New Drugs and Technologies

Cardiovascular Effects of the 3 Phosphodiesterase-5 Inhibitors Approved for the Treatment of Erectile Dysfunction

Robert A. Kloner, MD, PhD

Within the last year, 2 new phosphodiesterase-5 (PDE5) inhibitors have been approved by the US Food and Drug Administration (FDA) for the treatment of erectile dysfunction (ED). Currently, sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) are on the market. These agents have been shown to be effective in a broad population of men with ED, including patients with vascular disease, coronary artery disease, hypertension, and diabetes.1–5 Because the enzyme that they inhibit, PDE-5, is found in smooth muscle cells of the systemic arteries and veins throughout the body, these agents have mild vasodilator effects and thus, have the potential to impact the cardiovascular system.6 This fact is especially important for the patient with ED, because risk factors for ED include many of the same risk factors that are associated with coronary artery disease: lipid abnormalities, hypertension, smoking, diabetes, and lack of physical exercise.7,8 Because erection is a vascular event, endothelial dysfunction may inhibit it.9 Endothelial dysfunction, an early component of atherosclerosis, is rarely confined to the arteries supplying blood to the penis but more likely occurs throughout the vascular bed. Kaiser et al10 studied 30 men with ED and observed that brachial artery flow–mediated vasodilation and nitroglycerin-mediated vasodilation were reduced in these patients compared with men without ED. Thus, ED may be an early marker of vascular disease.10 Patients with frank coronary artery disease, known to be associated with endothelial dysfunction, and frank atherosclerosis often have ED, as we recently observed in 1 study, in which three fourths of the men with chronic stable angina also reported some degree of ED.11 Hence, the vasodilator effect of these PDE5 agents should be taken into consideration for the cardiac patient, both as a possible concern in some cases or a possible beneficial effect in others. The purpose of the present review is to describe the cardiovascular effects of the 3 available PDE5 inhibitors, the issue of nitrate interaction, differences and similarities in labeling regarding concomitant use of nitrates and α-blockers, their effect on the QT interval, their safety in regard to cardiac events, and the concept that these agents may eventually play a role in therapies for various cardiac conditions, including pulmonary hypertension and congestive heart failure.

Effect of PDE5 Inhibitors on Blood Pressure and Heart Rate

Sildenafil
Sildenafil was approved as an effective agent for treating ED in 1998, and its cardiovascular effects have been studied in great depth. It has a half-life of ~4 hours (Table). In 1 study of 8 volunteers,12 80 mg of intravenous sildenafil reduced systolic blood pressure from 131 ± 12 mm Hg with placebo to 122 ± 13 mm Hg (P < 0.001) with sildenafil. Diastolic blood pressure fell from 71 ± 12 to 64 ± 11, respectively, but heart rate did not change significantly (64 ± 10 to 66 ± 14 beats/min; mean ± SD). Jackson et al12 gave 8 healthy male subjects 100, 150, and 200 mg of oral sildenafil. The mean maximum reduction in supine systolic/diastolic blood pressure was 10/7 mm Hg at 3 hours after dosing, with no difference in the 200-mg versus the 100-mg dose. In most subjects, blood pressure returned to baseline within 6 hours. The authors did not observe a significant orthostatic drop in blood pressure or increase in heart rate in the standing position. Sildenafil, as expected, reduced vascular resistance.

In patients with stable ischemic heart disease 40 mg of intravenous sildenafil reduced systolic arterial pressure from 150 ± 12 to 141 ± 16 mm Hg (mean ± SD) and diastolic blood pressure from 74 ± 8 to 66 ± 10 mm Hg but had no effect on heart rate. Cardiac output was 5.6 ± 0.9 L/min at baseline and 5.2 ± 1.1 L/min after intravenous sildenafil. Pulmonary artery pressure fell from 16.7 ± 4.0 to 12.1 ± 3.9 mm Hg. Subsequent studies verified that sildenafil results in small reductions in systolic and diastolic blood pressure, with little or no effect on heart rate.13–15 In addition, sildenafil was shown in numerous studies of pulmonary hypertension to reduce pulmonary vascular resistance and pulmonary artery pressure (PDE5 is rich within the pulmonary vasculature).16–18

Vardenafil
Vardenafil was the second PDE5 inhibitor to come to market in the United States, and it was approved by the FDA in 2003.
It has many similarities to sildenafil; in fact, its molecular structure is very similar (Figure), and they share a half-life of about 4 hours. In healthy volunteers, vardenafil caused a transient reduction in supine blood pressure with a mean maximum decrease of 7 mm Hg systolic and 8 mm Hg diastolic. Maximum reduction occurred between 1 and 4 hours after dosing. A 20-mg dose of vardenafil resulted in a mean maximum increase in heart rate of 4 beats/min.

**Tadalafil**

Tadalafil was the third PDE5 inhibitor to come to market in the United States and was approved by the FDA at the end of 2003. Its chemical structure differs substantially from that of sildenafil and vardenafil, and it has a unique, long half-life of 17.5 hours. In healthy subjects, a single oral dose of 10 or 20 mg of tadalafil did not drop systolic blood pressure significantly compared with placebo. The decrease in systolic blood pressure with 20 mg tadalafil versus placebo was 0.2 mm Hg (95% confidence interval [CI], −7.1 to 6.6) in the standing position. The mean decrease in diastolic blood pressure compared with placebo was 4.6 mm Hg (95% CI, −7.9 to −1.2) in the standing position. Diastolic blood pressure was generally lower for 12 hours after administration of the drug, but the decrease in pressure remained small. Changes were even less marked in the supine position. Standing and supine heart rates were not significantly different from those with placebo.

In patients with coronary artery disease, who had higher systolic blood pressures at baseline than did healthy volunteers, 10 mg tadalafil reduced standing systolic blood pressure from 134 to 127 mm Hg (−7 mm Hg) and diastolic blood pressure from 78 to 74 mm Hg (−4 mm Hg) at time to maximum plasma concentration ($T_{max}$; 2 hours) after dosing.

Hence, all 3 of the PDE5 inhibitors are mild vasodilators and may cause small drops in arterial pressure. However, the degree of drop in blood pressure is usually small. Although this is rarely a concern in healthy individuals, in cardiovascular patients with low blood pressure or hypotension at baseline, this could be a concern, as described next. This vasodilating property would also be a concern for patients with left ventricular outflow obstruction or aortic stenosis. This property also becomes an issue regarding the concomitant use of nitrates and α-blockers, as described next.

**Nitrates Interaction**

PDE5 inhibitors work to improve ED by preventing the breakdown of cyclic GMP, the substance that promotes relaxation of smooth muscle cells in the arteries, arterioles, and sinuses of the corpus cavernosal of the penis. Nitric oxide (NO) donors, such as nitroglycerin (short or long acting), isosorbide dinitrate, isosorbide mononitrate, and others stimulate guanylate cyclase, which increases the production of cyclic GMP. When NO donors are given at the same time as PDE5 inhibitors, there is both an increase in the production of cyclic GMP (due to the NO donor) and an inhibition of its breakdown (due to the PDE5 inhibitor) that can lead to a build-up of cyclic GMP with pronounced vasodilation and, in some patients, frank hypotension. Organic nitrates are contraindicated with all 3 PDE5 inhibitors on the market. Details of interaction studies are presented in the online supplement to this article.

**Duration of PDE5 Inhibitor–Nitrate Interaction**

If a patient with coronary artery disease takes a PDE5 inhibitor and then develops angina pectoris, when is it safe to administer nitroglycerin?

**Sildenafil**

A consensus statement from the American College of Cardiology/American Heart Association suggested that for sildenafil, 6 half-lives, or 24 hours (4 hours × 6), pass between sildenafil intake and the administration of a nitrate. This time frame was chosen to allow full washout of drug from the tissues. In a previous analysis, at 24 hours after sildenafil, there was no interaction with sublingual nitroglycerin. In a recent preliminary study of healthy individuals, the sildenafil-nitroglycerin interaction appeared to be gone as early as 4 hours.

**Vardenafil**

Although a detailed time-course study of the interaction between vardenafil and nitrates is not available, 1 unpub-
Aspects of 3 PDE5 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>50 mg taken ∼1 hour before sexual activity. May be taken 4 hours to 0.5 hour before sexual activity. Dose may be increased to 100 mg or decreased to 25 mg</td>
<td>10 mg taken ∼60 minutes before sexual activity. May be increased to 20 mg or decreased to 5 mg</td>
<td>10 mg taken before anticipated sexual activity. May be increased to 20 mg or decreased to 5 mg</td>
</tr>
<tr>
<td>Effect on other PDEs</td>
<td>4000 times more selective for PDE5 than PDE3; &gt;80-fold more selective than for PDE1; &gt;700-fold more selective for PDE5 than for PDE2-4 and 7-11. Only ∼10-fold as potent for PDE5 compared with PDE6</td>
<td>&gt;1000-fold more selective for PDE5 than PDE2-4 and 7-10; &gt;300-fold relative to PDE11; &gt;130-fold relative to PDE1; &gt;15-fold relative to PDE6</td>
<td>&gt;10 000-fold more potent for PDE5 than for PDE1-4 and 7; &gt;9000-fold more potent for PDE5 than PDE8-10; &gt;700-fold more potent for PDE5 than PDE6; 14-fold more potent for PDE5 than PDE11 A1</td>
</tr>
<tr>
<td>Tmax</td>
<td>Median, 60 minutes; high-fat meal reduces Cmax by 29% and delays Tmax by 4 hours</td>
<td>Median, 60 minutes; high-fat meal reduces Cmax by 18% to 50%</td>
<td>Median, 2 hours; not influenced by food</td>
</tr>
<tr>
<td>Mean terminal half-life</td>
<td>4 hours</td>
<td>4–5 hours.</td>
<td>17.5 hours</td>
</tr>
<tr>
<td>Dosage adjustment</td>
<td>Lower starting doses in elderly, hepatic impairment, severe renal impairment, potent cytochrome P450 3A4 inhibitors; consider lower doses (25 mg) with concomitant α-blockers</td>
<td>Lower doses in patients with moderate hepatic impairment, strong CYP3A4 inhibitors, erythromycin, elderly</td>
<td>Lower doses in patients with severe renal insufficiency, mild to moderate hepatic impairment, potent CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Contraindication</td>
<td>Organic nitrates (regular or intermittent use)</td>
<td>Nitrate and NO donors (regular or intermittent use), α-blockers</td>
<td>Organic nitrates (regular or intermittent use), α-blockers other than 0.4 mg tamsulosin</td>
</tr>
<tr>
<td>Adverse events reported by &gt;2% of patients</td>
<td>Headache, flushing, dyspepsia, nasal congestion, urinary tract infection, abnormal vision, diarrhea, dizziness</td>
<td>Headache, flushing, rhinitis, dyspepsia, accidental injury, sinusitis, flu syndrome, dizziness, increased creatine kinase, nausea</td>
<td>Headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, pain in limb</td>
</tr>
<tr>
<td>Other cardiac precautions and warnings</td>
<td>Doses of 50 or 100 mg sildenafil should not be taken within 4 hours of α-blocker administration</td>
<td>Patients with congenital QT prolongation and those taking class IA or Class III antiarrhythmic agents should avoid vardenafil</td>
<td>Warning regarding left ventricular outflow obstruction, in that patients may be sensitive to vasodilators in this situation</td>
</tr>
</tbody>
</table>

Caution in patients with left ventricular outflow obstruction or severely impaired autonomic control of blood pressure

Caution in patients with left ventricular outflow obstruction and those patients for whom physician would be concerned about giving any vasodilator

Avoid excess alcohol

Precaution in patients in whom vasodilators may be a concern, including patients with severely impaired autonomic control of blood pressure

Tmax indicates time to maximum plasma concentration; Cmax, maximum plasma concentration.

lished study did suggest a lack of interaction at 24 hours, consistent with a 4-hour half-life.

**Tadalafil**

A nitrate-tadalafil interaction study was recently reported. In a population of patients who were healthy or had controlled hypertension or diabetes, 20 mg tadalafil or placebo was given daily for 7 days. On the seventh day, sublingual nitroglycerin was administered at 2, 4, 8, 24, 48, 72, or 96 hours. There was evidence that tadalafil augmented the nitrate-induced decrease in blood pressure within the first 24 hours of its administration. At and beyond 48 hours, the interaction was not detectable, as assessed by mean maximal falls in blood pressure or outlier criteria. Thus, the manufacturer suggests that if a patient has taken tadalafil and develops chest pain and it is deemed medically necessary that nitrates be given, at least 48 hours should elapse after the last dose of tadalafil before nitrates are given. Even then, nitrates should be given only under close medical supervision and appropriate hemodynamic monitoring.

What should a patient do if he/she develops chest pain after having taken a PDE5 inhibitor? The patient should call for emergency assistance for hospital transport and apprise the emergency medical technicians and emergency physicians regarding use of the PDE5 inhibitor. Organic nitrates are initially contraindicated. The American College of Cardiology/American Heart Association Consensus document reminds physicians that other antianginal agents can be considered in such situations. β-Blockers, calcium channel blockers, morphine, and other anti-ischemic agents, such as oxygen, aspirin, and statins, may be safely given in the setting of a PDE5 inhibitor. Furthermore, should a patient develop a myocardial infarction while taking a PDE5 inhibitor, usual care—thrombolytics, antiplatelet agents, and percutaneous coronary intervention—is indicated. Only organic nitrates should be avoided. If a patient has taken a PDE5 inhibitor, inadvertently receives a nitrate, and becomes hypotensive, the American College of Cardiology/American Heart Associ-
Interaction With Common Antihypertensive Agents Other Than α-Blockers

Several studies investigated the interactions of sildenafil, vardenafil, and tadalafil on blood pressure in patients already taking usual antihypertensive medicines, such as calcium channel blockers, diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. In general, these studies suggested that when a PDE5 inhibitor was administered to patients already taking antihypertensive medications, small additive drops in blood pressure occurred that were roughly equivalent to or less than the drops in pressure that occurred when the PDE5 inhibitors were taken without concomitant antihypertensive agents.

Sildenafil

Webb et al. studied men who were already receiving amloprimine for the treatment of hypertension for at least 1 month. These authors showed that 100 mg sildenafil given 2 hours after a morning dose of 5 or 10 mg amloprimine resulted in a mean maximal change from baseline blood pressure of −8 mm Hg supine systolic and −7 mm Hg supine diastolic compared with men who received placebo plus amloprimine. The differences in standing systolic and diastolic blood pressures were −10 and −8 mm Hg, respectively.

Even smaller additional reductions in blood pressure were reported when the PDE5 inhibitor sildenafil was administered to patients already taking β-blockers, diuretics, or angiotensin-converting enzyme inhibitors. There was no increase in adverse events in patients treated with sildenafil who received antihypertensive medicines, even multiple antihypertensive medicines. No increase in syncope or postural hypotension was reported when sildenafil was given to patients already taking these common antihypertensive drugs. Furthermore, the most common side effects of sildenafil (headache, flushing, dyspepsia, visual disturbance, rhinitis) were not worsened in patients on concomitant antihypertensive medicines, even if the patients were taking 2 or more antihypertensive medicines. The efficacy of sildenafil to improve ED remained high (≈72%) in hypertensive patients taking antihypertensive agents.

Vardenafil

Vardenafil was associated with a small or no fall in blood pressure when administered to patients taking their usual antihypertensive medicines. Vardenafil 20 mg produced an additional fall in mean systolic/diastolic blood pressure of 6/5 mm Hg versus placebo when it was concomitantly administered with slow-release nifedipine (30 or 60 mg) in patients whose blood pressure had been controlled with this calcium channel blocker.

Tadalafil

Kloner et al. reported a series of studies in which 10 or 20 mg tadalafil was administered to patients with hypertension taking antihypertensive medications or to healthy individuals who received an antihypertensive medicine. In healthy individuals receiving 5 mg amlodipine daily for at least 14 days, 20 mg tadalafil had no significant additional effect with a mean change in systolic/diastolic blood pressure of −1/1 mm Hg compared with placebo. This ambulatory blood pressure monitoring study showed no interaction between 5 mg amlodipine and 20 mg tadalafil. Tadalafil 10 mg given to hypertensive patients who had been receiving the thiazide diuretic bendroflumazide was associated with an additional reduction in supine systolic/diastolic blood pressure of 6/4 mm Hg and in standing systolic/diastolic pressure of the same degree. Tadalafil 10 mg administered to patients taking metoprolol (25 to 200 mg daily) resulted in an additional mean reduction in supine systolic/diastolic blood pressure of 5/3 mm Hg and in standing systolic/diastolic blood pressure of 7/4 mm Hg. Tadalafil 10 mg administered to patients taking enalapril (10 to 20 mg per day) was associated with a mean reduction in supine systolic/diastolic blood pressure of 4/1 mm Hg and in standing systolic/diastolic blood pressure of 3/1 mm Hg. In an ambulatory BP monitoring study, 20 mg tadalafil given to patients already receiving various angiotensin receptor blockers was associated with an additional mean reduction in ambulatory systolic/diastolic blood pressure of 8/4 mm Hg. The incidence of adverse events in tadalafil-treated patients in general was similar to that in patients receiving or not receiving concomitant antihypertensive medicines, similar to observations with the other PDE5 inhibitors.

In general, sildenafil, vardenafil, and tadalafil appear to be well tolerated and safe in patients receiving most concomitant antihypertensive agents. There appears to be no or only small additive drops in blood pressure that occur when the PDE5 inhibitor is administered in addition to the antihypertensive medicines. The 1 exception to this appears to be α-blockers, as described next.

Interaction of PDE5 Inhibitors With α-Blockers

Sildenafil

There were recent changes to the labeling of sildenafil regarding concomitant use in patients receiving α-blockers. One study assessed concomitant administration of the nonselective α-blocker doxazosin with sildenafil in patients with benign prostatic hypertrophy who had been taking α-blockers for at least 8 weeks. Doxazosin is given for both hypertension and benign prostatic hypertrophy. Two of 20 patients receiving 4 mg doxazosin and 50 mg sildenafil developed symptomatic hypotension. Interestingly, no (0/20) patients receiving 4 mg doxazosin and 100 mg sildenafil had symptomatic hypotension. Also, the 25-mg dose of sildenafil, when coadministered with 4 mg doxazosin, was not associated with hypotension. The label precaution (not contraindication) now advises that 50 or 100 mg sildenafil should not be taken within a 4-hour window of α-blocker administration. A 25-mg dose of sildenafil may be taken at any time in relation to an α-blocker.

Vardenafil

Vardenafil is contraindicated in patients taking α-blockers. When 10 or 20 mg vardenafil was administered to healthy individuals receiving 5 mg amlodipine daily for at least 14 days, 20 mg tadalafil had no significant additional effect with a mean change in systolic/diastolic blood pressure of −1/1 mm Hg compared with placebo. This ambulatory blood pressure monitoring study showed no interaction between 5 mg amlodipine and 20 mg tadalafil. Tadalafil 10 mg given to hypertensive patients who had been receiving the thiazide diuretic bendroflumazide was associated with an additional reduction in supine systolic/diastolic blood pressure of 6/4 mm Hg and in standing systolic/diastolic pressure of the same degree. Tadalafil 10 mg administered to patients taking metoprolol (25 to 200 mg daily) resulted in an additional mean reduction in supine systolic/diastolic blood pressure of 5/3 mm Hg and in standing systolic/diastolic blood pressure of 7/4 mm Hg. Tadalafil 10 mg administered to patients taking enalapril (10 to 20 mg per day) was associated with a mean reduction in supine systolic/diastolic blood pressure of 4/1 mm Hg and in standing systolic/diastolic blood pressure of 3/1 mm Hg. In an ambulatory BP monitoring study, 20 mg tadalafil given to patients already receiving various angiotensin receptor blockers was associated with an additional mean reduction in ambulatory systolic/diastolic blood pressure of 8/4 mm Hg. The incidence of adverse events in tadalafil-treated patients in general was similar to that in patients receiving or not receiving concomitant antihypertensive medicines, similar to observations with the other PDE5 inhibitors. In general, sildenafil, vardenafil, and tadalafil appear to be well tolerated and safe in patients receiving most concomitant antihypertensive agents. There appears to be no or only small additive drops in blood pressure that occur when the PDE5 inhibitor is administered in addition to the antihypertensive medicines. The 1 exception to this appears to be α-blockers, as described next.

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Vardenafil

Vardenafil is contraindicated in patients taking α-blockers. When 10 or 20 mg vardenafil was administered to healthy
volunteers either simultaneously or 6 hours after a 10-mg dose of the α₁-blocker terazosin (used for both hypertension and benign prostatic hypertrophy), significant hypotension was observed. When 10 mg vardenafil was given at the same time as 10 mg terazosin, 6 of 8 volunteers developed a standing systolic blood pressure <85 mm Hg. In a study with 20 mg vardenafil, simultaneous administration of 10 mg terazosin resulted in 2 of 9 subjects dropping their standing systolic blood pressure to <85 mm Hg. When dosing was separated by 6 hours, 7 of 28 subjects dropped their standing systolic blood pressure to below 85 mm Hg. Results with tamsulosin (a selective α₁-blocker, which is more selective for prostatic tissue and mainly used to treat benign prostatic hypertrophy) also showed an interaction with vardenafil but to a lesser extent. Two of 16 subjects who received 10 mg vardenafil plus 0.4 mg tamsulosin developed a standing systolic blood pressure below 85 mm Hg. Thus, when vardenafil was released in the United States, it carried an absolute contraindication in patients taking α-blockers. However, a recent analysis suggests that this interaction is much less marked when vardenafil is administered to patients with benign prostatic hypertrophy who have been on long-term α-blocker therapy.

**Tadalafil**

Tadalafil is contraindicated in patients taking α-blockers except for 0.4 mg tamsulosin (α₁-blocker). In 1 study, 20 mg tadalafil augmented the hypotensive effect of 8 mg doxazosin with a mean maximal decrease in standing systolic blood pressure that was greater than placebo (mean difference of 9.8 mm Hg). The number of subjects with a standing systolic blood pressure of <85 mm Hg was greater after doxazosin plus tadalafil (28%) versus doxazosin plus placebo (6%). In a separate analysis, 0.4 mg tamsulosin was given with 10 or 20 mg tadalafil. In subjects taking this α-blocker, tadalafil produced mean maximal reductions in standing systolic blood pressure that were similar to those seen with placebo (mean difference of 1.7 mm Hg with 10 mg tadalafil and of 2.3 mm Hg with 20 mg tadalafil). Furthermore, none of the subjects receiving tamsulosin plus tadalafil dropped their standing systolic blood pressure to <85 mm Hg.

**QT Interval**

Vardenafil was associated with small increases in QTC in 1 study and carries the label warning that it should be avoided in patients with congenital QT prolongation and patients taking class IA (eg, quinidine, procainamide) or class III (eg, amiodarone, sotalol) antiarrhythmic medications. Tadalafil and sildenafil do not carry this statement. To date, there have been no known cases of torsade de pointes in patients receiving PDE5 inhibitors. In our experimental animal studies of acute coronary artery occlusion, administration of sildenafil was not associated with an increase in ventricular arrhythmia. Additional details on QT interval may be found in the online supplement to this article.

**Do the PDE5 Inhibitors Exacerbate Ischemia?**

Studies with sildenafil, vardenafil, and tadalafil showed that when these agents were given to patients with coronary artery disease during exercise stress testing, there was no exacerbation of ischemia compared with placebo. A very important aspect of these studies was that the level of exercise was similar to or exceeded that achieved during sexual intercourse. In a few of these studies, sildenafil and vardenafil actually appeared to have a beneficial effect on exercise-induced ischemia. A study performed in the cardiac catheterization laboratory by Hermann et al observed that when oral sildenafil was administered to patients with severe coronary artery disease, it had no adverse effects on coronary artery diameter or coronary artery flow velocity and actually improved coronary artery vasodilator reserve induced by adenosine. Halcox et al demonstrated a slight vasodilating effect of sildenafil on epicardial coronary arteries. The effects of vardenafil and tadalafil on coronary artery hemodynamics are unknown at this time.

**Do PDE5 Inhibitors Cause Myocardial Infarction or Death?**

After the initial release of sildenafil, there were anecdotal reports of myocardial infarction and death. However, sexual activity itself may be associated with a small but definite increase in risk of myocardial infarction. Patients with ED are more likely to have risk factors for coronary artery disease (such as age ≥ 45, smoking, lipid abnormalities, diabetes, hypertension, and lack of physical activity) or have frank heart disease. Analysis of double-blind, randomized, controlled studies and open-label studies did not show an increase in the rates of myocardial infarction or death in patients receiving sildenafil versus placebo or when compared with age-matched expected events. Similar results have been reported with tadalafil and vardenafil. Postmarketing surveys in the United Kingdom and in the United States, including 1 by the FDA, did not show a rate of myocardial infarction, ischemic heart disease, or mortality in men who took sildenafil to be greater than expected than in an age-matched population. In fact, death rates tended to be less in the population taking sildenafil (perhaps suggesting that healthier men were receiving the drug). Postmarketing data regarding cardiovascular event rates in men taking vardenafil or tadalafil have yet to be reported and will be important.

**Other Cardiovascular Effects**

PDE5 inhibitors have potential therapeutic use for a number of cardiovascular disorders, including pulmonary hypertension, congestive heart failure, hypertension, and endothelial dysfunction. Details are described in the online supplement.

**Summary**

There are currently 3 PDE5 inhibitors available for the treatment of ED. All are effective in patients with organically based ED, including ED due to vascular disease. Sildenafil and vardenafil have relatively short half-lives of ≈ 4 hours, whereas the half-life of tadalafil is 17.5 hours. These agents are all mild vasodilators and have minimal effects on blood pressure. Sildenafil, vardenafil, and tadalafil are all contraindicated with nitrate use. Should a patient develop chest pain
while taking sildenafil or vardenafil, nitrate may be admin-
istered under close supervision at 24 hours (and possibly earlier);
should a patient take tadalafil and develop chest pain, nitrate
may not be given until at least 48 hours after the tadalafil dose
and then again, only under close monitoring. α-Blockers are a
contraindication to the use of vardenafil. Except for 0.4 mg
tamsulosin, α-blockers are a contraindication to the use of
tadalafil. Sildenafil >25 mg should not be given within 4
hours of an α-blocker. Doses of sildenafil of 25 mg may be
administered at any time in relation to an α-blocker. Varden-
afil should not be administered to patients taking class IA
or III antiarrhythmic drugs or to patients with congenital QT
prolongation. The PDE5 inhibitors do not adversely affect
total exercise time or time to ischemia during exercise stress
testing. The PDE5 inhibitors are safe to administer to patients
taking antihypertensive medicines (except for the α-blockers,
as described earlier). The PDE5 inhibitors are effective for
the treatment of ED in patients with cardiac disease, including
patients with chronic coronary artery disease57 and hyperten-
sion. Data from controlled clinical trials do not suggest an
increase in myocardial infarction or death rates in patients
taking PDE5 inhibitors. These agents appear safe and effective
in most patient populations but have not been studied
extensively in patients with baseline severe or unstable
cardiac conditions.

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