Erectile dysfunction (ED) is a powerful predictor of coronary artery disease (CAD), especially in men <60 years of age. Conversely, a high percentage of men with chronic stable CAD have ED. ED usually precedes the onset of angina by 2 to 3 years and adverse cardiovascular events by 3 to 5 years, thus allowing time for risk factor modification to delay or prevent major adverse cardiovascular events. Despite the abundance of evidence linking these vascular diseases, application of this knowledge to clinical practice has been limited. Here, 2 theoretical cases are described with the goal of illustrating clinical practice guidelines to improve the management of patients with ED and CAD.

Case 1
A 44-year-old previously healthy man presented to primary care complaining that “I haven’t had sex in 3 months because I can’t get an erection.” The patient did not report any cardiovascular symptoms with exercise but admitted to a sedentary lifestyle. The patient’s father suffered his first myocardial infarction at 53 years of age. The patient’s blood pressure was 128/84 mm Hg. The patient denied any other cardiovascular symptoms or risk factors.

The patient is diagnosed with ED, defined as the persistent inability to achieve and maintain an erection adequate for satisfactory sexual intercourse. ED is a cardiac risk factor and independently predicts mortality, primarily as a result of increased cardiovascular mortality (hazard ratio, 1.43). ED usually precedes angina by 2 to 3 years and adverse cardiovascular events by 3 to 5 years. A cardiovascular assessment is initiated to define the patient’s risk of future cardiovascular events and to guide therapy.

Cardiac risk factors are investigated, and risk factor modification is initiated. This patient’s body mass index is 24 kg/m², fasting glucose is 95 mg/dL, and fasting low-density lipoprotein cholesterol is 150 mg/dL. A low-fat, low-cholesterol diet is recommended. Reduced caloric intake should be recommended to obese men, and smoking cessation should be discussed with cigarette smokers. Diabetes mellitus and hypertension should be managed according to published guidelines. Therapy is initiated with a statin with a goal to reach a low-density lipoprotein of <100 mg/dL (National Cholesterol Education Program guidelines for a patient with ≥2 risk factors: goal low-density lipoprotein <130 mg/dL, therapeutic option <100 mg/dL). In the future, ED may be considered a coronary heart disease equivalent with lower corresponding low-density lipoprotein goals (goal <100 mg/dL, therapeutic option <70 mg/dL).

Testosterone and selectively free testosterone levels are measured. Testosterone deficiency syndrome causes ED and is associated with all-cause mortality, cardiovascular mortality, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, and other cardiovascular risk factors. Routine testing should be considered in all men with ED, especially men with obesity, diabetes mellitus, or heart failure or men who do not respond to therapy with a phosphodiesterase type 5 inhibitor (PDE5-I). There is controversy relative to the effect of testosterone replacement therapy on cardiovascular risk. This patient’s testosterone level is normal.

The Second Princeton Consensus Conference defined low-, intermediate-,
and high-risk cardiovascular categories for patients with ED (Table 1 and the Figure). Patients at low risk can safely engage in sexual intercourse and an exercise program, whereas high-risk patients should avoid such activities until their cardiac condition has been stabilized. Patients at intermediate risk should undergo cardiovascular testing to further define their cardiac risk before resuming sexual activity.

In addition to gender, the patient has major cardiovascular risk factors: dyslipidemia, a sedentary lifestyle, and a family history of premature CAD (other risk factors include age, hypertension, diabetes mellitus, and cigarette smoking). Patients with ED who have no cardiac symptoms but cardiovascular risk factors (excluding gender) are classified as intermediate risk. The patient is instructed to refrain from exercise and sexual activity, and a nuclear imaging stress test is scheduled. Nuclear imaging demonstrates moderate-sized areas of reversible ischemia in the anterior and lateral myocardium. Accordingly, coronary angiography demonstrates 85% stenosis in the middle left anterior descending coronary artery and 80% stenosis in the proximal left circumflex coronary artery. The patient undergoes staged percutaneous coronary intervention with drug-eluting stent implantation in each lesion. After successful percutaneous coronary intervention, the patient is deemed low risk and may resume sexual activity. An exercise program is encouraged, beginning with mild intensity and then gradually increasing intensity.

In patients with CAD, PDE5-Is are efficacious for ED and do not increase the risk of myocardial infarction or cardiovascular death (rate of myocardial infarction or cardiovascular death per 100 person-years in a meta-analysis of placebo-controlled trials: 0.91 for sildenafil-treated versus 0.84 for placebo-treated patients, \( P = 0.88; 0.56 \) for open-label sildenafil). PDE5-Is are contraindicated for patients taking nitrates. Caution and decreased doses may be indicated when PDE5-Is are coadministered with \( \beta \)-blockers or with drugs that affect the cytochrome P450 3A4 metabolic pathway such as erythromycin, ketoconazole, or HIV-protease inhibitors. The patient is not currently taking any of the above medications, so he is prescribed a standard-dose PDE5-I (Table 2).

Follow-up is scheduled at regular intervals to assess cardiovascular status and response to ED treatment. After 4 weeks, the patient returns to clinic and reports that, after PDE5-I inges-
tion, he is able to maintain an erection and complete satisfactory sexual activity. On questioning, he reports no symptoms with exercise or sexual activity and no cardiac symptoms in general. He is scheduled to return to clinic in 3 months.

In conclusion, when a patient presents with ED, a cardiovascular risk factor workup should be instituted. This patient was found to have dyslipidemia and ultimately CAD that were subsequently successfully treated. They may not have been discovered had the patient not presented with ED or if the diagnosis of ED did not prompt the physician to institute a cardiovascular workup.

Case 2

A 63-year-old man with diabetes mellitus and hypertension is known to have CAD; he underwent percutaneous coronary intervention 1 year ago. He had been followed up regularly by a cardiologist and a primary care physician, but he recently relocated from out of state and presents to establish care. As part of the initial evaluation, the new physician asks about sexual health and the patient reports symptoms of ED for the past 4 years. His medications include insulin, hydrochlorothiazide, atenolol, and nitroglycerin.

Patients with ED have many of the same risk factors as patients with cardiovascular disease, including hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, and the metabolic syndrome. Moreover, up to 75% of patients with chronic stable CAD have ED. Too often, doctors do not ask about sexual health, especially in patients with cardiac risk factors or CAD who are at increased risk for ED. In men with type 2 diabetes mellitus, ED is a marker for silent CAD. Physicians should inquire about ED in men with diabetes mellitus at least annually. Although evidence is limited and conflicting, a number of medications have been associated with an increased risk for ED, including β-blockers, thiazide diuretics, calcium channel blockers, statins, and angiotensin-converting enzyme inhibitors. If ED develops or worsens within 4 weeks of initiation of a new medication, it is reasonable to stop the suspected medication and switch to a new drug class or to a new drug within the same class. If ED symptoms develop >4 weeks from initiation of drug therapy, it is unlikely that the drug caused ED. Because hypertension and many antihypertensive medications increase the risk for ED symptoms, patients should be asked about ED symptoms before initiating antihypertensive therapy. Preliminary evidence suggests that nebivolol and angiotensin receptor blockers decrease symptoms of ED. This patient reports that his ED symptoms began before he began his current medications, so hydrochlorothiazide and atenolol are not thought to have caused his ED. However, these medications are discontinued and replaced with nebivolol and an angiotensin receptor blocker, which may improve his erectile function.

In men with type 2 diabetes mellitus and angiographically documented silent CAD, the presence of ED predicted major adverse cardiac events (hazard ratio, 2.1). In men with CAD and ED, statin use and PDE5-I use significantly reduced the incidence of major adverse cardiovascular events. In men taking multiple antihypertensive medications, PDE5-Is are efficacious and do not increase the risk of adverse cardiovascular events. PDE5-Is are contraindicated with nitrates because of the risk of severe hypotension that can result from a marked increase in cGMP (Nitrates increase the production of cGMP, and PDE5-Is prevent the breakdown of cGMP). Although this patient listed nitroglycerin as a current medication, on questioning he says that he has not used nitroglycerin since his percutane-

### Table 2. Dosing, Pharmacokinetics, and Precautions of PDE5-Is

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting or Usual Dose, mg</th>
<th>Low Dose, mg*</th>
<th>Maximum Dose, mg</th>
<th>Half-Life, h</th>
<th>Time to Peak Plasma Concentration, min</th>
<th>Reduced Absorption With High-Fat Meal</th>
<th>Contraindicated With Nitrates</th>
<th>α-Blocker Prolonged QTc</th>
<th>Concomitant Use of Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>As needed‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil (Viagra)</td>
<td>50</td>
<td>25</td>
<td>100</td>
<td>4</td>
<td>60</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vardenafil (Levitra)</td>
<td>10</td>
<td>2.5, 5</td>
<td>20</td>
<td>4</td>
<td>60</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tadalafil (Cialis)§</td>
<td>10</td>
<td>2.5, 5</td>
<td>20</td>
<td>17.5</td>
<td>120</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Once daily</td>
<td></td>
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<tr>
<td>Tadalafil (Cialis)§</td>
<td>2.5</td>
<td>5</td>
<td>17.5</td>
<td>120</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Initiate therapy at low dose for all PDE5-Is if hepatic impairment or if coadministered with a potent cytochrome P450 3A4 inhibitor or stable α-blocker therapy (with caution); for sildenafil, if >65 years of age or if creatinine clearance <30 mL/min; for vardenafil, if >65 years of age; for tadalafil, if creatinine clearance ≥50 mL/min. If coadministered with ritonavir or >1 of the above criteria, consider lower doses: maximum for sildenafil, 25 mg in 48 hours; tadalafil, 10 mg in 72 hours; vardenafin, 2.5 mg in 72 hours.

†A maximum of once daily.

§Tadalafil is often increased to 5 mg for once-daily dosing; restrictions on daily dosing apply for the conditions described above.

A portion of this table appeared in Schwartz and Kloner.
ous coronary intervention 1 year ago. The patient is instructed to stop his nitroglycerin and discard any remaining pills. He is told that use of nitroglycerin, even occasional use of short-acting nitrates, is an absolute contraindication to PDE5-Is. He is informed of the potential for life-threatening hypotension if he coadministers a PDE5-I and a nitrate, including nitroglycerin from a friend or family member. In the event of an emergency, he is instructed to inform all emergency and healthcare personnel of his most recent PDE5-I intake so that nitrates can be avoided. Therapy is initiated with a statin and a PDE5-I.

In addition to improving erectile function, therapy with a PDE5-I for men with ED has emotional benefits and improves self-esteem. At the patient’s 4-week follow-up visit, he is delighted and reports that he and his wife enjoyed sexual intercourse for the first time in years and profoundly thanks his physician.

In conclusion, physicians should ask about ED symptoms in men with CAD and risk factors for CAD. PDE5-Is are efficacious and safe in men taking multiple antihypertensive medications but are used cautiously with α-blockers and are contraindicated with nitrates.

**Conclusion**

ED and CAD often coexist. Men with CAD or cardiac risk factors should be asked about ED. ED increases the risk for major adverse cardiovascular events and usually precedes angina by 2 to 3 years and adverse cardiovascular events by 3 to 5 years, allowing time for risk factor modification. Men with ED should undergo a thorough cardiovascular evaluation with investigation of cardiac risk factors. Risk factor modification should include diet, exercise, smoking cessation, and management of hypertension, diabetes mellitus, and dyslipidemia. Before resuming exercise or sexual activity, men with ED should be categorized as low, intermediate, or high risk according to the Second Princeton Consensus Conference guidelines. Low-risk patients should engage in an exercise program and may resume sexual activity. High-risk patients require disease modification, and intermediate-risk patients require further evaluation before resuming sexual activity. Evaluation of intermediate-risk patients generally involves a cardiac stress test to assess for asymptomatic CAD. In patients with stable CAD or on multiple antihypertensive medications, PDE5-Is are efficacious for ED and do not increase the risk of adverse cardiovascular events. With an appropriate cardiovascular evaluation and therapy, men presenting with ED can enjoy sexual activity and delay or prevent adverse cardiovascular events.

**Disclosures**

Dr Kloner has been a consultant and speaker for Pfizer and Lilly. The other authors report no conflicts.

**References**


**Key Words:** coronary artery disease ■ hypotension ■ men ■ nitroglycerin ■ sex
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