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REVIEW ARTICLE

Two Birds with One Stone: Regular Use of PDE5 Inhibitors for Treating Male Patients with Erectile Dysfunction and Cardiovascular Diseases

Zhonglin Cai[1] · Jianzhong Zhang[1] · Hongjun Li[1]

Abstract

Patients with cardiovascular disease (CVD) frequently have erectile dysfunction (ED) because the two conditions have similar risk factors and potential mechanisms. The therapeutic effect of CVD is strongly dependent upon long-term management of the condition. Patients with CVD tend to have poor medication compliance, and the coexistence of ED often discourages patients with CVD from continuing their long-term CVD management, thus worsening CVD treatment compliance. The two major reasons for poor compliance are that (i) the adverse effects of cardiovascular medications on erectile function drive people to reduce the prescribed dosage or even stop taking the medications to obtain satisfactory sexual arousal and (ii) a worsening mental state due to ED reduces medication compliance. The regular administration of phosphodiesterase-5 inhibitors (PDE5is) guarantees that the prescribed medication dosages are easy to comply with and that they improve the mental status of patients by enhancing their erectile function, resulting in improved long-term management of CVD through medication compliance. PDE5is themselves also play a role in reducing cardiovascular events and improving the prognosis. We recommend prescribing PDE5is for ED and suggest that PDE5i administration is a promising strategy to improve the long-term management of patients with both ED and CVD.

Keywords Cardiovascular disease · Erectile dysfunction · Long-term management · Medication compliance · Phosphodiesterase-5 inhibitor

Introduction

Erectile dysfunction (ED) is defined as the inability of the penis to become erect or maintain sufficient erection rigidity to accomplish satisfactory sexual activity [1]. ED is a common type of sexual dysfunction that significantly influences quality of life. Cardiovascular disease (CVD), such as coronary disease, hypertension, and hyperlipidemia, has risk factors similar to those of ED, including aging, lipid metabolism disorders, obesity, and smoking [2, 3]. Therefore, ED often occurs concurrently with CVD [4]. Accumulating evidence shows that ED, as an independent risk factor, predicts the risk of CVD [5–7]. Many experimental and clinical studies have demonstrated that phosphodiesterase-5 inhibitors (PDE5is) have protective effects against cardiovascular problems such as heart failure (HF), myocardial infarction (MI), and pulmonary arterial hypertension (PAH) [8–12]. PDE5i administration may be an ideal treatment strategy for male patients with both ED and CVD.

✉ Hongjun Li
lihongjun@pumch.cn

Zhonglin Cai
714833558@qq.com

Jianzhong Zhang
15895827758@163.com

[1] Department of Urology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China

Relationship Between ED and CVD

ED as a Predictor of CVD

The symptoms of CVD in patients with both CVD and ED are more serious than those in patients with CVD alone [13], and the severity of ED is positively associated with CVD [6]. Additionally, patients with ED have a higher risk of ischemic cardiac disease, HF, and peripheral vascular disease than those

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without ED [13]. Hippisley-Cox et al. developed updated QRISK3 risk prediction models and concluded that the presence of ED helps to identify patients most at risk for heart disease and stroke [14]. Therefore, ED can be used as an independent risk factor to predict the risk of CVD and cardiovascular events [6, 15]. A reduction in erectile hardness is also closely related to the risk of cardiovascular events, and severely low erectile hardness is associated with a greatly increased risk of cardiovascular events [16]. The relationship between erection rigidity and CVD risk directly demonstrates the relationship between ED and CVD. Finally, in a comparison of ED and the prognosis of CVD, a negative association has been observed between the effort capacity in patients with post-acute MI and the presence and degree of ED [17]. Overall, evidence of the relationships among ED, CVD, and the prognosis of CVD indicates that ED indirectly reflects the severity of CVD and is a predictor of CVD.

ED Reduces the Frequency of Sexual Intercourse, Resulting in an Increased Risk of CVD

A sexual intercourse frequency of four or more times per month is associated with a lower risk of CVD compared with a sexual intercourse frequency of fewer than once per month [6]. Hall et al. reported that a sexual intercourse frequency of once or less than once per month is related to an increased risk of CVD compared with a sexual intercourse frequency of two to three times per week. Additionally, the association with the frequency of sexual intercourse was still present after adjusting for the impact of ED [18]. According to these results, a lower frequency of sexual intercourse increases the risk of CVD and is an independent risk factor. Therefore, patients with ED who have a lower frequency of sexual intercourse also have an increased risk of CVD.

Regular Use of PDE5is for ED and CVD

Reduction of CVD Risk by Administration of PDE5is

One study showed that patients who were treated with a PDE5i for ED had lower mortality and a lower risk of hospitalization for HF compared with those who were not treated for ED [19]. Many experimental studies have shown that PDE5is are cardioprotective, particularly for HF and MI [10, 20–24]. A clinical trial regarding the direct effect of PDE5is on MI demonstrated that the use of a PDE5i is associated with a lower risk of overall mortality and mortality in those with a history of acute MI [25]. Studies of PDE5is and mortality in men with type 2 diabetes, which is closely associated with the prevalence of CVD, have also shown that PDE5i use is independently associated with decreased mortality in patients with type 2 diabetes, suggesting independence of the PDE5i effect on mortality[26, 27]. These findings indicate that the decreased risk of CVD and the improved CVD prognosis in patients treated with PDE5is for ED is primarily due to the cardiovascular protection provided by PDE5is [19, 26, 27].

Protective Mechanisms of PDE5is on CVD

PDE5 is expressed in vascular smooth muscle cells, cardiac myocytes, and platelets as well as in the penile vasculature [28]. Under pathological conditions, PDE5 expression is significantly elevated in cardiovascular tissues, such as the myocardial cells of HF tissues [29]. PDE5i treatment has positive effects on most CVDs, such as thrombus-related CVD, HF, MI, and PAH [8–12, 30, 31]. The protective mechanism of PDE5is on CVD is closely related to the cGMP/protein kinase G (PKG) and cAMP/protein kinase A pathways [32] (Fig. 1).

PDE5is, Platelets, and Thrombi

Fibrinogen, Ca^{2+}, and glycoprotein IIb/IIIa are the three most important factors involved in the aggregation of platelets. The intracellular calcium (Ca^{2+}) level is downregulated by nitric oxide and/or the PDE5i-mediated cGMP-PKG signaling pathway in platelets, which functions through phosphorylation of G protein 18, inositol 1,4,5-triphosphate (IP3) receptor 1 channel, and IP3 receptor-associated cGK I substrate protein [33]. All of these participate in regulation of the intracellular Ca^{2+} level [33]. cGMP-PKG signaling phosphorylates Rap1, thus suppressing activation of glycoprotein IIb/IIIa by inhibiting small GTPase signaling [34]. The changes in the Ca^{2+} level and activation of glycoprotein IIb/IIIa inhibit the activation and aggregation of platelets [34]. P-selectin expression and RhoA activation are also inhibited by PKG, inhibiting the shape change in platelets and the formation of platelet-leukocyte complexes, which adhere to endothelial cells [35, 36]. Additionally, elevated cGMP competes with phosphodiesterase3 (PDE3), which hydrolysates cAMP, and increases cAMP by binding to the PDE3-binding site of cAMP [32, 37]. Protein kinase A is activated by elevated cAMP and is involved in inhibiting the change in the platelet shape induced by thrombin via phosphorylation of a vasodilator-stimulated phosphoprotein [37].

PDE5i, Cardiomyocytes, and HF

The onset of heart failure is typically preceded by cardiac hypertrophy and/or cardiac remodeling [38]. The cGMP/PKG pathway induced by PDE5is inhibits cardiac remodeling by inhibiting the activity of calcineurin or reducing the

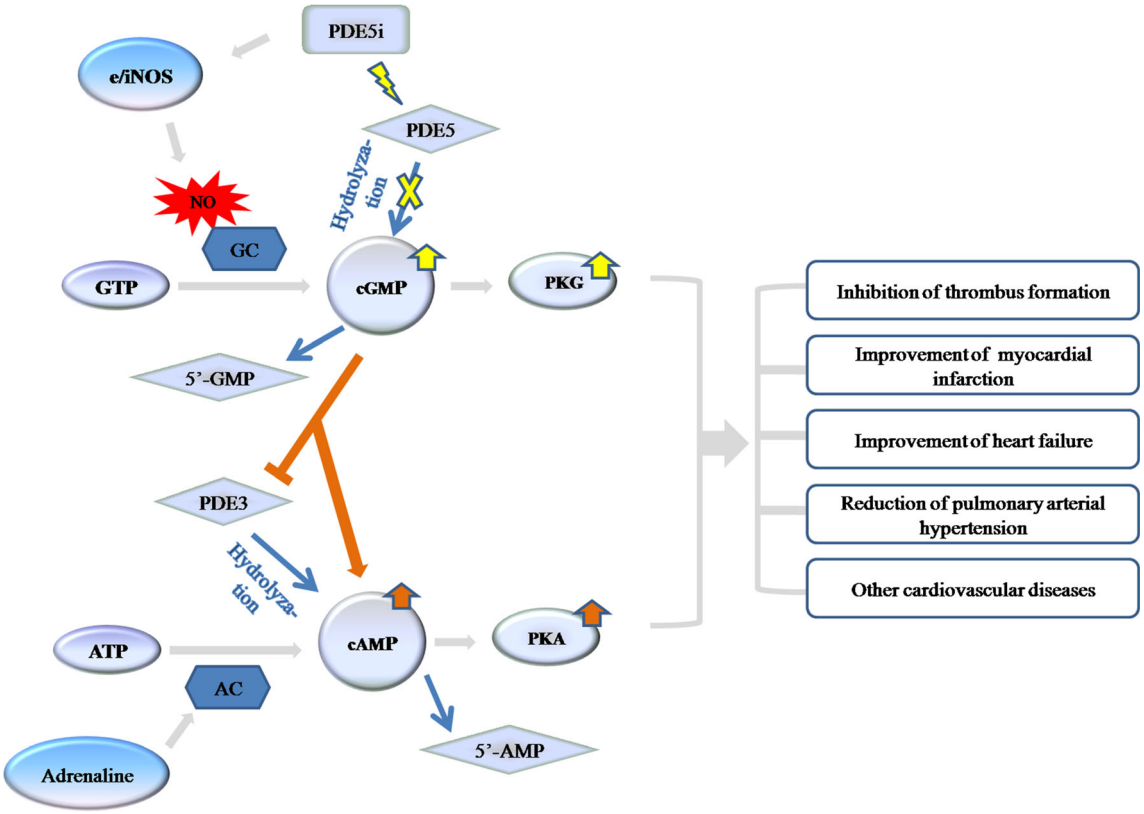

Fig. 1 NO, catalyzed and synthesized by nitric oxide synthase, activates GC, which changes GTP into cGMP activating PKG; AC that is activated by adrenaline changes ATP into cAMP, which activates PKA. PDE5 hydrolyzes cCGMP into 5′-GMP, and PDE3 hydrolyzes cAMP into 5′-AMP. PDE5i inhibits PDE5, whose hydrolyzation is inhibited and promotes the expression of e/i NOS. Finally, the expression levels of cGMP and PKG are increased. cGMP can bind to the PDE3-binding site of cAMP, and then, PDE3 hydrolyzation of cAMP is inhibited. Lastly, the expression levels of cAMP and PKA are increased. Both PKG and PKA have the positive roles in the cardiovascular protection including the inhibition of thrombus formation, improvement of myocardial infarction and heart failure, reduction of pulmonary arterial hypertension, and so on. NO nitric oxide, NOS nitric oxide synthase, GC guanosine cyclase, AC adenylate cyclase, cGMP cyclic guanosine monophosphate, cAMP cyclic adenosine monophosphate, PDE phosphodiesterase, GTP guanosine triphosphate, ATP adenosine triphosphate, PKA protein kinase A, PKG protein kinase G

expression of brain natriuretic peptide by phosphorylating extracellular regulated kinase (ERK) [10]. Additionally, PKG causes a decrease in the influx of Ca^{2+} by phosphorylating the transient receptor potential canonical channel and subsequently decreasing calcineurin activity, leading to reduced dephosphorylation of nuclear factor of activated T cells, which promotes cardiac hypertrophy in an active state [39]. The RhoA/Rho-kinase pathway and regulator of G protein signaling 2 (RGS2) are also inhibited by the cGMP/PKG pathway, resulting in improved cardiac hypertrophy [29, 40, 41]. Furthermore, PKG induced by PDE5is phosphorylates titin to enhance diastolic compliance and cardiac troponin I to reduce Ca^{2+} sensitivity of the myofilaments [32]. PDE5is may be associated with anti-apoptosis in cardiomyocytes through an increase in the Bcl-2-to-Bax ratio or reduced endoplasmic reticulum stress [42–44]; anti-inflammation through Gq signaling regulatory action by inhibiting RGS2, RGS3, or RGS4 [45]; and fibrosis by inhibiting transforming growth factor-β [21, 46] to improve HF via the cGMP/PKG pathway.

PDE5is, Cardiomyocytes, and MI

The area of an MI is dependent on cardiomyocyte apoptosis, and mitochondria are key in determining the MI area [11]. PDE5is reduce the mitochondrial area and ameliorate the adhesion force of the mitochondrial surfaces [11]. The molecular mechanism of PDE5is in MI involves the mitoK_{ATP} and mitochondrial Ca^{2+}-sensitive potassium channels (BK), both of which are activated by the cGMP/PKG pathway (Fig. 2) [12, 47]. BK knockout in cardiomyocytes causes higher serum levels of cardiac troponin I as a marker of MI [12]. PKG induced by PDE5is via elevated cGMP decreases Ca^{2+} influx by inhibiting BK, subsequent amounts of reactive oxygen species, and phosphorylated ERK/AKT levels, resulting in apoptosis of cardiomyocytes [12, 48, 49]. PKG phosphorylates ERK1/2 and glycogen synthase kinase 3 beta and, with the help of increased Bcl-2, subsequently opens mitoK_{ATP} channels, preserves ATP, and decreases Ca^{2+} influx in the mitochondria by inhibiting the mitochondrial permeability transition pore [47].

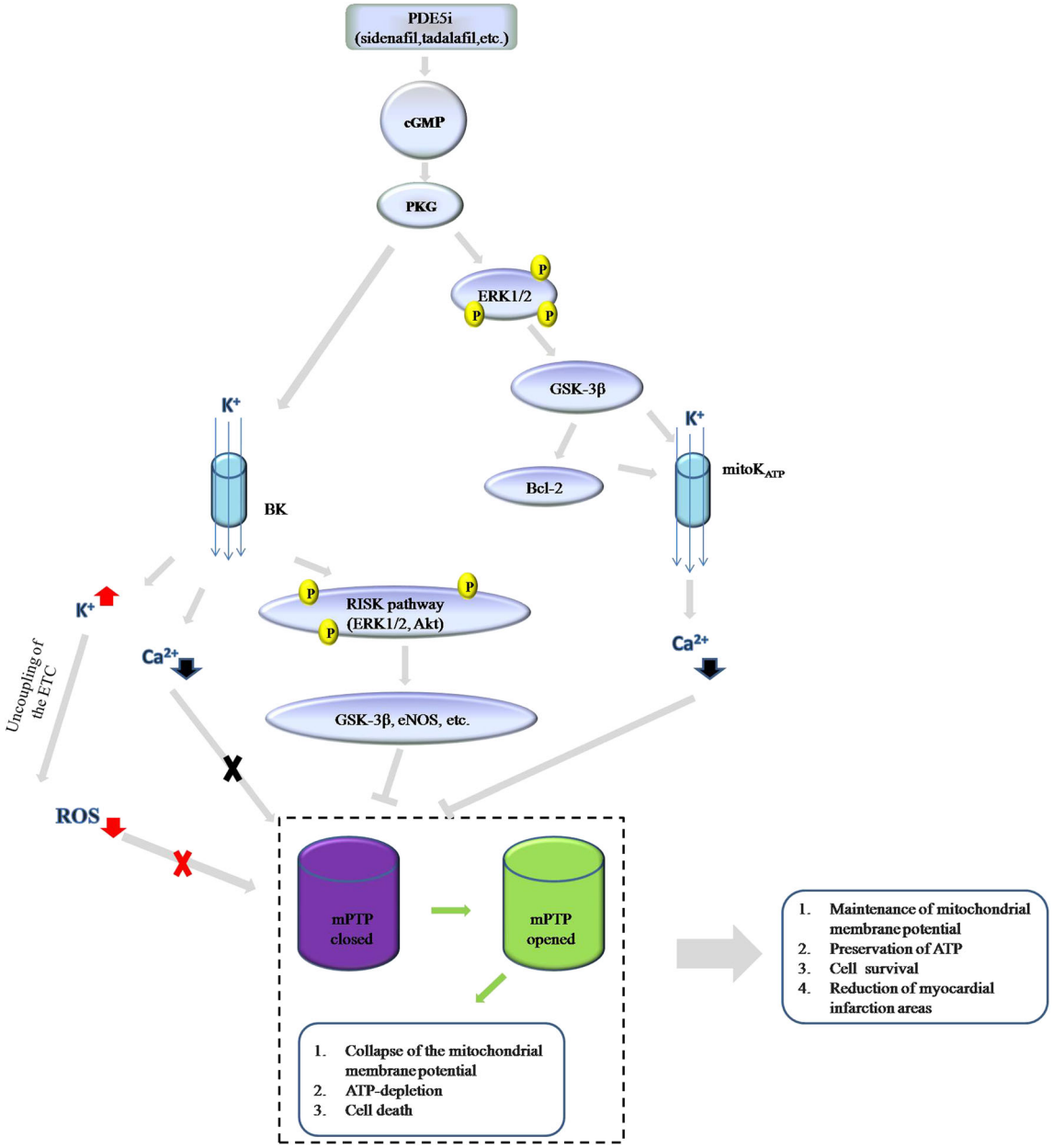

Fig. 2 Normally, after an ischemic episode during MI, the reperfusion damage of cardiomyocytes is associated with open mPTP in mitochondria, which induce a collapse of the mitochondrial membrane potential, ATP depletion, and cell death. Having closed mPTPs is essential to cell survival after reperfusion in MI. Whether the mPTP is opened or closed depends on BK and mitoK$_{ATP}$ of mitochondria. First, PKG induced by PDE5i is beneficial for opening the BK channel and, thereby, causes the K^+ influx, decreased Ca^{2+}, and the phosphorylation of RISK pathway-related molecules, e.g., ERK1/2 and Akt. The K^+ influx causes the high mitochondrial matrix K^+ content and provokes the uncoupling of the ETC, thereby resulting in low amounts of ROS. Phosphorylated ERK1/2 and Akt activate downstream molecules, e.g., GSK-3β. Low amounts of ROS, decreased Ca^{2+}, and molecules downstream of the RISK pathway inhibit the opening of the mPTP. Second, PKG causes phosphorylation of ERK1/2 and GSK3β and increases the expression of Bcl-2. The increased Bcl-2-to-Bax ratio prevents the cardiomyocyte apoptosis. With the help of Bcl-2, phosphorylated GSK3β opens mitoK$_{ATP}$ and causes K^+ influx, which results in decreased Ca^{2+}. Decreased Ca^{2+} is also not beneficial to the openness of the mPTP. Finally, the openness of the mPTP is restricted, resulting in the maintenance of the mitochondrial membrane potential, preserving ATP, promoting cell survival, and reducing the myocardial infarction areas. MI myocardial infarction, mPTP mitochondrial permeability transition pore, ATP adenosine triphosphate, BK Ca^{2+}-activated K^+ channels of the BK type, mitoK$_{ATP}$ mitochondrial ATP-dependent K^+ channels, PKG protein kinase G, ERK extracellular regulated protein kinases, Akt protein kinase B, GSK-3β glycogen synthase kinase-3β, ROS reactive oxygen species, Bcl-2 B cell lymphoma-2

PDE5is, Pulmonary Vascular Smooth Muscle Cells, and PAH

The pulmonary artery pressure is closely related to the vascular smooth muscle, where PDE5is increases cGMP expression and activates PKG by inhibiting PDE5, resulting in the dilation of vascular smooth muscle cells [50, 51]. The balance between proliferation and apoptosis of pulmonary vascular smooth muscle cells (PVSMCs) is associated with pulmonary vascular remodeling, which can increase pulmonary artery pressure [52, 53]. Ca^{2+} is essential in the reduced proliferation and enhanced apoptosis of PVSMCs, and the cGMP/PKG pathway induced by PDE5is is activated by PKG downstream proteins such as mitogen-activated protein kinase phosphatase-1 and peroxisome proliferator-activated receptor gamma [54–56]. The transient receptor potential canonical gene, which encodes a related protein on the store-operated Ca^{2+} channel that is activated by the Ca^{2+} store depletion, is then inhibited, and capacitive Ca^{2+} entry via this channel is reduced, resulting in decreased intracellular levels of Ca^{2+} [55, 56]. The low level of Ca^{2+} affects transcription factors associated with the expression of proliferation-related genes and inhibits the proliferation of PVSMCs [56, 57]. Additionally, the low level of Ca^{2+} relieves the inhibition of Ca^{2+} for phosphorylating Smad, which is a nuclear transcription factor that promotes the expression of pro-apoptosis genes and enhances apoptosis of PVSMCs [57].

The PDE5i Strategy for Patients with Both ED and CVD

The PDE5i medication dosing protocols for treatment of ED include once daily (taking the medicine once daily) and on demand (taking the medicine some time before sexual activity) [58]. Some patients following the on-demand PDE5i protocol for ED have a poor response to PDE5is. This occurs because ED is often caused by dysfunction of the vascular endothelium, which is closely related to CVD [59–61]. Compared with on-demand treatment, once-daily treatment has a higher therapeutic effect in terms of the International Index of Erectile Function (IIEF) and Sexual Encounter Profile (SEP) and is safe and generally well tolerated [62–64]. The once-daily protocol improves vascular endothelial function and has positive effects on ED [60, 65–67], which may be due to cumulative drug effectiveness [68, 69]. One study on the effect of 5-mg once-daily versus 5-mg alternate-day tadalafil for ED revealed no significant differences in the therapeutic effects as measured by the IIEF, International Prostate Symptom Score, and SEP-Q3 between the two groups [70]. The abovementioned results suggest that the cumulative effect of regular PDE5i administration is closely associated with the therapeutic effects and that the frequency of PDE5i administration is not limited to once daily. Additionally, compelling clinical evidence demonstrates that therapeutic effects can be obtained by regular dosing of a PDE5i, such as 10-mg vardenafil twice daily [71] or 50-mg sildenafil twice daily [72] for Raynaud's disease or 40-mg sildenafil three times daily [73], 5-mg vardenafil twice daily [74], or 40 mg/day tadalafil [75] for PAH. Therefore, regular, chronic administration of a PDE5i at a fixed frequency and prescribed dose may be suitable for patients with ED and CVD.

PDE5is can cause adverse effects such as vasodilatation, facial flushing, and an accelerated heart rate [32]. However, the adverse effects are moderate, transient, and reversible, and they gradually disappear over the course of administration [32]. The regular PDE5i treatment dose for ED and CVD is the therapeutic dose or the lowest recommended dose, which does not cause remarkable adverse effects and is well tolerated by patients [76]. Additionally, cumulative evidence shows that PDE5is combined with anti-CVD drugs, including diuretics, β-blockers, α1-blockers, angiotensin-converting enzyme inhibitors, and Ca^{2+} channel blockers, have no obvious adverse effects; the only exception is nitrate ester medications [77, 78]. However, it is safe to administer nitrates 24 h after using either sildenafil or vardenafil and 48 h after using tadalafil [79, 80]. Interestingly, some cardiovascular medications have synergistic actions with PDE5is. Atorvastatin enhances the response to sidenafil in patients with hypercholesterolemia and improves the curative effect of PDE5is [81]. The combination of fasudil with sidenafil had synergistic effects on animal models of PAH and in clinical trials, where it improved exercise capacity and reduced hospitalization rates [82, 83]. The combination of diltiazem and tadalafil attenuates ischemia reperfusion injury [84]. Hence, regular use of a PDE5i for ED and CVD is safe, effective, and feasible.

Regular Use of PDE5is Improves Treatment Adherence in Patients with ED and Concomitant CVD

Poor adherence reduces the CVD treatment effects, accelerates the progression of the disease, and increases the incidence rate, risk of complications, and healthcare costs [85]. A study of acute ischemic stroke and statins showed that the risk of recurrent stroke increases with reduced adherence to treatment after adjusting for related factors [86]. Another clinical study also demonstrated that good adherence to statin medication results in a lower relative risk of adverse cardiovascular events than poor adherence in discharged patients with acute coronary syndrome [87]. Interestingly, the protective effects of good adherence between different statin dose groups are similar [87]. Reduced adherence increases not only the disease burden but also the total medical care expenses and is negatively correlated with medical care costs [88].

ED is a common complication of CVD but can also be caused by some anti-CVD drugs, such as peripheral

sympatholytics and central sympatholytics, diuretics, β-blockers, and aldosterone antagonists, which negatively affect sexual activity [89–91]. Patients with medication-treated CVD might adjust the dose and frequency of the medication or even discontinue the drug without permission to reduce the adverse effects on erectile function and obtain a satisfactory sexual life [92]. This is the primary reason why ED decreases medication compliance in patients with CVD. ED, which causes lower erection rigidity, has negative effects on self-esteem, self-confidence, and mood [93, 94]. In one epidemiological study, subjects with ED had significantly lower scores on self-confidence and self-esteem scales than non-ED subjects, and there was an increased incidence of depressive symptoms in patients with ED [95, 96]. Negative spirituality, such as reduced self-confidence, frustrated self-esteem, anxiety, and annoyance, which directly affect the motivation of patients to chronically manage CVD and adhere to anti-CVD medication, results in reduced therapeutic effects [97–99]. This is another reason why ED reduces the compliance of CVD treatment for patients with both ED and CVD.

Compliance with PDE5is is positively associated with an increased frequency of sexual activity and improved erection hardness [100]. PDE5is have high treatment success rates for ED and allow patients to achieve satisfactory sexual activity [101]. Recent meta-analyses have shown IIEF-EF, which reflects overall erectile function, and SEP3, which reflects erectile function sufficient for successful intercourse, superiority with once-daily tadalafil, which more patients prefer [102, 103]. Thus, regular use of a PDE5i for patients with both ED and CVD not only improves compliance but also prevents patients from discontinuing the prescribed anti-CVD medication to achieve satisfactory sexual activity, resulting in further improved compliance. Finally, psychology is an important factor that can affect adherence to CVD medication and their therapeutic effects on CVD [104]. Treating ED with a PDE5i improves self-confidence and self-esteem [105, 106]; thus, PDE5is serve as psychological supportive therapy to improve compliance. Overall, PDE5is may be candidate medications for both CVD and ED to improve therapeutic effects and decrease total medical care expenses through better treatment adherence.

Prospects

CVD is a chronic disease in men of advanced age and is frequently accompanied by ED. As a predictor of CVD, ED can be used to foretell the severity of CVD and the risk of cardiovascular events. Regular use of a PDE5i for ED and CVD achieves optimal effectiveness to improve vascular endothelial function, enhanced erectile function and cardiovascular protection, and improved compliance to medications. PDE5is consequently may play a role reducing cardiovascular events and improving the prognosis of CVD. Interestingly, prostate tissue expresses PDE5, which helps to regulate the dynamic activity of smooth muscle in the transitional zone and secretory function and the proliferation of tissue in the prostate [107]. PDE5is have positive therapeutic effects on benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS) and have been approved for the treatment of BPH/LUTS [108, 109]. BPH/LUTS is believed to be one of the most common comorbidities of ED, and the association between ED and BPH/LUTS becomes stronger with age [110–112]. The concurrence of BPH/LUTS and ED is believed to be associated with the metabolic syndrome, which is characterized by multiple metabolic disorders including obesity, hyperglycemia, hypertension, and dyslipidemia [113]. These metabolic disorders, which are the pathological basis of CVD and diabetes mellitus, cause oxidation and degradation of the soluble guanylate cyclase (sGC) and reduced cyclic GMP (cGMP) levels. This results in LUTS and ED through strong contraction of smooth muscle in the prostate and penile cavernous body via a weakened NO-sGC-cGMP signaling pathway [114]. Thus, a close relationship exists among ED, CVD, and BPH/LUTS, and PDE5 is the common target. In addition, while the PDE5is may be ideal candidate medications for both ED and CVD, PDE5i administration is most likely to be an important future direction for treating older patients with simultaneous ED, CVD, and BPH/LUTS and decreasing medical care costs because these diseases are common and have huge health economic impacts on men of advanced age.

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Declarations

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Compliance with Ethical Standards

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Consent for publication Not applicable.

Ethics Approval and Consent to Participate Not applicable.

Abbreviations *cAMP*, Cyclic adenosine monophosphate; *cGMP*, Cyclic guanosine monophosphate; *CVD*, Cardiovascular disease; *ED*, Erectile

dysfunction; *GPCR*, G protein–coupled receptor; *HF*, Heart failure; *IIEF*, International Index of Erectile Function; *IP3*, Inositol 1,4,5-triphosphate; *MI*, Myocardial infarction; *MKP-1*, Mitogen-activated protein kinase phosphatase-1; *PAH*, Pulmonary arterial hypertension; *PDE5i*, PDE5 inhibitors; *PDE3*, Phosphodiesterase3; *PKG*, Protein kinase G; *PPARγ*, Peroxisome proliferator-activated receptor gamma; *PVSM*, Pulmonary vascular smooth muscle; *Rap1*, Ras-related protein 1; *SEP*, Sexual encounter profile; *SOC*, Store-operated Ca^{2+} channel; *TRPC*, Transient receptor potential canonical

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