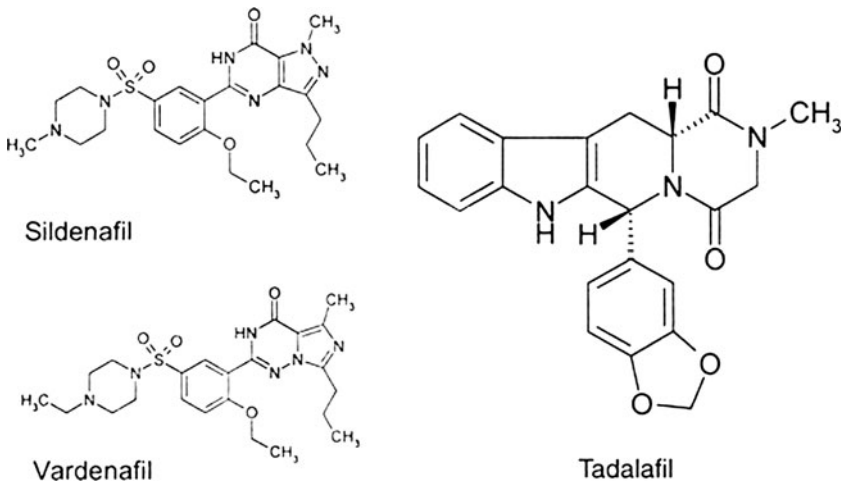

Fig. 1 This figure depicts the chemical structures of the 3 PDE 5 inhibitors, sildenafil, vardenafil, and tadalafil, which have been approved by the FDA for the treatment of ED. The chemical structures of sildenafil and vardenafil are similar and both drugs have similar half lives. In contrast, the chemical structure of tadalafil is different and also its half life is much longer than the two other PDE 5 inhibitors

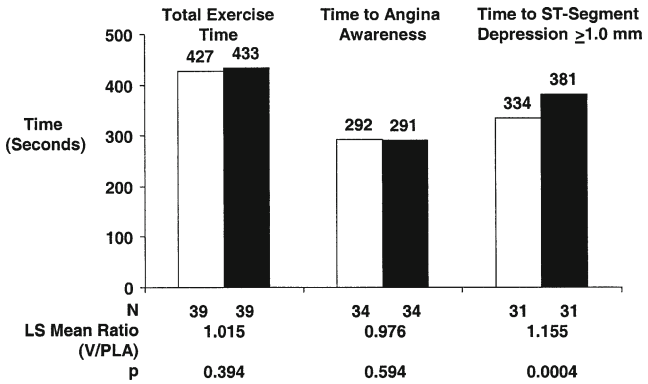

Fig. 2 This figure shows the effects of vardenafil (V) 10 mg, compared to placebo (PLA) on the exercise parameters in patients with stable CAD. Vardenafil increased significantly the time to onset of ST depression of ≥1 mm from baseline compared to placebo ($p<0.0004$). The other two parameters were no different than placebo. *Reprinted from Journal of the American College of Cardiology*, 40, Thadani et al. [29], The effect of vardenafil, a potent highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease, 2006–2012, 2002, with permission from Elsevier

respect to the effects of sildenafil and ISMN on BP, ISMN produced greater reductions in mean arterial pressure (MAP) than sildenafil (-22 vs. -10 mmHg, respectively). These data demonstrate the danger of combining PDE 5 inhibitors and nitrates, because they could result in severe or even lethal reduction of BP since both agents are NO donors.

Essential Hypertension

Several lines of evidence indicate that there is an increased prevalence of ED in patients with hypertension compared to normotensive subjects. This prevalence has been estimated to range from 15 % to 46 % depending on the characteristics of studied populations [34]. Hypertension is associated with endothelial dysfunction due to decreased NO, which in turn affects the balance between vasodilation and vasoconstriction. The reduced NO constitutes a link between hypertension and ED, since ED is considered a vascular disease and the bioavailability of NO is also reduced in ED. Besides hypertension, ED is also a common complication of antihypertensive drugs among which the most important are the central sympatholytics, the peripheral sympatholytics, the diuretics, the aldosterone antagonists, and the β-blockers. The calcium channel blockers (CCB), the angiotensin converting enzyme (ACE) inhibitors, and the angiotensin receptor blockers (ARB) are rarely implicated as a cause of ED [35, 36]. The antihypertensive effectiveness and possible adverse events of PDE 5 inhibitors have been analyzed in several studies. In one study, the data from 4,274 subjects with hypertension and ED, 18 years old or older, from 18 different, double-blind, placebo-controlled studies were analyzed [37]. Of these patients, 2,881 who were not taking any antihypertensive drug, were randomized to sildenafil 50–200 mg /day (n=1,837) or placebo (n=1,044). Of the other 1,094 patients who were taking≥1 antihypertensive drugs / day were also randomized to sildenafil 50–200 mg/day (n=704) or placebo (n=390). All patients were followed for 6 weeks to 6 months. The drug classes involved in the treatment of hypertensive patients were diuretics, β-blockers, α1- blockers, ACE inhibitors, and CCBs. All the subjects included in these studies were in a stable relationship with a female partner and did not have any anatomic defects of their penis. Patients with BP>170/110 mmHg or<90/50 mmHg at screening were excluded from participation. The incidence rates of treatment-related adverse events in patients taking sildenafil in combination with antihypertensive medications were not different from those taking sildenafil in combination with placebo. The adverse events noted were very rare including hypotension (< 1 %) and (0 %) for cardiovascular events [37]. With respect to the incidence of ED, this was noted in 30 % of those taking sildenafil in combination with antihypertensive drugs compared to 28 % for those taking sildenafil in combination with placebo ($p=0.93$). Similar results have been reported from a review of 19 studies in hypertensive patients with multiple comorbidities and on various antihypertensive regimens randomized to sildenafil, vardenafil, or tadalafil [38•]. This meta-analysis showed that PDE 5 inhibitors were effective, safe, and well tolerated regardless of the etiology and severity of the comorbid conditions. In another study of 371 subjects with hypertension on single or multiple antihypertensive drugs randomized to tadalafil 10 mg/day or placebo [39], demonstrated similar reductions in BP and adverse events (Table 2). Similarly, in another double-blind, placebo-controlled, multicenter trial 568 patients with hypertension and ED taking multiple antihypertensive drugs were randomized to sildenafil 50–100 mg/day (281) or placebo (281) and were followed for 12 weeks [40]. Sildenafil improved ED and did not cause any serious adverse BP effect or other effects that were different from placebo.

In a proof of concept study, the acute effects of sildenafil 50 mg given either alone or in combination with ISMN 10 mg on brachial and central BP were tested in six patients with resistant hypertension taking≥3 drugs [41]. The baseline brachial and central BP was 169/93 mmHg and 135/82 mmHg, respectively. Adding sildenafil to baseline drugs, resulted in further reductions in brachial and central BP of 10/8 mmHg and 8/7 mmHg, respectively compared with placebo ($p<0.05$). The addition of the combination of sildenafil with ISMN resulted in greater reduction in brachial and central BP of 20/14 mmHg and 22/14 mmHg, respectively ($p=0.002$) compared with placebo. In addition, the augmentation index adjusted for heart rate (HR) and the reflected pressure wave

Table 1 Hemodynamic changes from baseline with sildenafil placebo subtracted in patients with stable coronary artery disease. Mean changes (95 % CI). *Data from* Jackson et al. [32]

Sildenafil-Placebo				
Parameter	1 hour	2 hours	4 hours	6 hours
SBP (mmHg)	- 9.6 (-20.2, 1.1)	- 13.5 (-25.8,-2.2)	- 5.3 (-16.5, 6.0)	- 6.0 (-17.8, 5.8) 5.8)
DBP (mmHg)	- 3.8 (-11.5, 3.9)	- 5.2 (-12.8, 2.4)	- 5.0 (-11.7, 1.7)	- 4.3 (-10.8, 2.2)
MAP (mmHg)	- 5.4 (13.3, 2.4)	- 6.5 (-15.1, 2.0)	- 5.3 (-12.6, 2.0)	- 4.6 (-12.7, 3.4)
PAWP (mmHg)	- 0.4 (-2.2, 1.4)	- 0.2 (-1.8, 1.4)	0.6 (-1.1, 2.3)	0.3 (-1.4, 2.0)
MPAP (mmHg)	- 1.5 (-4.0, 1.0)	- 1.4 (-3.5, 0.7)	- 2.6 (-4.9, -0.4)	- 1.5 (-3.3, 0.3)
HR (b/min)	5.0 (-0.2, 10.2)	0.6 (-4.2, 5.4)	- 1.2 (-5.2, 2.9)	- 1.2 (-6.5, 4.1)
CI (L/min/m2)	0.33 (0.01, 0.65)	0.33 (-0.02, 0.67)	0.24 (-0.09, 0.58)	0.04 (-0.36, 0.44)
SVI (ml/m2)	2.0 (-2.6, 6.7)	5.4 (-0.61, 11.4)	4.4 (-1/1, 10.0)	1.9 (-4.7, 8.6)
SVR (dyn/sec/cm5)	-255 (-498, - 11)	-242 (-500, 16)	-199 (-375, 24)	- 114 (-343, 116)
PAVR (dyn/sec/cm5)	-28 (-56, -0.7)	-28 (-57, 0.4)	-65 (-97, -34)	-23 (-54, 7)

CI Confidence intervals; *SBP* Systolic blood pressure; *DBP* Diastolic blood pressure

MAP Mean arterial pressure; *PAWP* Pulmonary artery wedge pressure; *MPAP* Mean pulmonary artery pressure; *HR* Heart rate; *CI* Stroke index; *SVI* Stroke volume index

SVR Systemic vascular resistance; *PAVR* Pulmonary artery vascular resistance

were significantly reduced with the addition of the combined drugs ($p<0.002$). The pulse wave velocity and HR were not significantly affected, and no significant adverse clinical effects were noted with the addition of sildenafil with ISMN to background antihypertensive drugs.

Heart Failure

The prevalence of ED is high in patients with HF, and yet PDE 5 inhibitors are not routinely given in these patients for lack of experience and the fear of side effects. However, several small, short-term studies have demonstrated a beneficial effect of PDE 5 inhibitors regarding ED and cardiac function in such patients [42, 43]. In a small study, 20 patients aged 20–88 years with stable HF and an ejection fraction<35 % were randomized to sildenafil 50 mg/day or placebo in a double-blind, two-way crossover study of 7-day intervals between the two phases, after the patients were off their background therapy for 12 days [43]. Sildenafil improved the cardiac index (CI) by 0.37 L/min/m2 from a baseline of 2.3 L/min/m2, ($p<0.0001$), as well as the other study parameters (Table 3). In other small studies, sildenafil reduced the systemic vascular resistance and aortic stiffness and improved exercise time, 6-minute walk distance, and quality of life [44]. It has been demonstrated that the

Table 2 Mean changes from baseline in SBP and DBP with Tadalafil 10 mg/day or placebo in hypertensive patients taking one or more drugs. Data from Kloner et al. [38•]

One drug	Tadalafil (n=140)	Placebo (n=59)
MBSBP (mmHg)	143	142
Mean change (mmHg)	- 5.7	- 3.4
MBDBP (mmHg)	83	85
Mean change (mmHg)	- 2.2	- 2.1
Two or more drugs	Tadalafil (n=126)	Placebo (n=44)
MBSBP (mmHg)	139.6	136.6
Mean change (mmHg)	- 2.6	0.89
MBDBP (mmHg)	83.5	81.6
Mean change (mmHg)	- 2.7	- 2.2

MBSBP Mean baseline systolic blood pressure; *MBDBP* Mean baseline diastolic blood pressure

Table 3 Hemodynamic changes with sildenafil 50 mg or placebo in patients with CHF. Data from Hirata et al. [42]

	Baseline parameters (M + - SD)		Parameters (Difference)		*P* value
	Sildenafil	Placebo	Sildenafil	Placebo	
Brachial SBP (mmHg)	131	130	- 8.6	+ 4.9	<0.0001
Brachial DBP (mmHg)	67	67	- 4.8	+ 3.8	<0.0001
Aortic SBP (mmHg)	117	117	- 7.5	6.4	<0.0001
Aortic DBP (mmHg)	67	67	- 5.1	+ 4.0	<0.0001
Aix (%)	14	13	- 0.8	+ 2.1	<0.0001
SVR (dyn/sec/cm5)	1705	1660	- 326	+ 153	<0.0001

Aix Augmentation index

expression of the PDE 5 enzyme is minimal in normal myocardium and is upregulated in diseased myocardium [45]. In this study, the myocardial PDE 5 enzyme expression and its cellular distribution were determined in left ventricular samples from patients with end-stage HF and from normal heart donors. The myocardial PDE 5 protein was 4.5 times higher in the samples from HF hearts compared to normal hearts, and also the PDE 5 enzyme expression was significantly correlated with the myocardial expression of markers of oxidative stress. In this and other studies [46], the histological examination showed that the PDE 5 enzyme was mainly expressed in the vascular smooth muscle of donor hearts, whereas in diseased hearts it was increased in both the cardiac myocytes and vascular smooth muscle.

The beneficial effects of the PDE 5 inhibitor sildenafil in patients with HF have been attributed to the increased production of cAMP. In diseased hearts, the protein kinase G activity induced by cGMP is inhibited; therefore, cGMP shifts its action preferentially, in the production of cAMP, which in turn activates protein kinase A leading to increase in intracellular calcium concentration and improvement of myocardial contractility. In addition, sildenafil activates other mechanisms that prevent the adverse cardiovascular remodeling after myocardial infarction in the mouse model [46]. Sildenafil in comparison to placebo, preserved left ventricular function and decreased fibrosis, apoptosis, and left ventricular hypertrophy (LVH) through the inhibition of the RhoA/Rho-kinase pathway. The inhibition of this pathway has been associated with prevention of atherosclerosis, post-myocardial remodeling, and LVH [46].

Recently, the focus of research interest has been shifted to the mitochondrial function of the failing myocardium [47••]. It has been shown that the mitochondria contribute to myocardial function, but their number is decreased in the sick myocardium. Therefore, one of the ways to improve myocardial contractility is to increase the number of mitochondria, the "mitochondrial biogenesis" [48, 49]. Recent studies suggest the importance of ENOS/NO/cGMP pathway in the biogenesis of mitochondria. The endothelial nitric oxide synthase (eNOS) synthesizes NO, which in turn enhances the production of cGMP. Both the NO and cGMP are expressed in the heart where they activate many potential cardioprotective pathways among which, is the activation of mitochondrial biogenesis [49, 50]. The eNOS/NO/cGMP pathway can be modulated pharmacologically through inhibition of PDE 5. It has been shown that PDE 5 inhibitors stimulate mitochondrial biogenesis through upregulation of peroxisome proliferator-activated receptor gamma coactivator 1a (PGC1a) with subsequent increase in mitochondrial DNA (mtDNA) content [51]. Compelling evidence suggests that PDE 5 inhibitors can delay the progression of HF and reverse cardiac remodeling in animal models and humans. A literature review from 1980 to 2011 found an improvement in CI, ejection fraction, and other markers of heart function in patients with HF NYHA functional class II-III treated with PDE 5 inhibitors [52].

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a progressive disease resulting from the remodeling of the small pulmonary arteries, which leads to the elevation of pulmonary artery pressure (PAP). The end result is right ventricular hypertrophy (RVH), right heart failure and eventual death [53]. The cause of PAH is either primary (idiopathic), or secondary to various other causes. PAH is defined hemodynamically, as a mean PAP>25 mmHg at rest or>30 mmHg with exercise. If PAH is left untreated, the survival rate is approximately 68 %, 48 %, and 34 % in 1, 3, and 5 years, respectively. With treatment, the survival rate improved to 91 % to 97 % after one year, and 84 % to 91 % after 2 years of treatment [54]. PAH is also associated with ED and treatment with PDE 5 inhibitors improves both ED and PAH.

Sildenafil has been shown to be effective in patients with PAH, either primary or secondary [41, 55–58]. In a randomized, double-blind, placebo-controlled study, 278 patients with PAH functional class II- III were randomized to sildenafil or placebo and followed for 12 weeks, in the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER-1) study [56]. Then, they entered an open-label, uncontrolled extension study (SUPER- 2) that continued until the last patient completed 3 years of treatment. In the SUPER- 1 study, the patients received sildenafil 40 mg three times/day, or placebo for 6 weeks and were uptitrated to sildenafil 80 mg three times/day as tolerated and were followed for 3 years. At the end of 3 years, 187 patients of the 259 patients who entered the SUPER-2 study were alive, 53 had died, and 37 had been censored. Of the alive patients, 46 % increased their 6-min walk distance and 60 % maintained or improved their baseline functional class status. In another double-blind, placebo-controlled study, 66 Chinese patients with PAH functional class II- III, were randomized 2:1 to vardenafil 5 mg/day for 4 weeks, then to 5 mg twice daily (n=44), or placebo (n=22) and were followed for 12 weeks. All patients who completed the double-blind trial, were given the opportunity to enter a 12-week open label extension study with vardenafil 5 mg twice daily irrespective of their double-blind treatment regimen. Vardenafil increased the 6-min walk distance by 59 meters compared to placebo which decreased it by 10 meters. The mean placebo-corrected increase in the 6-min distance with vardenafil was 69 meters (95 %, CI 41–68, $p<0.001$). Also, the mean PAP was decreased with vardenafil ($p<0.047$), but not with placebo [57]. In addition, the mean Borg dyspnea index was decreased with vardenafil by – 0.4 (95 % CI – 0.9 to – 0.0, $p<0.046$). In a third representative

study, 406 patients with PAH either treatment naïve, or on background therapy with bosentan were randomized to placebo (n=82), and tadalafil 2.5 mg/day (n=82), 10 mg/day (n=80), 20 mg/day (n=82), or 40 mg/day (n=79) in the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST-1) study and were followed for 16 weeks. Tadalafil increased—dose-dependently—the 6 min walk distance, but only the 40 mg/day dose achieved statistical significance ($p<0.001$). The placebo- corrected effect of tadalafil in the 6-min walk distance in the bosentan-naïve patients, was 33 meters, whereas in the bosentan treated patients was 44 meters. There were no significant changes in the functional class noted with either tadalafil or placebo [58]. From the patients who completed the PHIRST-1 study, 357 were enrolled into the PHIRST- 2 study, an open-label extension [59]. These patients received tadalafil 20 or 40 mg/day and were followed for a total of 52 weeks. Of the 357 patients who entered the PHIRST- 2 study, 293 completed it. All these patients maintained their 6-min walk distance and all the other parameters achieved in the PHIRST- 1 study. In all these studies, the drugs were well tolerated and there were no significant adverse events noted.

Diabetes Mellitus

Diabetes mellitus is a common disease and its incidence increases with the gain of weight and the advancement of age. Also, ED is a highly prevalent disorder among patients with DM [60, 61]. The pathophysiology of ED in diabetic patients is multifactorial and involves endothelial dysfunction, decreased function of the NO/cGMP pathway, diabetic control, oxidative stress, microangiopathy, and diabetic neuropathy. The management of ED in diabetic patients has been revolutionized with the discovery of PDE 5 inhibitors, which are now the first-line therapeutic option for diabetic patients with ED. The effectiveness of PDE 5 inhibitors in these patients is due to the improvement of NO/cGMP pathway, which is deficient in these patients [62]. This is one of the reasons diabetic subjects are less responsive to PDE 5 inhibitors than non diabetic subjects. Regardless of this resistance to treatment, several prospective, randomized, double-blind, placebo-controlled studies have shown that PDE 5 inhibitors to be effective and safe in such patients [63–65]. Some studies have also shown that PDE 5 inhibitors, besides improving sexual function, they also benefit the diabetic subjects by decreasing HA1c levels, and decreasing proteinuria [66].

Rainaud's Disease, Raynaud's Phenomenon

For simplicity and because the treatment is the same for both conditions, the term Raynaud's phenomenon (RP) will be used exclusively in this review. RP is a common condition with an incidence of 3–5 % in healthy persons [67]. It is also a complication of collagen diseases, especially scleroderma. It was first described by Maurice Raynaud in 1862 and is defined by a cold-induced episodic onset of vasospasm of digital arteries and precapillary arterioles, with tissue discoloration and may lead to superficial ulceration or tissue necrosis requiring amputation. Different medical therapies have been tried for this condition including calcium channel blockers (CCB), ACE inhibitors, $\alpha 1$ adrenoceptor blockers, and selective serotonin reuptake inhibitors with limited success [68]. Recently, PDE 5 inhibitors have been used for this condition with greater success [69–74]. In an open-label pilot study, 40 subjects with RP were treated with vardenafil 10 mg twice daily for 2 weeks. Digital blood flow was measured by laser Doppler flowmetry at room temperature and during cold exposure before treatment, 1 hour after initial drug administration, and after 2 weeks of treatment. Blood flow was improved by vardenafil in 28 (70 %) of patients, and did not change in 12 (30 %) of patients [69]. The blood flow changes were 21.0±4.9 % (SEM) at 1 hour and 30.0±5.7 % at 2 weeks of treatment in room temperature, and 18.8±4.4 % at 1 hour and 35.1±7.5 % in cold temperature after 2 weeks of treatment ($p<0.01$). Similar results have been reported in a double-blind, placebo-controlled study of 16 symptomatic patients treated with sildenafil 50 mg twice daily or placebo [70]. The symptoms decreased significantly with sildenafil compared to placebo (52±18 % vs. 35±14 %, $p<0.006$), and the digital blood flow was quadrupled with sildenafil compared to placebo ($p<0.0004$). In another study of 15 patients with primary RP, the symptoms and skin lesions were improved with sildenafil 100 mg compared to 50 mg [71]. Beneficial effects have also, been reported with tadalafil in 25 patients with secondary RP resistant to vasodilator therapy [72]. In other studies, tadalafil improved the symptoms and skin lesions in significantly more patients than placebo ($p<0.0001$) in one study, whereas in another study, tadalafil was not different than placebo in decreasing the cold-induced vasoconstriction in patients with RP [73]. Beneficial effects of PDE 5 inhibitors have also been reported from a review of small clinical trials and case report series from 1990 to 2008 [74].

Discussion and Conclusions

The PDE 5 inhibitors are selective blockers of the PDE 5 enzyme, which catalyzes the hydrolysis of cGMP, a potent vasodilator and NO donor to its inactive metabolites. The inhibition of the widely distributed PDE 5 enzyme is associated with several beneficial pleiotropic effects discussed in this concise review. From the data presented in previous sections of this review, it appears that PDE 5 inhibitors are

safe and well tolerated by patients with ED coexistent with other comorbid conditions such as CAD, hypertension, HF, DM, PAH, and RP. Their administration to patients with CAD is associated with cardiovascular protection [20–25], hemodynamic improvement, and relief of symptoms, including prolongation of walking distance [19, 28–32]. Care should be taken with patients receive nitrates in which case, their coadministration is prohibited, because both agents increase the levels of NO and cGMP and could lead to severe hypotension and even death. However, in patients who have received either sildenafil or vardenafil, nitrates can be safely administered 24 hours after the use of these drugs [19]. Regarding tadalafil, nitrates can be safely administered 48 hours later since this drug has a prolonged duration of action [19]. Concerning the coadministration of nebivolol, an NO donor with phosphodiesterase 5 inhibitors the clinical information is limited. However, an in vitro study has shown that the addition of sildenafil to nebivolol did not increase its vasodilating effects in contrast to the addition of sildenafil to nitrates, which increased significantly its vasodilating effects [75]. According to this study, nebivolol can be safely coadministered with PDE 5 inhibitors in patients with CAD and hypertension.

Also, patients with ED and hypertension receiving other antihypertensive drugs, the addition of PDE 5 inhibitors is well tolerated and improves sexual function and BP [35–37, 38•, 39, 40]. Some caution should be exercised in the presence of α1 adrenoceptor blockers and potent arterial vasodilators such as dihydropyridine CCBs, in which case the administration of PDE 5 inhibitors could potentiate their antihypertensive effect.

Regarding patients with stable HF, PDE 5 inhibitors given in tolerated doses, provide hemodynamic improvement, decrease their symptoms and improve their quality of life, in addition to the improvement in their sexual function [43–45]. Recent studies have shown the upregulation of cGMP and NO in experimental animals [46] and the induction of mitochondrial biogenesis with improvement in the contractile function of the heart [47••, 48–52].

The PDE 5 inhibitors have also, shown important beneficial effects in patients with PAH for which have been approved by the FDA as a first line therapy. They improve the cardiac hemodynamic function of these patients by lowering pulmonary vascular resistance, improve their quality of life, and prolonging their life expectancy [53–59]. In addition, they improve their sexual function in the presence of ED.

In patients with DM and ED, PDE 5 inhibitors are safe, well tolerated and improve their sexual function [60–65]. In addition, they do not affect the action of antidiabetic drugs, and may show beneficial effects by lowering the microalbuminuria and decreasing the levels of HA1c [66].

Finally, The PDE 5 inhibitors have, lately, been used successfully for the treatment of RP, for which they have been approved by the FDA as a primary indication. They alleviate or prevent the cold-induced vasospastic attacks, increase the digital skin blood flow and help the healing of skin lesions.[67–74]. In addition, they improve sexual function in the presence of ED.

In conclusion, the presented data indicate that that the PDE 5 inhibitors used in all the conditions previously discussed, are effective, safe and fairly well tolerated by most patients. The most common adverse effects noted from their administration, include headaches, facial flushing and rhinitis which are of mild to moderate severity. They can be safely administered in patients receiving other drugs with the exception of patients with CAD receiving nitrates, in whom their coadministration could cause severe hypotension, and even death. Therefore, their coadministration in these patients is strictly prohibited. However, nitrates can be safely administered after 24 hours from the last use of sildenafil and vardenafil, and 48 hours after the last use of tadalafil.

Compliance with Ethics Guidelines

Conflict of Interest Steven G. Chrysant declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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