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Cardiac Effects of Phosphodiesterase-5 Inhibitors: Efficacy and Safety

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Abstract

The coexistence of cardiovascular disease and erectile dysfunction is widespread, possibly owing to underlying endothelial dysfunction in both diseases. Millions of patients with cardiovascular disease are prescribed phosphodiesterase-5 (PDE5) inhibitors for the management of erectile dysfunction. Although the role of PDE5 inhibitors in erectile dysfunction therapy is well established, their effects on the cardiovascular system are unclear. Preclinical studies investigating the effect of PDE5 inhibitors on ischemia-reperfusion injury, pressure overload-induced hypertrophy, and chemotoxicity suggested a possible clinical role for each of these medications; however, attempts to translate these findings to the bedside have resulted in mixed outcomes. In this review, we explore the biologic preclinical effects of PDE5 inhibitors in mediating cardioprotection. We then examine clinical trials investigating PDE5 inhibition in patients with heart failure, coronary artery disease, and ventricular arrhythmias and discuss why

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Author Contribution

ISJ and SR had the idea for the article. SR wrote the first draft. All authors contributed to literature search, drafting, and critically revising the work. All authors approved the final version.

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Competing Interests

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the studies have yet to show positive results and efficacy with PDE5 inhibition despite no safety concerns.

Keywords

Cardiovascular disease; Phosphodiesterase 5 inhibitor; Heart failure; Cardioprotection

Introduction

Cardiovascular disease remains the leading cause of death internationally. The World Health Organization (WHO) estimated the number of cardiovascular deaths in 2016 to be approximately 18 million people, and lifetime risk of cardiovascular disease exceeds 60% [1, 2]. In the USA, about 700,000 people die annually of cardiovascular disease [3, 4]. The estimated economic burden of heart disease in the USA is $219 billion per year [4].

Erectile dysfunction (ED) is a widespread, often underreported medical condition. Surveys in the USA have estimated the national prevalence of ED at 30% of men aged 50–59 years, with rising prevalence associated with increasing age [5, 6]. Generally perceived as a vascular complication due to poor perfusion, ED is commonly found coexisting with other medical comorbidities including cardiovascular disease, diabetes, and obesity [7].

The discovery of oral phosphodiesterase-5 (PDE5) inhibitors that revolutionized management of ED in the late 1990s was an incidental observation during cardiac research [8, 9]. Since PDE5 hydrolyzes cyclic guanosine monophosphate (cGMP) in the cardiopulmonary vasculature, researchers aimed to establish a new anti-anginal agent using PDE5 inhibitors to prolong cGMP activity and promote vasodilation of the coronary arteries. However, with early unconvincing results suggesting PDE5 is minimally present in cardiomyocytes, this pursuit was abandoned [9–12]. During these studies, however, patients with ED reported improved erectile function, leading to extensive research culminating with the United States Food and Drug Administration (FDA) ultimately approving PDE5 inhibitors for ED treatment.

PDE5 inhibitors modulate the cardiovascular system through the interplay of cGMP and nitric oxide (NO), a potent vasodilator facilitating smooth muscle relaxation. NO, produced by the vascular endothelium, upregulates intracellular cGMP, triggering a cyclical pathway propagating further NO production [13]. PDE5 degrades cGMP, reversing the vasodilatory effects described. Therefore, modulation of PDE5 plays a crucial role in circulatory regulation and vascular tone.

Due to the common coexistence of cardiovascular disease and ED, the cardiac impact of PDE5 inhibition has since been revisited, and daily PDE5 inhibitor use as a dual-pronged approach as management of ED and cardiovascular disease has been proposed [14]. This literature review examines the background research, preclinical animal studies, and clinical trials of PDE5 inhibitors in patients with cardiovascular disease.

Methods

This is a narrative review of the literature discussing the evidence behind and potential implications of use of PDE5 inhibitors in cardiovascular disease. Data and manuscripts reported here were identified through the United States National Library of Medicine PubMed/MEDLINE database, with keywords including “phosphodiesterase-5 inhibitors,” “cardiovascular,” “ischemia-reperfusion,” “myocardial infarction,” “volume overload,” “heart failure,” “arrythmia,” and “cardioprotection”. Ongoing clinical trials were identified using the United States Clinical Trials website using the search terms “phosphodiesterase-5 inhibitors” and “cardiac” and restricting results to “recruiting” or “active, not recruiting” status.

PDE5 Expression

The general consensus is that cardiomyocytes likely normally express a minimal, basal level of PDE5 [9–12]. PDE5 upregulation has been reported in diseased cardiac tissue such as in the setting of heart failure [15–18]. However, the degree to which PDE5 is upregulated in cardiovascular disease is unclear and likely varies. The limited effect of PDE5 inhibitors in the cardiovascular system may be explained, at least in part, by the basal level of PDE5 in healthy cardiomyocytes compared to the degree of upregulation of PDE5 expression in patients with cardiovascular disease. To some extent, it could be reasonable to assume that the conflicting data from clinical studies were derived from patients with a varying degree of upregulated PDE5 among those with cardiovascular disease.

Pharmacokinetics of PDE5 Inhibitors

The most common PDE5 inhibitors are sildenafil, vardenafil, and tadalafil, each of which presents differences in pharmacokinetics. Sildenafil is categorized as class 1 by the Biopharmaceutical Classification System, suggesting high solubility and high permeability. Sildenafil is rapidly absorbed and reaches peak plasma concentration within 0.5–2.5 h, and it is primarily metabolized by the cytochrome P-450 isoenzyme CYP3A4, with a half-life of approximately 3–5 h [19]. Vardenafil is considered class 2 by the Biopharmaceutical Classification System, suggesting low solubility and high permeability. Vardenafil is rapidly absorbed achieving peak plasma concentration within 0.25–3 h, and it is primarily metabolized by CYP3A4, with a half-life of approximately 4–5 h [19]. Tadalafil is also a class 2 agent by the Biopharmaceutical Classification System, and it is similarly rapidly absorbed reaching peak plasma concentration at an average of 2 h. Tadalafil is primarily metabolized by CYP3A4 as well, but it has a half-life of approximately 17–20 h [19].

Preclinical Studies of PDE5 Inhibition in Cardiovascular Disease

In preclinical studies, cardioprotective effects of PDE5 inhibitors have been identified following ischemia-reperfusion injury, pressure overload-induced hypertrophy, and chemotoxicity. PDE5 inhibition in ischemia-reperfusion injury has improved cardiac function and decreased cardiomyocyte apoptosis and necrosis [20]. In addition, PDE5 is upregulated in cardiac pressure overload, with PDE5 being directly associated with pro-

hypertrophic effects [21]. Via cGMP and protein kinase G (PKG) subtype I-alpha, PDE5 inhibition likely mediates an anti-remodeling response to left ventricular pressure overload [22]. Furthermore, doxorubicin-induced chemotoxicity has been significantly reduced by PDE5 inhibition, likely by reducing cardiomyocyte death via upregulation of NO synthase and activation of PKG [23, 24]. Taken together, these biologic effects have been particularly revealing given the general consensus that cardiomyocytes normally express minimal PDE5 [9–12].

Preclinical Studies in Myocardial Infarction

Ischemia-reperfusion injury occurs due to an interval of ischemia inducing downstream reactive oxygen species overproduction. This reduces NO release, leading to an imbalance causing inflammation and apoptosis despite reperfusion [25]. With lower levels of NO available during ischemia, less cGMP is produced, contributing to negative effects on cardiac function and vascular circulation.

PDE5 inhibitors demonstrated a protective, anti-apoptotic effect in isolated cardiomyocytes exposed to ischemia-reperfusion injury [20, 23]. The cardioprotective effects of PDE5 inhibition were mediated, at least in part, by increased NO production and activation of protein kinase C [26, 27]. It is worth noting that different isoforms of protein kinase C appear to have opposing mechanistic roles in cardiac ischemia-reperfusion injury [28]. The interplay of these mechanisms leads to downstream phosphorylation of additional intermediary factors including extracellular signal-regulated kinases (ERK) and glycogen synthase kinase 3 beta before ultimately opening ATP-sensitive potassium (K_{ATP}) channels [20, 29]. The critical step of opening mitochondrial K_{ATP} channels limits against ischemia-reperfusion injury through regulation of intracellular calcium and ATP and may represent the final step in the mechanism by which PDE5 inhibitors convey cardioprotection.

Early studies in a rat model showed improved ventricular recovery and decreased myocardial infarction following ischemia-reperfusion injury and PDE5 inhibition [30]. In another study, PDE5 inhibition in rabbits showed significantly reduced ventricular infarct size following ischemia-reperfusion injury [29]. These findings were essentially consistent over two time intervals of analysis whereby treatment was administered either acutely before ischemia or 24 h prior, suggesting that PDE5 inhibition could convey a sustained cardioprotective effect against ischemia [29].

The mechanism by which PDE5 inhibitors exhibit cardioprotection remained unclear, with subsequent experiments focusing on whether preconditioning could be a contributing factor. Several pathways have been proposed to explain this cardioprotective concept, with bradykinin among the important factors [31, 32]. Bradykinin increased NO production resulting in cGMP upregulation and opening of mitochondrial K_{ATP} channels in a rabbit model [33]. Further studies identified that PDE5 inhibitors reduced ventricular infarct size in an animal model of ischemia-reperfusion, at least in part, through activation of mitochondrial K_{ATP} channels [12]. In addition, selective blockade of mitochondrial K_{ATP} channels negated the recovery in infarct size observed with PDE5 inhibition, suggesting that activation of mitochondrial K_{ATP} channels is crucial to mediating the cardioprotective effects of PDE5 inhibitors [29]. Importantly, opening of mitochondrial K_{ATP} channels not

only protects mitochondria from calcium overload induced- and oxidant stress-induced injury, but also triggers redox signals that inhibit glycogen synthase kinase (GSK)-3ß-mediated signaling, which inhibits opening of the mitochondrial permeability transition pore [34–36]. In addition, cardioprotection in the context of improved recovery of ventricular contractile function after ischemia-reperfusion is not necessarily limited to infarct size, as attenuation of myocardial stunning is possibly also involved in the post-ischemic reperfusion process [36]; this latter effect may also be at play in the discussion of the effect of PDE5 inhibitors on heart failure.

Taken together, several studies demonstrated reduced myocardial infarction with PDE5 inhibition when given either prior to occlusion or at reperfusion, and various mechanisms were implicated, including mitochondrial K_{ATP} channels, NO, and protein kinase C [12, 27, 29, 37]. A pathway independent of NO/cGMP has also been proposed, with one study reporting reduced myocardial infarct size in eNOS- and iNOS-null animals [37].

While most preclinical studies with PDE5 inhibitors demonstrated a reduction in experimental myocardial infarct size, not all studies were positive. In one study in rabbits, sildenafil did not reduce infarct size but did have a modest effect on improving collateral flow during occlusion and reducing specific vascular resistance and reducing left ventricular end diastolic pressure [38]. In a multicenter, randomized, blinded study, sildenafil reportedly failed to reduce myocardial infarct size in experimental models of infarct size, though final publication of results are still pending [39, 40]. Importantly, the protocol of sildenafil administration employed in this study differed from prior investigations, in that bolus injection was given [40] in place of slow infusion over an hour as was previously reported [12]. This alternative approach to sildenafil administration could significantly alter the impact of PDE5 inhibition in a hemodynamically unstable condition in the setting of myocardial infarction. Taken together, the effect of PDE5 inhibitors on reduction of myocardial infarct size has shown promise but is overall somewhat unclear in experimental animal studies.

Preclinical Studies in Heart Failure

PDE5 is generally believed to be present in minimal amounts or even absent in normal cardiomyocytes; however, PDE5 upregulation has been reported in cardiac tissue in heart failure [15–18]. Dysfunction of the cGMP-PKG axis is one of the primary processes implicated in the progression of heart failure [16, 41]. With upregulation of PDE5 in cardiac hypertrophy, there is increased conversion of cGMP to 5′GMP, and therefore decreased PKG [42]. The downstream effects of these changes are ultimately upregulation of cAMP and increased intracellular calcium [17, 20].

Further research investigating how intracellular calcium imbalance could contribute to heart failure progression suggested these detrimental effects could be a result of increased endoplasmic reticulum stress, and mechanistic studies identified increased sarcoplasmic reticulum calcium ATPase (SERCA) activity to be a mediating factor [43]; and given the direct relationship, phospholamban regulation likely played a role. SERCA improves muscle relaxation by lowering cytosolic calcium while restoring sequestered calcium availability necessary for subsequent muscle contraction [44]. Phospholamban, when dephosphorylated,

modulates calcium sequestration by inhibiting SERCA; therefore, phosphorylation of phospholamban leads to increased SERCA activity and improved calcium handling, contributing to improved cardiac contractility [45]. Isolated cardiomyocytes from mice with transverse aortic constriction (TAC)-induced heart failure showed worsening sarcomere shortening and relaxation along with poor intracellular calcium handling, which recovered with PDE5 inhibition [46] (Figure 1).

Mechanistic study of how PDE5 inhibition could improve cardiomyocyte calcium cycling showed that TAC-induced heart failure led to SERCA-2A and phospholamban suppression, which was reversed with sildenafil administration, leading to enhanced phospholamban phosphorylation and thereby improved calcium uptake [46]. In addition, chronic high-pressure exposure to cardiomyocytes increased calcineurin, which inhibits protein phosphatase inhibitor-1 activity ultimately leading to decreased phospholamban phosphorylation causing dysregulation of calcium handling [46–48]. A similar mechanism is at play with upregulation of protein kinase C noted in the TAC animal model, leading to phospholamban dephosphorylation (Nagayama). Administration of PDE5 inhibitor showed improved calcium handling in TAC-induced heart failure via suppression of overexpressed calcineurin and protein kinase C [46]. Taken together, PDE5 inhibitors may impart beneficial effects on cardiomyocytes in pressure-overload settings by regulating intracellular calcium cycling, thereby facilitating improved contractility [43, 46].

Persistent pressure and volume overload in the heart inflict maladaptive processes at the molecular, cellular, and functional levels, which progress toward cardiac dysfunction manifesting as congestive heart failure. Hearts of transgenic mice with cardiomyocyte-specific overexpression of PDE5 exhibited more pronounced left ventricular systolic and diastolic dysfunction, increased hypertrophy, and impaired inotropy compared to wild-type mice [49]. PDE5 inhibition showed suppressed chamber and cellular hypertrophy in the pressure-overloaded mouse model of heart failure and reversed pre-established hypertrophy while restoring cardiac function [41]. In addition, early ischemic cardiomyopathy treated with PDE5 inhibitor showed significant recruitment of eNOS/iNOS and recovery of left ventricular end-diastolic diameter and fractional shortening in mice [50].

Preclinical Studies in Ventricular Arrhythmia

PDE5 inhibition has been suggested to reduce the risk of ventricular arrhythmias, and the precise mechanism remains under investigation [51]. Acute suppression of triggered ventricular arrhythmias with PDE5 inhibition was recently demonstrated in vivo, likely mediated by suppression of cellular calcium waves [52].

Increased adrenergic drive has been associated with several cardiac pathologies including the development of ventricular arrhythmias and sudden cardiac death [53, 54]. Effective use of beta blockade has demonstrated reversal of left ventricular dysfunction as well as reduction of ventricular arrhythmias. Therefore, research was undertaken investigating whether PDE5 inhibition could mediate a direct anti-arrhythmic effect through manipulation of beta-adrenergic receptors. While PDE5 inhibition blunted the enhancement in sarcomere shortening caused by isoproterenol in adult cardiomyocytes, such modulation of sarcomere shortening in cardiomyocytes isolated from genetically engineered mice lacking ß3

adrenergic receptors with PDE5 inhibition was prevented. This suggests that suppression of myocardial beta-adrenergic drive may be a plausible pathway by which PDE5 inhibition exerts its anti-arrhythmic effect [51, 55].

Cardiac ischemic injury leads to increased sympathetic nerve regeneration and density mediated by nerve growth factor (NGF) that has been associated with ventricular arrhythmia and sudden cardiac death [56–58]. PDE5 inhibition has been shown to activate K_{ATP} channels, which in turn dampens sympathetic drive and inhibits NGF following myocardial infarction [59, 60].

Furthermore, PDE5 inhibitor-induced mitochondrial K_{ATP} channel activation suppressed the over-recruited sympathetic innervation and associated arrhythmias [60]. Animals administered PDE5 inhibitor showed a significant decrease in inducible ventricular tachycardia and ventricular fibrillation [60].

The mechanism by which PDE5 inhibition imparts an anti-arrhythmic effect may be via modulation of beta-adrenergic signaling [61, 62], possibly mediated by NGF given the studies described. In addition, PDE5 inhibition has demonstrated protection against ventricular arrhythmias associated with the early stages of cardiac ischemia [63]. There may be an anti-arrhythmic therapeutic range of PDE5 inhibition, since high-dose PDE5 inhibitor administration increased the incidence of ventricular fibrillation [30].

Clinical Studies of PDE5 Inhibition in Cardiovascular Disease

Studies in Myocardial Infarction

The frequency of coexisting CAD and ED has led to extensive study into the safety of PDE5 inhibitor use in these patients. Initial post-marketing reports identified myocardial infarction and sudden death in patients recently started on PDE5 inhibitors, but direct association between the medication and cardiac adverse effects was not possible [64]. However, myocardial infarctions associated with the use of PDE5 inhibitors were rare and may have been related to the increase in oxygen demand that occurs with sexual activity. An early study evaluated the hemodynamic effects of PDE5 inhibitor use in men with stable angina and at least one known severely occluded coronary artery [65]. Investigators assessed the hemodynamic effects of oral sildenafil in 14 men, finding minimal decrease in systemic arterial and pulmonary arterial pressures, no significant effect on pulmonary-capillary wedge pressure, right atrial pressure, heart rate, or cardiac output. Coronary hemodynamics including peak flow velocity and vascular resistance were unchanged. Taken together, no significant adverse cardiovascular effects were reported in this study [65].

In a Swedish study in men with first myocardial infarction, treatment with PDE5 inhibitors was associated with a lower risk of death and cardiovascular events [66]. Limitations of this study included the control group not receiving any treatment for ED, potentially confounding for indication. This led to a recent subsequent study investigating the association between PDE5 inhibition versus prostaglandin E1 (PGE1) in men with stable CAD [67]. Results from this study showed that in men with stable CAD, treatment with PDE5 inhibitor is associated with lower cardiovascular outcomes including death,

myocardial infarction, heart failure, and revascularization, compared to treatment with PGE1 [67]. The study was observational and thus, no inferences of causality could be made but the results confirmed the earlier findings.

The effect of PDE5 inhibition on exercise-induced ischemia was studied in symptomatic patients with stable CAD [68]. Several parameters were evaluated including symptom-limited treadmill exercise time, time to first awareness of angina, and time to ischemic threshold during exercise tolerance testing. The exertional metabolic equivalent (MET) goal in this study was 5–10 METs. At peak exercise, PDE5 inhibition did not demonstrate any significant hemodynamic change in blood pressure or heart rate. Similarly, there was no significant change with PDE5 inhibition when assessing treadmill time or time to first awareness of angina. Patients with PDE5 inhibition did exhibit significantly prolonged time to ischemic threshold by approximately 15% [68]. Taken together, findings from this study suggest that PDE5 inhibitor use in patients with stable, symptomatic CAD, does not limit functional capacity at an exertional level of 5–10 METs. However, in another study, the effect of PDE5 inhibition on exercise tolerance times was neutral in patients with stable coronary artery disease [69].

A research team in Denmark retrospectively investigated the risk of cardiovascular disease in patients who had been prescribed PDE5 inhibitors with the end points including acute myocardial infarction and the development of heart failure [70]. In the first 3 years of PDE5 inhibition, in patients who had no prior cardiovascular disease, there was a decreased risk of acute myocardial infarction. In addition, the study reported a trend toward decreased risk of the development of heart failure in the first 3 years of ED therapy. Overall, there was a decrease in the risk of cardiovascular disease in the first 3 years after initiating treatment for ED [70].

Due to the coexistence of cardiovascular disease and ED, the high frequency of PDE5 inhibitor therapy for ED, and the natural progression of CAD, a subset of patients ultimately require evaluation for coronary artery bypass graft (CABG) surgery for CAD management. The safety of PDE5 inhibitors was investigated in a pilot study of patients undergoing CABG surgery, with results suggesting PDE5 inhibitor use prior to CABG surgery is safe [71]. Given its natural biologic effects as described previously, there is evidence to suggest adjunctive use of PDE5 inhibitors in patients with upcoming CABG surgery could be beneficial [72].

A meta-analysis of randomized, placebo-controlled trials examined whether PDE5 inhibition could indeed impart beneficial cardiac effects [73]. Trials were selected reporting any cardiovascular outcomes, as either primary or secondary endpoints, and independent of the baseline characteristics of the study population. Across 24 trials assessed, nearly 1000 patients were treated with PDE5 inhibitors while approximately 750 were given placebo. Given the criteria for study selection, a significant percentage of these patients had known pulmonary hypertension or congenital heart disease. Several outcomes were evaluated including parameters of cardiac geometry and function as well as overall safety and tolerability of PDE5 inhibitors. The outcomes analyzed included left ventricular mass index, end-diastolic volume index, ventricular transverse diameter, cardiac index, ejection fraction,

E/A ratio, and hemodynamics including systemic vascular resistance index. Findings from this meta-analysis suggested that chronic PDE5 inhibitor use imparts a beneficial cardiac inotropic effect together with anti-remodeling properties across different populations [73]. These results favor that PDE5 inhibition could promote positive remodeling and offer potentially promising impact on surrogate endpoints.

Due to the systemic effect of PDE5 inhibition on improving endothelial function, researchers have investigated whether using these medications could improve cardiac risk factors mediated by endothelial dysfunction including diabetes. Since initial proposal of this hypothesis [74], studies with PDE5 inhibitors have led to positive clinical outcomes in patients with cardiac risk factors including diabetes [75]. One trial demonstrated PDE5 inhibition to lower the risk of overall mortality in patients with diabetes and a history of acute myocardial infarction [76]. A non-randomized study reported that PDE5 inhibitors may reduce the occurrence of major adverse cardiac events in patients with coronary artery disease, diabetes, and erectile dysfunction [77]. Taken together, PDE5 inhibition could be cardioprotective by improving outcomes in patients with cardiac risk factors including diabetes, though these studies offered limitations in methodology as well as in assessment of the specifics of PDE5 use in the populations studied.

To the best of our knowledge, PDE5 inhibitors have not been tested in a systematic fashion in clinical trials of acute myocardial infarction. Due to their contraindication in the setting of nitroglycerin use, PDE5 inhibitors are unlikely to ever be tested in humans with acute myocardial infarction.

Studies in Heart Failure

Clinical studies investigating PDE5 inhibition in heart failure have yielded mixed results. Exercise capacity was evaluated in patients with HFrEF using cardiopulmonary exercise testing (CPET), with PDE5 inhibition for 3–6 months showing sustained improvement in exercise ventilation and aerobic efficiency [78]. A trial of patients with HFrEF showed improved functional capacity and left ventricular echocardiographic parameters, including reversal of maladaptive remodeling and left ventricular diastolic function, with PDE5 inhibition [79]. Furthermore, PDE5 inhibition in patients with HFrEF complicated by secondary pulmonary hypertension improved exercise capacity and quality of life, as evidenced by superior peak oxygen uptake (VO_2) and 6-minute-walk distance, respectively [80]. However, the utility of PDE5 inhibitors in HFrEF remains unclear due to conflicting reports (Table 1), such as one study reporting no significant functional or quality of life improvement in patients with HFrEF, as measured by 6-minute walk distance and New York Heart Association (NYHA) functional class [81].

The effect of PDE5 inhibitors in patients with heart failure with preserved ejection fraction (HFpEF) has been similarly inconclusive. Patients with HFpEF treated with 6 months of PDE5 inhibitor exhibited several beneficial effects including improved left ventricular structural changes and improved pulmonary pressures [82], while another clinical trial also studying patients with HFpEF on 6 months of PDE5 inhibitor did not show significant functional improvement [83]. The disparity in outcomes between these two trials could be at least partly explained by differing therapy regimens.

A meta-analysis investigating the role of PDE5 inhibition in patients with heart failure suggested chronic PDE5 inhibition may modestly improve exercise capacity in patients with HFrEF or HFpEF, though significant heterogeneity was noted in the studies analyzed [84, 85]. The marginal benefit is further tempered because increased mortality with PDE5 inhibitor use could not be ruled out [84].

Studies in Ventricular Arrhythmia

Given the association between increased adrenergic drive and ventricular arrhythmia [53], and the link between PDE5 inhibition and suppression of beta-adrenergic drive in vivo [60–63], studies have investigated whether PDE5 inhibition demonstrates similar anti-adrenergic and thereby anti-arrhythmic effects clinically. PDE5 inhibition showed significantly reduced beta-adrenergic response in healthy volunteers, as determined by multiple echocardiographic and contractility indices including suppressed ejection fraction and peak power [61]. These results suggest that PDE5 inhibition could indeed reduce ventricular arrhythmia in the clinical setting by suppressing adrenergic drive. However, in contrast, there have been reports of patients suffering ventricular arrhythmia after initiating PDE5 inhibitor [86, 87]. Subsequent research did not identify any clinically significant difference in QT duration in healthy patients prescribed PDE5 inhibitors, and there have been conflicting reports on the effect of PDE5 inhibitors on cardiac repolarization [88–91]. Taken together, the potential utility of PDE5 inhibitors in an anti-arrhythmic role remains unclear.

Studies of PDE5 Inhibition in LVAD Patients

Given the known effects of PDE5 inhibitors on pulmonary hypertension and the evolution of the left ventricular assist device (LVAD) as an option for end-stage heart failure management, studies have investigated the safety and impact of PDE5 inhibitors pre- and post-LVAD implantation. Although PDE5 inhibitor use in patients with LVADs is thought to be safe and well-tolerated [92], findings from studies evaluating efficacy of PDE5 inhibition pre- and post-LVAD implantation have been inconclusive. A recent report raised concern that pre-LVAD PDE5 inhibition was associated with increased right-sided heart failure in the post-LVAD setting [93]. Another study investigated the effect of PDE5 inhibitors on right ventricular dysfunction in the post-LVAD implantation and found no significant difference in clinical outcomes [94]. In addition, patients with right ventricular dysfunction and pulmonary hypertension requiring LVAD implantation had improved outcomes with perioperative PDE5 inhibition [95]. A systematic review aiming to identify a specific role of PDE5 inhibition in LVAD patients to attenuate right ventricular failure noted mixed results and weak evidence overall [96].

PDE5 Inhibition in Pulmonary Arterial Hypertension

PDE5 inhibitors are one of the major drug categories to treat pulmonary arterial hypertension, a disease process generally characterized by gradual progression of pulmonary vascular resistance ultimately leading to right heart failure. Due to the beneficial effect on smooth muscle in the context of erectile dysfunction, studies have evaluated whether PDE5 inhibitors could have similar improvements in the pulmonary vasculature. In contrast to the previously discussed cardiovascular disease processes, the success of PDE5 inhibition in

pulmonary arterial hypertension has been well established, possibly due to a high basal level of PDE5 in healthy pulmonary tissue that is further upregulated in pulmonary hypertension [97, 98]. A full discussion on PDE5 inhibitors on pulmonary hypertension is beyond the scope of this report, but it is important to note that there is strong evidence clearly demonstrating improved functional parameters and quality of life measures with the use of sildenafil or tadalafil in patients with pulmonary arterial hypertension [99–103].

Conclusions

The coexistence of cardiovascular disease and ED is common likely due to the vascular changes contributing to both disease pathologies. The resultant high frequency of patients with cardiovascular disease being prescribed PDE5 inhibitors for ED has led scientists to identify several mechanisms by which these medications may exert cardioprotective effects, and a number of clinical trials have evaluated the role of PDE5 inhibitors in patients with cardiac disease.

Some but not all studies have demonstrated evidence of cardioprotection with PDE5 inhibitors in preclinical models. Chronic administration of PDE5 inhibitors has shown promising results in reducing adverse cardiac outcomes, especially in those with underlying risk factors such as diabetes. However, these findings have not translated consistently as treatment for patients with congestive heart failure, myocardial infarction, or ventricular arrhythmia. Reports convincingly showing that PDE5 inhibitors have potential as cardiovascular therapy is still infrequent. The reasons underlying the lack of translatability of PDE5 inhibitors from bench to bedside remain unclear, though they may be related to in vitro PDE5 inhibitor dosages being used and relevance of animal models, particularly given the known challenges of translating the ischemia-reperfusion animal model. In addition, variable usage of different PDE5 inhibitors and differences in their respective pharmacokinetics could be contributing to conflicting findings. Furthermore, the limited effect of PDE5 inhibitors in the cardiovascular system may be explained, at least in part, that the conflicting data from clinical studies were derived from patients with a varying degree of upregulated PDE5 among those with cardiovascular disease.

Limitations of data interpretation include the observational and retrospective nature of some reports, incomplete information related to medication adherence in some cases, and increased surveillance of blood pressure after initiation of PDE5 inhibitors. Caution is needed in data interpretation because if ED is considered a risk factor for vascular disease, it is difficult to explain an improved outcome with reduction in fatal and non-fatal ischemic events when these patients are treated with PDE5 inhibitors as compared to patients without ED, and there are no randomized trials available to clarify the distinction.

The resultant unclear role of PDE5 inhibition in clinical cardiac pathologies has contributed to the lack of indications for prescribing PDE5 inhibitors in the treatment of cardiovascular disease. Importantly, the safety and tolerability of PDE5 inhibitors in patients with cardiovascular disease have been well established [104], and this review did not identify significant risks to using PDE5 inhibitors as adjunctive therapy in heart failure, coronary

disease and myocardial infarction, or ventricular arrhythmia, with the exception of concurrent nitrate use.

Current clinical trials incorporating PDE5 inhibitors are focused on right ventricular dysfunction in patients with LVADs, congenital heart disease, or cystic fibrosis; no studies are investigating the potential utility of PDE5 inhibitors in myocardial infarction, heart failure, or arrhythmia (Table 2). Further trials are warranted to better understand the role of PDE5 inhibitors in patients with cardiovascular disease. Carefully designed dose-dependent and time-course studies to optimize clinical PDE5 inhibition could pave the path toward large-scale, randomized-controlled clinical trials exploring the efficacy of PDE5 inhibitors on cardiac outcomes in coronary artery disease, heart failure, and ventricular arrhythmia Results from such investigations could help reconcile some of the discrepancies in the literature on the role of PDE5 inhibitors in cardiovascular disease.

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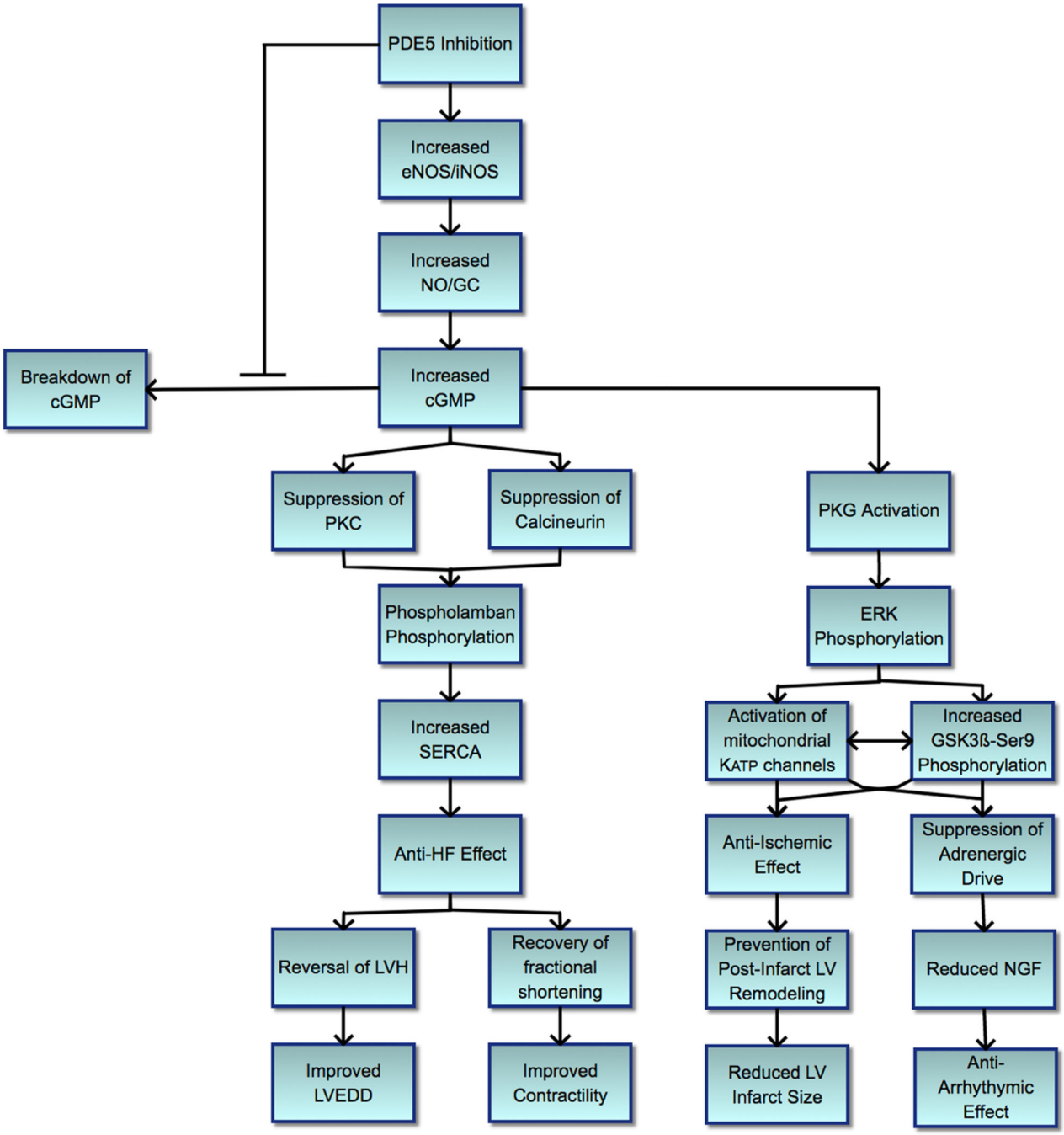

Figure 1.

Effect of phosphodiesterase-5 inhibitors in cardiovascular disease. Schematic summary of the proposed mechanisms by which phosphodiesterase-5 inhibitors exert their cardioprotective effect. The PKG-mediated suppression of calcineurin, leading to suppression of cardiomyocyte hypertrophy, and PKG-mediated phosphorylation of phospholamban at Ser16, leading to restored SERCA activity, are parallel events. Redox signals from mitochondria with activated mitochondrial Katp channels lead to phosphorylation of GSK-3beta-Ser9, which inhibits opening of mitochondrial permeability

transition pores, protecting against necrosis. cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinases; GC, guanylate cyclase; GSK3ß-Ser9, glycogen synthase kinase 3 beta serine 9; HF, heart failure; iNOS, inducible nitric oxide synthase; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVH, left ventricular hypertrophy; mitochondrial K_{ATP}, mitochondrial ATP-sensitive potassium; NGF, nerve growth factor; NO, nitric oxide; PDE5, phosphodiesterase-5; PKG, protein kinase G; SERCA, sarcoplasmic reticulum calcium ATPase

Table 1

Clinical trials investigating the effects of PDE5 inhibitors on cardiac disease

Author, year [reference no.]	Study design	Number of subjects	Intervention	Targeted disease	Primary endpoint	Overall findings
Guazzi M et al, 2007 [78]	Randomized controlled trial	46 (23 allocated to sildenafil and 23 to placebo)	Sildenafil 50 mg TID vs placebo	Heart failure with reduced ejection fraction	Assessment of cardiopulmonary exercise testing, echocardiograp hy, and Holter monitoring	Cardiopulmonary exercise testing in patients with HFrEF treated with PDE5 inhibitor for 36 months showed improved exercise ventilation and aerobic efficiency (P<0.01)
Guazzi M et al, 2011 [79]	Randomized controlled trial	45 (23 allocated to sildenafil and 22 to placebo)	Sildenafil 50 mg TID vs placebo	Heart failure with reduced ejection fraction	Assessment of a drug-induced beneficial effect on diastolic function and chamber remodeling	Sildenafil improved echo parameters, exercise capacity, and quality of life in HFrEF patients (P<0.01)
Lewis D et al, 2007 [80]	Randomized controlled trial	34 (17 allocated to sildenafil and 17 to placebo)	Sildenafil 25 mg uptitrated to 75 mg TID vs placebo	Heart failure with reduced ejection fraction complicated by secondary pulmonary hypertension	Assessment of change in peak VO_2 from baseline through cardiopulmonary exercise testing	PDE5 inhibition in HFrEF patients complicated by secondary pHTN improved exercise capacity and quality of life (P<0.05)
Amin A et al, 2013 [81]	Randomized controlled trial	106(53 allocated to sildenafil and 53 to placebo)	Sildenafil 25 mg BID to 50 mg TIW vs placebo	Heart failure with reduced ejection fraction	Assessment of change in 6-minute walk distance from baseline	No significant functional or quality of life improvement with PDE5 inhibitor in HFrEF patients (P=0.67)
Guazzi M et al, 2011 [82]	Randomized controlled trial	44 (22 allocated to sildenafil and 22 to placebo)	Sildenafil 50 mg TID vs placebo	Heart failure with preserved ejection fraction	Assessment of pulmonary and left heart hemodynamics	HFpEF treated with PDE5 inhibitor exhibited improved left ventricular structural changes and pulmonary pressures (P<0.01)
Redfield MM et al, 2013 [83]	Randomized controlled trial	216 (113 allocated to sildenafil and 103 to placebo)	Sildenafil 20 mg TID uptitrated to 60 mg TID vs placebo	Heart failure with preserved ejection fraction	Assessment of change in peak oxygen consumption	Chronic PDE5 inhibitor use in HFpEF patients did not improve cardiac functional status (P>0.05)
Guay CA et al, 2018 [84]	Meta-analysis	5448 (over 22 studies)	Pulmonary HTN-directed therapy including PDE5 inhibitor vs placebo	Heart failure with reduced ejection fraction and heart failure with preserved ejection fraction	Assessment of changes in exercise capacity	Pulmonary HTN-directed therapy including PDE5 inhibitor use in HF patients showed improved exercise capacity (P<0.01)
Zhuang X et al, 2014 [85]	Meta-analysis	612 (over 9 studies)	Sildenafil vs placebo	Heart failure with reduced ejection fraction	Assessment of adverse events and peak oxygen consumption (peak VO_2)	PDE5 inhibitor use in HFrEF patients improved HF hemodynamic parameters (P<0.01)
Thadani U et al, 2002 [68]	Randomized controlled trial	41 (crossover study)	Vardenafil 10 mg vs placebo	Coronary artery disease	Assessment of effect on total exercise time in patients with exertional angina of moderate severity	PDE5 inhibitor use did not alter functional capacity in stable, symptomatic CAD (P>0.05)

Author, year [reference no.]	Study design	Number of subjects	Intervention	Targeted disease	Primary endpoint	Overall findings
Vestergaard N et al, 2017 [70]	Cohort	71,710 (cohort study)	Erectile dysfunction therapy including PDE5 inhibitor vs general population	Overall risk of cardiovascular disease	Patients were followed until emigration, death, cardiovascular event, or end of follow-up period	Overall risk of cardiovascular disease was decreased in the first 3 years of erectile dysfunction therapy including PDE5 inhibition (P<0.05)
Ali A et al, 2013 [71]	Pilot phase II vs retrospective	57 (10 allocated to vardenafil compared to 47 retrospective)	Vardenafil 10 mg once prior to CABG vs no vardenafil	Coronary artery disease, pre-surgical candidates	Assessment of drug safety and tolerability (mortality and hypotension)	PDE5 inhibitor use is safe prior to CABG
Giannetta E et al, 2014 [73]	Meta-analysis	1622 (over 24 studies)	Sildenafil, vardenafil, or tadalafil vs placebo	Cardiovascular disease	Studies were selected that reported any cardiovascular outcome as primary or secondary endpoint	Chronic PDE5 inhibitor use improves inotropy and remodeling (P<0.05)

Table 2

Current ongoing clinical trials investigating the effects of PDE5 inhibitors on cardiac disease

Study objective (NCT number)	Study design	Number of subjects	Intervention	Primary outcome(s)
Determine whether sildenafil can prevent right heart failure after LVAD placement (NCT03356353)	Open label, single arm	24	Sildenafil 40 mg TID	Change in pulmonary vascular resistance (PVR)
Determine right ventricular function in LVAD patients before and after discontinuation of phosphodiesterase-5 inhibitor (NCT04117659)	Open label, single arm	30	Pre-treatment with PDE5 inhibitor with subsequent discontinuation	Change in right ventricular global longitudinal strain (GLS)
Determine whether pre-treatment with sildenafil could significantly impact breath-hold and SCUBA diving-induced pulmonary hypertension in patients with PFO or IPAVA (NCT03945643)	Randomized controlled trial	80 (40 allocated to sildenafil and 40 to placebo)	Sildenafil 50 mg once, 1 h prior to measurements vs placebo	Change in pulmonary arterial pressure by ultrasound, as well as several cytokine blood tests
Determine the safety profile of udenafil in adolescents with single-ventricle congenital heart disease after Fontan palliation (NCT03013751)	Open label, single arm	300	Udenafil for 52 weeks	Occurrence of adverse events
Determine whether PDE5 inhibition improves right ventricular size and function in adults with congenital subaortic right ventricular positioning (NCT03049540)	Randomized controlled trial	100 (50 allocated to tadalafil and 50 to placebo)	Tadalafil 20 mg daily for 3 years vs placebo	Change in right ventricle end systolic volume
Determine whether PDE5 inhibition improves exercise tolerance in patients with cystic fibrosis (NCT04039087)	Randomized controlled trial	40 (20 allocated to sildenafil and 20 to placebo)	Sildenafil 40 mg TID vs placebo	Change in 6-minute walk distance