The Relationship Between Erectile Dysfunction and Cardiovascular Disease. Part II: The Role of PDE-5 Inhibition in Sexual Dysfunction and Cardiovascular Disease

Vishal Kapur, MD, Christopher V. Chien, MD, Justin E. Fuess, MD, Ernst R. Schwarz, MD, PhD, FACC, FESC, FSCAI

Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA

Erectile dysfunction (ED) is a sensitive indicator of wider arterial insufficiency and an early correlate for the presence of ischemic heart disease. Among patients with coronary artery disease, prevalence reports of ED range from 42% to 75%. The US Food and Drug Administration has approved 3 phosphodiesterase-5 (PDE-5) inhibitors for treatment of male sexual dysfunction: sildenafil, tadalafil, and vardenafil. PDE-5 inhibitors also have cardiovascular effects. They inhibit PDE-5 enzymes in pulmonary vasculature, which causes vasodilation that decreases pulmonary vascular pressure. Sildenafil is approved for treatment of patients with pulmonary hypertension. PDE-5 inhibition with sildenafil improves cardiac output by balancing pulmonary and systemic vasodilation, and augments and prolongs the hemodynamic effects of inhaled nitric oxide in patients with chronic congestive heart failure and pulmonary hypertension. In vivo and in vitro studies are examining the possible beneficial effects of PDE-5 inhibitors in conditions such as myocardial infarction and endothelial dysfunction.
[Rev Cardiovasc Med. *2008;9(3):187-195*]

Key words: Erectile dysfunction • PDE-5 inhibitors • Pulmonary hypertension • Heart failure • Myocardial infarction • Endothelial dysfunction

The number of men in the United States at risk for erectile dysfunction (ED) is expected to rise from 12 million in 1995 to 21 million by the year 2025.[1] Phosphodiesterase-5 (PDE-5) inhibitors are a class of medications approved by the US Food and Drug Administration (FDA) for the treatment of ED. Inhibition of the enzyme PDE-5 maintains a nitric oxide (NO)–mediated vasodilation in penile tissue and thereby facilitates erection.[2] The multisystemic

effects of PDE-5 inhibitors have prompted their evaluation for use in other disease processes. They have been shown to inhibit PDE-5 enzymes in pulmonary vasculature, which causes vasodilation that decreases pulmonary vascular pressure, and are being used for treatment of pulmonary hypertension.[3] In vivo and in vitro studies are also examining the possible beneficial effects of PDE-5 inhibitors in cardiac disease, including myocardial infarction, heart failure (HF), and endothelial dysfunction.

In the Fall 2007 issue of *Reviews in Cardiovascular Medicine*, we critically examined the background, pathophysiology, and mechanisms behind sexual dysfunction and its close correlation to cardiovascular disorders.[4] Here we will discuss the potentials of PDE-5 inhibition in the treatment of male sexual dysfunction and other conditions.

Pathophysiology

In men, sexual stimulation causes the release of NO from nerve endings and endothelial cells in penile tissue, which activates the enzyme guanylate cyclase. This process results in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells in the corpus cavernosum. The increase in cGMP mediates a decrease in intracellular calcium that leads to smooth muscle relaxation in the corpus cavernosum, which in turn allows for increased blood flow into the penis, resulting in erection.[5] The degradation and resulting tissue concentration of cGMP is regulated by phosphodiesterases (PDEs). Eleven subtypes of PDEs have been identified in human tissues. PDE-2, 3, 4, 5, and 11 are found in penile tissues, with PDE type 5 the predominant type.[6] Inhibition of PDE-5 enhances erectile function (EF) by increasing the amount of NO- and cGMP-mediated smooth muscle relaxation and vasodilation in the corpus cavernosum. This property forms the basis of the use of PDE-5 inhibitors in patients with ED.

The PDE-5 Inhibitors

Several studies on the efficacy of PDE-5 inhibition in men with sexual dysfunction led the FDA to approve the first PDE-5 inhibitor, sildenafil (Viagra®, Pfizer Inc., New York, NY), in 1998. In 2004, 2 additional medications of the same class, tadalafil (Cialis®, Eli Lilly and Co., Indianapolis, IN) and vardenafil (Levitra®, Bayer HealthCare Pharmaceuticals Corp., Wayne, NJ), emerged in the market. PDE-5 inhibitors are the first class of oral agents to provide effective therapy for ED. The differences among sildenafil, tadalafil, and vardenafil can be understood through the pharmacologic characteristics of selectivity, potency, and bioavailability (Table 1). All PDE-5 inhibitors are metabolized primarily through the hepatic cytochrome P450 enzyme 3A4 and secondarily through the P450 enzyme 2C9.[7] Plasma levels of a PDE-5 inhibitor can be increased by the concomitant use of the drug with a potent cytochrome P450 3A4 inhibitor (erythromycin, ketoconazole, and itraconazole, among several others) or the nonspecific cytochrome P450 (CYP) inhibitor cimetidine.[3,5-8]

Sildenafil

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-ethylpiperazine citrate. It is a short-acting PDE-5 inhibitor, with duration of action of 4 hours. The onset of action of this drug is between 15 and 30 minutes, and it has a half-life of 3 to 4 hours. Sildenafil is converted to an active metabolite with a bioavailability of 40% and is excreted 80% in feces and 20% in urine. The main side effects observed with sildenafil use are headache, flushing, nasal congestion, dyspepsia, back pain, and visual changes.

Several worldwide clinical trials have established the efficacy and safety of sildenafil as a therapy for ED. Meuleman and colleagues[8] observed that the overall response rate to sildenafil therapy was 68%. However, lower response rates were seen in diabetic patients (for type I, 59%; for type II, 64%) by Boulton and coworkers.[9] The phase III trials of sildenafil demonstrated that the highest response rates to the global efficacy question were observed in men for whom ED was thought to be predominantly psychogenic (response rates: sildenafil 84%, placebo 24%). The efficacy of sildenafil was maintained in long-term studies (36 to 52 weeks), with only 5% of patients discontinuing treatment because of lack of efficacy.[10] The drug was well tolerated. In 3 open-label extension studies, Carson and colleagues[11] examined long-term (1 to 3 years) effectiveness of sildenafil in ED patients. Significantly improved EF was demonstrated with sildenafil for all efficacy parameters analyzed (with P values ranging from $< .02$ to $< .0001$). More than 95% of patients, regardless of age, race, body mass index, ED etiology, ED severity, ED duration, or the presence of various comorbidities, reported that they were satisfied with their erections while on long-term treatment. Fink and colleagues[12] performed a systematic review and meta-analysis on the safety and efficacy of sildenafil in the treatment of ED patients. The data analysis showed the pooled results of 14 parallel-group, flexible as-needed dosing trials. Sildenafil resulted in a

Table 1
Pharmacologic Characteristics of the PDE-5 Inhibitors

	Sildenafil	Vardenafil	Tadalafil
Onset of action (min)	15-30	15-45	15-30
Duration of action (h)	4	4	36
Half-life (h)	3-4	4-5	17.5
Bioavailability (%)	40	15	25
Active metabolite	Yes	Yes	No
Excretion	Feces—80% Urine—20%	Feces—90% Urine—5%	Feces—60% Urine—35%
Active metabolite	Yes	Yes	No
Contraindications	Hypersensitivity to drug, concomitant use of nitrates, α-blockers	Hypersensitivity to drug, concomitant use of nitrates	Hypersensitivity to drug, concomitant use of nitrates
Warnings/precautions	Recent stroke, myocardial infarction (within 6 months), resting hypotension (blood pressure < 90/50), unstable angina, retinitis pigmentosa	Hepatic and renal insufficiency, prolonged QT interval, left ventricular outflow obstruction, hypotension	Hepatic impairment, renal insufficiency

PDE-5, phosphodiesterase-5.

higher percentage of successful intercourse attempts than placebo (57% vs 21%; n = 2283 men), and a greater percentage of men experienced at least 1 successful intercourse episode during treatment with sildenafil (83% vs 45%; n = 2205 men).

Vardenafil

Vardenafil was the second drug approved by the FDA for use in patients with ED. It is structurally similar to sildenafil, but it is a more selective inhibitor of PDE-5. In vitro studies have shown that the potency of vardenafil in inhibiting PDE-5 purified from human corpus cavernosum tissue is approximately 25 times greater than that of sildenafil and 48 times greater than that of tadalafil.[13] Vardenafil has similar pharmacokinetics to sildenafil, with a time of onset between 15 and 45 minutes and a duration of action of about 4 hours. Vardenafil is also converted to an active metabolite with a half-life of 4 to 5 hours, and it has bioavailability of 15%, with principal excretion in the feces (90%). Additionally, since vardenafil is predominantly metabolized by the hepatic enzyme CYP3A4, and to a lesser extent by CYP3A5 and CYP2C, inhibitors of these enzymes may reduce vardenafil clearance. Consequently, concomitant use of vardenafil with potent CYP3A4 inhibitors such as ritonavir, indinavir, erythromycin, itraconazole, and ketoconazole is not recommended in order to minimize any possible adverse drug reactions.[14]

A recent pooled subgroup analysis of randomized, double-blind, placebo-controlled trials studied 1385 men with ED who were treated with placebo versus flexible-dose vardenafil over a 12-week period. The study showed a high response rate to vardenafil in all subgroups based on the International Index of Erectile Function (IIEF) survey[15] and on the Global Assessment Question (GAQ)—"Has the treatment improved your erections?" Vardenafil generated positive GAQ responses in approximately 71% of men younger than 45, 76% of men ages 45 to 64, and 85% of men older than 65 ($P = .001$ vardenafil vs placebo). At the end of the treatment period in all 3 age groups, vardenafil doses of 5, 10, and 20 mg were associated with statistically significant increases in the IIEF-EF domain score compared with placebo ($P < .03$ for vardenafil 5 mg; $P < .001$ for vardenafil 10 mg and 20 mg).[15] A retrospective analysis examined data from 2 randomized, double-blind studies of men with ED who received variably dosed vardenafil or placebo for 12 to 26 weeks. The success rate for achieving erections before sexual intercourse was significantly increased from 15 minutes through 6 hours after

dosing in patients treated with vardenafil as compared with placebo.[16] Furthermore, the ability to maintain an erection was increased by vardenafil (from as early as 15 minutes after dosing through 12 hours after dosing). It has also been reported that the cumulative probability that a man will achieve successful penetration and maintain an erection increased with the number of times that vardenafil was tried, at all 3 doses tested (5, 10, and 20 mg).[17] The cumulative probability stopped increasing by the fourth attempt with vardenafil.

Tadalafil

Tadalafil was the third PDE-5 inhibitor approved by the FDA for the treatment of ED. Compared with its predecessors, tadalafil is known for its long duration of action (36 hours), with a half-life of 17.5 hours. The onset of action is similar to sildenafil and vardenafil (15 to 30 minutes), but tadalafil is not converted to an active metabolite and is excreted both in feces (60%) and urine (35%).

The efficacy and safety of on-demand dosing of tadalafil in men with erectile dysfunction was assessed in a multicenter, double-blind, placebo-controlled study.[18] The 179 subjects were randomized to receive placebo or tadalafil at doses of 2 mg, 5 mg, 10 mg, or 25 mg, taken on-demand during a 3-week period. The primary endpoints were change from baseline in response to IIEF questions 3 (frequency of penetration) and 4 (frequency of maintained erections after penetration). The researchers noticed a significant improvement in IIEF question 3 scores at all doses versus placebo ($P \leq .003$). Tadalafil also significantly improved IIEF question 4 scores in all but the 2-mg group ($P \leq .0003$). The authors concluded that on-demand tadalafil at doses up to 25 mg was well tolerated and significantly improved erectile function.

To evaluate a population that was less responsive to PDE-5 inhibitors in other trials, a large, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study[19] examined patients with diabetes mellitus (type I and type II). Tadalafil at doses of 20 mg improved the mean IIEF-EF score to 18.8, with a mean increase of 7.3, a change comparable with that observed in the general population of ED patients treated with tadalafil. Tadalafil at 20 mg improved penetration ability and successful intercourse. The long-term safety and tolerability of tadalafil were recently examined in a multicenter, open-label, 24-month extension trial that involved more than 1000 patients who were started on a 10-mg dose of tadalafil that could be increased to 20 mg or decreased to 5 mg.[20] The most commonly treated emergent adverse events—headache (16%), dyspepsia (12%), nasopharyngitis (11%), and back pain (8%)—were considered mild or moderate. The discontinuation rate that resulted from these adverse events was 6.3%, and the rate for any individual event was less than 1%.

To review, PDE-5 inhibitors have been well studied in the treatment of ED and are now the treatment of choice for patients with sexual dysfunction. Combined medical therapy and psychological support can significantly improve the quality of life of the affected individuals.

PDE-5 Inhibitors for Treatment of Pulmonary Hypertension

PDE-5 inhibitors were initially approved for use in the United States for the purpose of treating ED. However, since their introduction, these drugs have been studied extensively in both animals and humans for possible use in several other disease processes, such as pulmonary hypertension, cardiomyopathy, and myocardial infarction. This potential application is based on the fact that NO plays a role in many cellular and cardiovascular phenomena, including regulation of vascular tone.

The benefit of PDE-5 inhibition on pulmonary vasculature has been well studied, and in June 2005, the FDA approved sildenafil for use in patients with pulmonary hypertension (Revatio®, Pfizer Inc., New York, NY). The FDA approval was based on results of a large, randomized, double-blind, placebo-controlled study that measured the exercise capability of 277 patients with pulmonary artery hypertension after 12 weeks of treatment with sildenafil.[21] Patients were randomized to receive placebo or sildenafil at 20 mg, 40 mg, or 80 mg 3 times a day. All 3 treatment groups showed highly significant improvements in the 6-minute walk distance (the standard measure of efficacy in pulmonary artery hypertension trials) as compared with placebo. However, there were no differences observed among the sildenafil doses studied—therefore, the approved dosage was limited to 20 mg 3 times daily. Patients taking sildenafil also showed improvements in mean pulmonary artery pressure. A long-term non–placebo-controlled extension trial was also conducted. At the end of 1 year, walk distance and functional class were stable, and 94% of patients were still alive.

To further establish the effectiveness of the use of sildenafil in pulmonary hypertension, a recent study by Garg and colleagues[22] showed that oral sildenafil improved functional capacity and hemodynamic parameters, and was safe in patients with severe pulmonary artery hypertension. The beneficial effects were evident as early as 2 weeks after initiation of the drug and were dose-related, although the FDA has only approved a fixed dose (20 mg 3 times daily) of Revatio. The most common side effects are

similar to those reported in the Viagra trials—headache, facial flushing, and upset stomach.

In patients with pulmonary hypertension secondary to congestive HF, inhaled NO increases pulmonary vascular smooth-muscle intracellular cGMP concentration, thereby decreasing pulmonary vascular resistance and increasing the cardiac index. Based on this hypothesis, Lepore and colleagues[23] studied the effects of oral sildenafil (50 mg), inhaled NO (80 ppm), and the combination of sildenafil and inhaled NO during right-heart and micromanometer left-heart catheterization. They found that sildenafil administered alone decreased mean pulmonary artery pressure by 12% ± 5%, pulmonary vascular resistance by 12% ± 5%, systemic vascular resistance by 13% ± 6%, and pulmonary capillary wedge pressure by 12% ± 7%. It increased the cardiac index by 14% ± 5% (all $P < .05$). The combination of inhaled NO and sildenafil decreased pulmonary vascular resistance by 50% ± 4%, decreased systemic vascular resistance by 24% ± 3%, and increased the cardiac index by 30% ± 4% (all $P < .01$). In addition, sildenafil prolonged the pulmonary vasodilator effect of inhaled NO. Administration of sildenafil alone or in combination with inhaled NO did not change systemic arterial pressure or indexes of myocardial systolic or diastolic function. In the end, the authors concluded that PDE-5 inhibition with sildenafil improves cardiac output by balancing pulmonary and systemic vasodilation, and augments and prolongs the hemodynamic effects of inhaled NO in patients with chronic congestive HF and pulmonary hypertension.

A study by van Wolferen and colleagues[24] in patients with pulmonary hypertension showed a significant finding: the addition of a 3-month course of sildenafil to a 12-month regimen of bosentan caused a significant decrease in right ventricular mass as compared with lone bosentan therapy. The authors postulated the following 2 mechanisms for the beneficial effect. First, right ventricular mass decreases because the pulmonary vascular resistance decreases, resulting in less right ventricular wall stress. The reduction in right ventricular wall stress is also supported by the decrease in N-terminal brain natriuretic propeptide (NTproBNP) after 3 months of sildenafil. Moreover, the reduction in NTproBNP correlated with the reduction in right ventricular dilation and hypertrophy. Second, sildenafil may have an intrinsic effect on the heart that has not been explored in detail.

Lunze and colleagues[25] also studied the effect of oral combination therapy of sildenafil and bosentan in pulmonary hypertension. The subjects were 11 patients with mean pulmonary arterial pressure exceeding 25 mm Hg. Clinical improvement was about 1 New York Heart Association (NYHA) class (mean 2.8 ± 0.4 to 1.6 ± 0.8; $P = .001$), which was associated with an increase of transcutaneous oxygen saturation (89.9 ± 9.9 to 92.3% ± 7.1%; $P = .037$), maximum oxygen uptake (18.1 ± 6.8 to 22.8 ± 10.4; $P = .043$), and 6-minute walking distance (351 m ± 58 m to 451 m ± 119 m; $P = .039$). Mean pulmonary arterial pressure measured invasively decreased (62 mm Hg ± 12 mm Hg to 46 mm Hg ± 18 mm Hg; $P = .041$). Thus, based on these studies and the existing literature, PDE-5 inhibitors have a promising future in the treatment of pulmonary hypertension, although further data may help substantiate the pulmonary effects.

PDE-5 Inhibitors and Ischemic Heart Disease

There have been increasing data regarding the close relationship between ED and cardiovascular disease (CVD). ED and CVD share common risk factors, such as diabetes,[26] hypertension,[27] smoking,[28] and hyperlipidemia.[29] At the molecular level, atherosclerosis and endothelial dysfunction have been shown to be common to both ED and CVD, with atherosclerosis being the most frequent cause of vasculogenic ED in older men. Among patients with coronary artery disease, prevalence reports of ED have ranged from 42% to 75%.[30-36] Montorsi and colleagues[31] reported the rate of ED in patients with coronary artery disease to be as high as 42% to 57%. Conversely, the incidence of positive exercise stress testing in patients with ED ranges from 5% to 56%.[37] ED has also been correlated with the coronary plaque burden and the number of diseased coronary arteries.[30,38]

With the approval of PDE-5 inhibitors for the treatment of ED, there has been marked interest in the role of PDE-5 inhibition in modifying CVD manifestations, such as ischemic heart disease. Interestingly, the initial trial of sildenafil was actually focused on treating patients with CVD. It was unsuccessful in treating CVD, but patients participating in the trials reported increased EF, which led to a refocusing of the clinical program that ultimately led to the approval of sildenafil for the treatment of ED. With further studies, it has been confirmed that there are certain PDE receptors/isoforms present in coronary and pulmonary vasculature, including PDE-5 receptors, and hence a possible beneficial effect has been suggested. ED is a sensitive indicator of wider arterial insufficiency and an early correlate for the presence of ischemic heart disease.[39-41] Assessment of cardiac risk after a complaint of erectile problems can potentially reduce subsequent morbidity and mortality.[42]

An important phenomenon in cardiac disease is ischemic preconditioning, which is characterized by

repeated brief episodes of ischemia that induce a cascade of intracellular signaling that helps prevent any further myocardial stunning and infarction. A possible hypothesis suggests that the vasodilatory action of sildenafil may potentially release endogenous mediators of preconditioning that may trigger a signaling cascade in the cardiac myocytes, resulting in the release of NO. The generation of NO could activate guanyl cyclase and form cGMP. cGMP may in turn activate protein kinase G that can subsequently open the mitochondrial adenosine triphosphate–sensitive K^+ (K_{ATP}) channel, leading to cardioprotective effects. There have been both animal studies and human studies to support this hypothesis. In a rabbit model, Salloum and colleagues[43] observed that vardenafil had a protective effect on the ischemic/reperfusion injury by opening the mitochondrial K_{ATP} channel. This study supported the hypothesis that PDE-5 inhibitors induce a protective effect in the ischemic heart. In a study involving the effect of sildenafil on the reperfusion function, infarct size, and cyclic nucleotide levels in an isolated rat heart model, du Toit and colleagues[44] found that:

- Pretreatment with low concentrations of sildenafil (20 to 50 nM) improved reperfusion function, whereas higher concentrations (200 nM) worsened it.
- Low concentrations of sildenafil (20 to 50 nM) decreased infarct size, but the higher concentrations had no effect.
- The protective properties of low concentrations of sildenafil may be related to its cGMP-elevating and cAMP-suppressing effects in the ischemic heart.
- Possible end-effectors for sildenafil in the ischemic heart include the mitochondrial and sarcolemmal K_{ATP} channels.

Ferreira-Melo and colleagues[45] hypothesized that in a model of reduced NO formation, the inhibition of PDE-5 by selective inhibitors such as sildenafil could be beneficial in restoring physiological functions by enhancing the intracellular levels of cGMP. In their study, they evaluated the effects of sildenafil on the hemodynamic and histological alterations induced in rats by long-term treatment with NΩ-nitro-L-arginine-methyl ester (L-NAME). After 8 weeks of concomitant treatment with sildenafil and L-NAME, arterial blood pressure was significantly lower ($P < .05$) than in the rats treated with L-NAME alone. The fall in blood pressure was associated with a slight reduction in the total peripheral vascular resistance ($P < .05$). Sildenafil partially prevented the decrease in cardiac output seen in L-NAME–treated rats. Morphologically, sildenafil reduced the total area of the myocardial lesions and attenuated the cardiomyocyte and vascular smooth muscle remodeling seen with L-NAME. These results showed that sildenafil prevented the deleterious hemodynamic and morphological alterations associated with L-NAME–induced hypertension. This beneficial effect was probably mediated by an increase in cardiac and vascular cGMP levels as reflected in circulating plasma cGMP levels.

Gori and colleagues[46] investigated whether sildenafil could also prevent the impairment in endothelium-dependent vasodilation induced by ischemia–reperfusion in humans. Ten healthy male volunteers were randomized to 50 mg oral sildenafil or placebo. Endothelium-dependent and flow-mediated dilation of the radial artery was measured before and after ischemia reperfusion. Sildenafil limited the impairment in endothelium-dependent vasodilation that was seen with placebo. This protective effect was prevented by an inhibitor of K_{ATP} channels, as was also seen in a study by Kukreja and coworkers.[47] Das and colleagues[48] had shown for the first time that sildenafil directly protects adult cardiomyocytes against necrosis and apoptosis after ischemia–reoxygenation injury. An NO synthase–dependent mechanism and the mitochondrial K_{ATP}-opening property of sildenafil both contribute to its role in inhibition of apoptosis and necrosis. These authors also demonstrated for the first time the presence of PDE-5 in murine ventricular cardiomyocytes. Therefore, based on these clinical models, it can be hypothesized that sildenafil might have a beneficial effect on the myocardium, specifically on ischemic preconditioning. More studies are needed to substantiate the effects of PDE-5 inhibitors on the myocardium.

PDE-5 Inhibitors and Heart Failure

Sexuality is an important component of quality of life, and sexual dysfunction is ranked among the most distressing symptoms reported by patients with congestive HF.[49] ED is common in the HF population, with an estimated prevalence ranging from 25% to 75%.[50-55] Jaarsma and colleagues[50] reported that approximately 75% of patients with HF had a marked decrease in sexual interest and frequency of sexual intercourse, with 32% of patients reporting cessation of all sexual activity because of their underlying illness. In another study of 63 HF patients at an HF and heart transplantation clinic, 59% reported problems with sexual performance and decreased frequency of sexual activity, and more than 80% of these patients reported partial or total loss of interest in sexual activities since the onset of HF.[55]

After the initial release of sildenafil, the American Heart Association/American College of Cardiology (AHA/ACC) expressed concerns about the use of this drug in patients with HF based on the lack of cardiovascular safety data in this population. In the 1999 consensus document by the AHA/ACC, HF was considered to be a relative contraindication to the use of sildenafil and other cardiac medications.[56] However, Katz and colleagues[57] undertook a multicenter, prospective, randomized, double-blind, placebo-controlled trial, which demonstrated that flexible dosing of sildenafil from 25 to 100 mg was well tolerated. They further demonstrated improved EF and increased satisfaction with sexual performance in ambulatory subjects who had mild to moderate congestive HF compared with subjects who received placebo. Stable HF was defined based on clinical criteria to include the absence of signs of congestion on physical examination, no emergency department visits or hospitalizations for HF or cardiac-related illness for more than 3 months, and a stable medical regimen without nitrates for more than 4 weeks. After 12 weeks, sildenafil-treated patients (n = 60) showed significant improvements in IIEF questions 3 (frequency of penetration) and 4 (frequency of maintained erections after penetration) compared with placebo-treated patients (n = 72; $P < .002$). Sildenafil-treated patients reported significant improvement in their erections (74%) and their ability to have intercourse (68%) as compared with placebo-treated patients (18% and 16%, respectively; $P < .0001$). Sildenafil was also associated with significantly higher mean scores on 10 of 11 Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) survey items when compared with placebo. There were no serious treatment-related adverse events in the study, and the incidence of all serious adverse events was low in the sildenafil group (3%) and the placebo group (5%). With the exception of flushing, no adverse cardiovascular events were attributable to sildenafil.

Bocchi and associates[58] studied the effect of sildenafil on exercise capacity and hemodynamics in 23 patients with HF and ED. In the first phase of the trial, researchers assessed the effects of a single oral dose of sildenafil 50 mg versus placebo on systemic hemodynamics in patients at rest and during submaximal and maximal exercise. As compared with placebo, sildenafil decreased the resting heart rate and attenuated the increase in heart rate during exercise. Systolic blood pressure at rest decreased by 8 mm Hg with sildenafil as compared with placebo. The second phase of the study determined the effects of sildenafil 25 to 150 mg on EF for a 1-month period. The IIEF and EDITS surveys were used to assess the efficacy and satisfaction of treatment. Sildenafil improved the overall EDITS score and the scores for questions 3 (frequency of penetration) and 4 (frequency of maintained erections after penetration) on the IIEF when compared with baseline. In a single-center, randomized, placebo-controlled trial by Webster and colleagues[59] studying the effects of a 6-week course of 50 mg sildenafil, there was no significant change in heart rate or blood pressure. Sildenafil use was also associated with increased quality-of-life questionnaire scores and amelioration of depressive symptoms as compared with placebo.

The hemodynamic effects of sildenafil in HF patients have been further studied. A small trial by Hirata and colleagues[60] confirmed that sildenafil use acutely decreased heart rate. Additionally, there was a significant increase in cardiac index (by 0.37 L/min/m^2), which was likely due to the observed reduction in total systemic resistance. Another potential hemodynamic benefit of sildenafil in HF is that, at low doses, it has been shown to increase endothelium-dependent flow-mediated vasodilation.

Main Points

- In 1 study, more than 95% of patients with erectile dysfunction were satisfied with their improvement while on long-term sildenafil therapy.
- Vardenafil treatment improves erections in 71% of men younger than 45, 76% of men ages 45 to 64, and 85% of men older than 65.
- Tadalafil is known for its long duration of action (36 hours), with a half-life of 17.5 hours.
- Sildenafil is approved for use in patients with pulmonary hypertension.
- Among patients with coronary artery disease, prevalence reports of erectile dysfunction have ranged from 42% to 75%.
- Trials have shown that phosphodiesterase-5 inhibitors can successfully treat erectile dysfunction, as measured by improvement of erections or other markers.

Although the newer PDE inhibitors vardenafil and tadalafil may not present additional cardiac risks, no clinical safety data on their use are available in the HF patient population. In general, trials have shown that PDE-5 inhibitors can successfully treat ED, as measured by improvement of erections or other markers, such as the IIEF score.

Conclusion

Available data from the literature and published trials have established the efficacy and safety of sildenafil and other PDE-5 inhibitors in ED. There has also been some positive evidence regarding the use of sildenafil in patients with pulmonary hypertension, which can be attributed to the presence of PDE-5 receptors in the various organ systems. However, exploration of the roles of PDE-5 inhibitors in cardiac ischemia, the myocardium, and HF is in the preliminary stage. More studies need to be undertaken to understand, in detail, the beneficial effects of this class of medications on the different organ system and disease processes. ■

References

1. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int*. 1999;84:50-56.
2. Burnett AL. Role of nitric oxide in the physiology of erection. *Biol Reprod*. 1995;52:485-489.
3. Mikhail GW, Prasad SK, Li W, et al. Clinical and haemodynamic effects of sildenafil in pulmonary hypertension: acute and mid-term effects. *Eur Heart J*. 2004;25:431-436.
4. Kapur V, Schwarz ER. The relationship between erectile dysfunction and cardiovascular disease. Part 1: pathophysiology and mechanisms. *Rev Cardiovasc Med*. 2007;8:214-219.
5. Andersson KE, Wagner G. Physiology of penile erection. *Physiol Rev*. 1995;75:191-236.
6. Lin CS, Lau A, Tu R, Lue TF. Expression of three isoforms of cGMP binding cGMP-specific phosphodiesterase (PDE5) in human penile cavernosum. *Biochem Biophys Res Commun*. 2000; 268:628-635.
7. Warrington JS, Shader RI, von Moltke LL, Greenblatt DJ. In vitro biotransformation of sildenafil (Viagra): identification of human cytochromes and potential drug interactions. *Drug Metab Dispos*. 2000;28:392-397.
8. Meuleman E, Cuzin B, Opsomer RJ, et al. A dose-escalation study to assess the efficacy and safety of sildenafil citrate in men with erectile dysfunction. *BJU Int*. 2001;87:75-81.
9. Boulton AJM, Selam JL, Sweeney M, Ziegler D. Sildenafil citrate for the treatment of erectile dysfunction in men with Type II diabetes mellitus. *Diabetologia*. 2001;44:1296-1301.
10. Briganti A, Salonia A, Deho F, et al. Clinical update on phosphodiesterase type-5 inhibitors for erectile dysfunction. *World J Urol*. 2005;23:374-384.
11. Carson CC, Burnett AL, Levine LA, Nehra A. The efficacy of sildenafil citrate (Viagra) in clinical populations: an update. *Urology*. 2002;60: 12-27.
12. Fink HA, MacDonald R, Rutks IR, et al. Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med*. 2002;162:1349-1360.
13. Gbekor E, Bethell S, Fawcett L, et al. Selectivity of sildenafil and other phosphodiesterase type 5 (PDE5) inhibitors against all human phosphodiesterase families. *Eur Urol*. 2002;42 (suppl 1):63.
14. Stark S, Sachse R, Liedl T, et al. Vardenafil increases penile rigidity and tumescence in men with erectile dysfunction after a single oral dose. *Eur Urol*. 2001;40:181-188.
15. Giuliano F, Donatucci C, Montorsi F, et al, for the Vardenafil Study Group. Vardenafil is effective and well tolerated for treating erectile dysfunction in a broad population of men, irrespective of age. *BJU Int*. 2005;95:110-116.
16. Valiquette L, Montorsi F, Hellstrom WJ, et al. Penetration and maintenance of erection with vardenafil: a time-from-dosing analysis. *Can J Urol*. 2005;12:2687-2698.
17. Hellstrom WJ, Elhilali M, Homering M, et al. Vardenafil in patients with erectile dysfunction: achieving treatment optimization. *J Androl*. 2005;26:604-609.
18. Padma-Nathan H, McMurray JG, Pullman WE, et al. On demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. *Int J Impot Res*. 2001;13:2-9.
19. Sáenz de Tejada I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care*. 2002;25: 2159-2164.
20. Montorsi F, Verheyden B, Meuleman E, et al. Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. *Eur Urol*. 2004;45:339-345.
21. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353:2148-2157.
22. Garg N, Sharma MK, Sinha N. Role of oral sildenafil in severe pulmonary arterial hypertension: clinical efficacy and dose response relationship. *Int J Cardiol*. 2007;120:306-313.
23. Lepore JJ, Maroo A, Pereira NL, et al. Effect of sildenafil on the acute pulmonary vasodilator response to inhaled nitric oxide in adults with primary pulmonary hypertension. *Am J Cardiol*. 2002;90:677-680.
24. van Wolferen SA, Boonstra A, Marcus JT, et al. Right ventricular reverse remodeling after sildenafil in pulmonary arterial hypertension. *Heart*. 2006;92:1860-1861.
25. Lunze K, Gilbert N, Mebus S, et al. First experience with an oral combination therapy using bosentan and sildenafil for pulmonary arterial hypertension. *Eur J Clin Invest*. 2006;36:32-38.
26. Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *J Urol*. 2004;171:2341-2345.
27. Jensen J, Lendorf A, Stimpel H, et al. The prevalence and etiology of impotence in 101 male hypertensive outpatients. *Am J Hypertens*. 1999;12:271-275.
28. Shabsigh R, Fishman IJ, Schum C, Dunn JK. Cigarette smoking and other vascular risk factors in vasculogenic impotence. *Urology*. 1991; 38:227-232.
29. Wei M, Macera CA, Davis DR, et al. Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. *Am J Epidemiol*. 1994;140:930-937.
30. Solomon H, Man JW, Wierzbicki AS, Jackson G. Relation of erectile dysfunction to angiographic coronary artery disease. *Am J Cardiol*. 2003;91:230-231.
31. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol*. 2003;44:360-365.
32. Wabrek AJ, Burchell C. Male sexual dysfunction associated with coronary artery disease. *Arch Sex Behav*. 1980;9:69-75.
33. Diokno AC, Brown MB, Herzog R. Sexual function in the elderly. *Arch Intern Med*. 1990;150: 197-200.
34. Dhabuwala CB, Kumar A, Pierce JM. Myocardial infarction and its influence on male sexual dysfunction. *Arch Sex Behav*. 1986;15:499-504.
35. Kloner R, Mullin S, Shook T, et al. Erectile dysfunction in the cardiac patient: how common and how should we treat? *J Urol*. 2003;170:S46-S50.
36. Tuttle WB, Cook WL, Fitch E. Sexual behavior in post-myocardial infarction patients. *Am J Cardiol*. 1964;13:140.
37. Montorsi P, Ravagnani PM, Galli S, et al. Common grounds for erectile dysfunction and coronary artery disease. *Curr Opin Urol*. 2004;14: 361-365.
38. Greenstein A, Chen J, Matzkin H, et al. Does severity of ischemic coronary disease correlate with erectile dysfunction? *Int J Impot Res*. 1997;9:123-126.
39. Russell ST, Khandheria BK, Nehra A. Erectile dysfunction and cardiovascular disease. *Mayo Clin Proc*. 2004;79:782-794.
40. Chiurlia E, D'Amico R, Ratti C, et al. Subclinical coronary artery atherosclerosis in patients with erectile dysfunction. *J Am Coll Cardiol*. 2005;46: 1503-1506.
41. Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. *JAMA*. 2005;294:2996-3002.
42. Feldman HA, Goldstein I, Hatzichristou DG, et al. Erectile dysfunction and cardiac risk factors: prospective results from the Massachusetts Male Aging Study. *Prev Med*. 2000;30:328-338.
43. Salloum F, Yin C, Xi L. Sildenafil induces delayed preconditioning through inducible nitric oxide synthase-dependent pathway in mouse heart. *Circ Res*. 2003;92:595-597.
44. du Toit EF, McCarthy J, Miyashiro J, et al. Effect of nitrovasodilators and inhibitors of nitric

oxide synthase on ischaemic and reperfusion function of rat isolated hearts. *Br J Pharmacol*. 1998;123:1159-1167.
45. Ferreira-Melo SE, Yugar-Toledo JC, Rizzi Coelho O, et al. Sildenafil reduces cardiovascular remodeling associated with hypertensive cardiomyopathy in NOS inhibitor-treated rats. *Eur J Pharma*. 2006;542:141-147.
46. Gori T, Sicuro S, Dragoni S, et al. Sildenafil prevents endothelial dysfunction induced by ischemia and reperfusion via opening of adenosine triphosphate-sensitive potassium channels. *Circulation*. 2005;111:742-746.
47. Kukreja RC, Salloum F, Das A, et al. Pharmacological preconditioning with sildenafil: basic mechanisms and clinical implications. *Vasc Pharmacol*. 2005;42:219-232.
48. Das A, Xi L, Kukreja RC. Phosphodiesterase-5 inhibitor, sildenafil preconditions adult cardiac myocytes against necrosis and apoptosis: essential role of NO signaling. *J Biol Chem*. 2005; 280:12944-12955.
49. Grady KL, Lalowiec A, Brusk BB, et al. Symptom distress in cardiac transplantation. *Heart Lung*. 1992;21:434-439.
50. Jaarsma T, Dracup K, Walden J, Stevenson LW. Sexual function in patients with advanced heart failure. *Heart Lung*. 1996;25:262-270.
51. Bohachick P, Anton BB. Psychosocial adjustment of patients and spouses to severe cardiomyopathy. *Res Nurs Health*. 1990;13:385-392.
52. Pifarre R, Kirklin JK, Bourge RC, Costanzo MR. Predictors of quality of life in patients with advanced heart failure awaiting transplantation. *J Heart Lung Transplant*. 1995;14:2-10.
53. Muirhead J, Meyerowitz BE, Leedham B, et al. Quality of life and coping in patients awaiting heart transplantation. *J Heart Lung Transplant*. 1992;11:265-272.
54. Mulligan T, Sheehan H, Hanrahan J. Sexual function after heart transplantation. *J Heart Lung Transplant*. 1991;10:125-128.
55. Westlake C, Dracup K, Walden JA, Fonarow G. Sexuality of patients with advanced heart failure and their spouses or partners. *J Heart Lung Transplant*. 1999;18:1133-1138.
56. Cheitlin MD, Hutter AM Jr, Brindis RG, et al. ACC/AHA expert consensus document: use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol*. 1999;33:273-282.
57. Katz SD, Parker JD, Glasser DB, et al. Efficacy and safety of sildenafil citrate in men with erectile dysfunction and chronic heart failure. *Am J Cardiol*. 2005;95:36-42.
58. Bocchi EA, Guimarares G, Mocelin A, et al. Sildenafil effects on exercise, neurohormonal activation, and erectile dysfunction in congestive heart failure. *Circulation*. 2002;106:1097-1103.
59. Webster LJ, Michelakis ED, Davis T, Archer SL. Use of sildenafil for safe improvement of erectile dysfunction and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-controlled, double-blind crossover trial. *Arch Intern Med*. 2004;164:514-520.
60. Hirata K, Adji A, Vlachopoulos C, O'Rourke MF. Effect of sildenafil on cardiac performance in patients with heart failure. *Am J Cardiol*. 2005;96:1436-1440.