



# Understanding the Link Between Erectile Dysfunction and Cardiovascular Disease

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It's been known for some time that erectile dysfunction (ED) and cardiovascular disease (CVD) share both etiologic and pathophysiologic characteristics.<sup>1</sup> Recent findings, however, highlight the importance of ED as a sentinel symptom of occult CVD.<sup>2-6</sup> In fact, it's becoming increasingly apparent that clinicians who recognize ED as a CVD harbinger and take appropriate action have the potential to protect patients from the development or progression of CVD,<sup>2</sup> which accounts for nearly 40% of all deaths in the United States.<sup>7</sup>

This article describes the crucial link between these two diseases, the science behind the association, and how knowledge of this relationship can be exploited to further screening and early intervention for CVD. The discussion then turns to phosphodiesterase type-5 (PDE-5) inhibitors, specifically, the role they may play in treating ED and their cardiac safety. Also considered are the factors clinicians must take into account when assessing risks for patients resuming sexual activity after a cardiac event and ways to optimize patient adherence to prescribed regimens.

## ED as a Predictor of CVD

A prospective analysis by Thompson et al<sup>2</sup> of the nearly 9,500 men randomly assigned to the placebo arm of the Prostate Cancer Prevention Trial revealed that men with ED are at significantly ( $P < .001$ ) greater risk of having a cardiovascular event—such as angina, myocardial infarction (MI), or stroke—than those without ED. Furthermore, the findings indicate that the relationship between incident ED (the first report of ED of any grade) and CVD is comparable to that

associated with current smoking, family history of MI, or hyperlipidemia.<sup>2</sup>

The Thompson analysis supports previous findings that ED may be an early sign of endothelial dysfunction, which precedes the development of overt CVD<sup>3-6</sup> and manifests itself as blunted vasodilation. It may result either from impaired production or release of the endothelial-derived vasorelaxant nitric oxide (NO) or from a cellular abnormality in the vascular endothelium.<sup>8</sup> To test for endothelial dysfunction, a blood pressure

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cuff may be used to stop the flow of blood through the brachial artery for several minutes. With release of the cuff, the normal response would be brachial dilation as the oxygen debt was repaid; endothelial dysfunction would blunt this reactive hyperemia.<sup>8</sup> Alternatively, endothelial dysfunction can be tested by infusing a blood vessel with a vasodilating substance such as acetylcholine. The vessel with endothelial dysfunction would fail to dilate and may even become constricted. Nonendothelial-dependent vasodilators, such as a nitrate, may be used to test specifically for a nonendothelial irregularity, such as a smooth muscle cell abnormality.<sup>8</sup>

Subsequent to the Thompson analysis and lending further support to the idea of ED as a precursor to CVD, Montorsi et al<sup>9</sup> investigated 285 patients with coronary artery disease (CAD). One key finding in the latter is that nearly all patients who developed CAD symptoms experienced ED symptoms first—on average, three years beforehand.<sup>9</sup> Findings such

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as these have prompted investigators to suggest that a presentation of ED should trigger an assessment of cardiovascular risk factors and, if appropriate, vigorous intervention.<sup>2,9</sup>

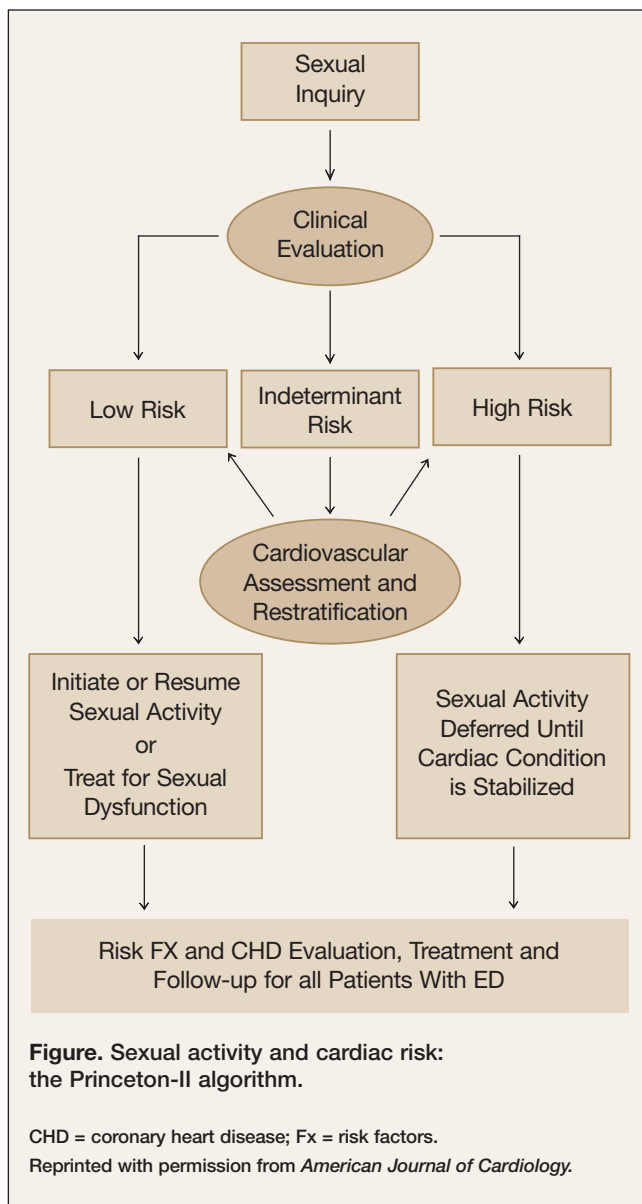
A follow-up report to the Second Princeton Consensus Conference on sexual dysfunction and cardiac risk specifically recommended screening men with ED of uncertain etiology for vascular disease and abnormal blood glucose, lipids, and blood pressure. In addition, it proposed that men with ED and no cardiac symptoms should be considered at risk for CVD until proven otherwise.<sup>10</sup>

### PDE-5 Inhibitors and Cardiac Morbidity

Three PDE-5 inhibitors—sildenafil, tadalafil, and vardenafil—have been approved by the US Food and

**Table 1. Major Risk Factors for Cardiovascular Disease<sup>17</sup>**

- Advanced age
- Male gender
- Hypertension
- Diabetes mellitus
- Cigarette smoking
- Dyslipidemia
- Sedentary lifestyle
- Family history of premature coronary artery disease



Drug Administration (FDA) as therapy for ED. The mechanism by which these drugs facilitate erectile function is covered in detail in another article in this supplement (see *First-Line Therapy for Erectile Dysfunction: The PDE-5 Inhibitors* on page 35). Since their introduction, however, questions have arisen regarding the safety of PDE-5 inhibitor use by patients with coronary heart disease and the potential for adverse interactions with common cardiovascular drugs.

Notably, the PDE-5 inhibitors were studied for their cardiovascular potential before they were investigated as a possible treatment for ED. Specifically, sildenafil was investigated as an antianginal drug.<sup>8</sup> Since PDE-5 is found throughout the vasculature, it was hoped that inhibiting this isoenzyme would potentiate a systemic vasodilatory response to NO.<sup>8,11,12</sup> Currently, investigational studies are underway examining the drugs' potential for treating heart failure, ischemic heart disease, and endothelial dysfunction.<sup>8,12</sup> Additionally, sildenafil has been shown to be beneficial for treating pulmonary hypertension and has recently been approved for that indication by the FDA.<sup>13</sup>

In double-blind, placebo-controlled and open-label studies, none of the three FDA-approved PDE-5 inhibitors has been associated with greater risk of MI or death than that which would be expected within the study populations.<sup>11,14-16</sup> When given to patients with CAD during exercise stress testing, none of the three exacerbated ischemia compared with placebo, and in some studies, sildenafil and vardenafil appeared to have reduced ischemia.<sup>17</sup>

An animal study suggested that sildenafil treatment reduces cardiac preload and afterload as well as measures of left ventricular contractility. It neither exacerbated nor reduced myocardial necrosis and microvascular dysfunction.<sup>18</sup>

In one study, vardenafil was associated with small increases in QTc. Its label, therefore, warns to avoid use in patients with congenital QT prolongation and in those taking antiarrhythmics medications of class IA (such as procainamide or quinidine) or class III (such

as amiodarone or sotalol). Prescribing information for sildenafil and tadalafil carry no such warning.<sup>17</sup>

Since PDE-5 inhibitors have mild vasodilatory effects, their use may be associated with small reductions in systolic and diastolic blood pressure. In most patients, this drop is clinically nonsignificant. In fact, PDE-5 inhibitors can be administered safely with antihypertensive medications, though concurrent administration may cause a slight additive drop in blood pressure.<sup>17</sup>

All three drugs interact to some degree with alpha-adrenergic blockers, though the clinical significance of the interaction leading to hypotension depends on the particular alpha blocker, when it is administered in relation to the PDE-5 inhibitor, the dose of both drugs, and the length of time the patient has been taking the alpha blocker (with interaction being less likely in patients who have undergone long-term alpha blocker therapy).<sup>11</sup>

Prescribing information for all three PDE-5 inhibitors recommends that patients whose conditions are stable with alpha blocker therapy can begin PDE-5 inhibitor therapy at the lowest recommended dose—and that patients taking an optimal dose of the PDE-5 inhibitor can initiate alpha blocker therapy at the lowest possible dose. Additionally, for any patient taking both a PDE-5 inhibitor and an alpha blocker, prescribing physicians are advised to consider volume status and any other antihypertensive medicines the patient may be taking as these factors will affect the safety of the combined therapy. Tamsulosin (0.4 mg daily) appeared to have least effect on blood pressure when given to men receiving tadalafil at stable doses.<sup>19-22</sup>

All PDE-5 inhibitors are contraindicated in patients taking organic nitrates.<sup>1,11</sup> Nitrates should not be administered within 24 hours of sildenafil or vardenafil use, or within 48 hours of tadalafil use.<sup>11</sup>

Clinicians may want to question whether patients with CAD are actually benefiting from nitrate therapy. Nitrates take away anginal pain but have never been shown to improve survival or outcome in patients with CAD. Very often, patients continue with nitrate therapy after angioplasty, stent placement, or coronary bypass surgery has eliminated their need for it simply because its necessity has never been questioned.<sup>1</sup>

### Assessing Cardiac Risks Associated With Sex and ED Treatment

The Princeton Consensus Conference on sexual activity and cardiac risk met in June 1999 to develop a system by which to categorize patients' cardiac risk and, accordingly, make recommendations related to sexual activity and treatment for sexual dysfunction.<sup>23</sup> The Second Princeton Consensus Conference was convened in June 2004 to review and update these guidelines based on subsequent epidemiologic and pharmacologic findings.<sup>24</sup>

**Table 2. Recommendations of the Second Princeton Consensus Conference Regarding Sexual Activity and ED Treatment<sup>23,24</sup>**

RISK	RECOMMENDATION
<b>Low</b>	No special cardiac testing or evaluation indicated before resumption of sexual activity or initiation of ED therapy
Asymptomatic with fewer than three major cardiovascular risk factors (excluding male gender)	
Controlled hypertension	
Mild, stable angina pectoris	
Postrevascularization with no residual ischemia	
History of myocardial infarction (six to eight weeks prior)	
Mild valvular disease	
Left ventricular dysfunction (NYHA class I)	
Other cardiovascular condition (such as pericarditis, mitral valve prolapse, or atrial fibrillation with controlled ventricular response)	
<b>Indeterminate</b>	
Asymptomatic with three or more major cardiovascular risk factors (excluding male gender)	
Moderate, stable angina pectoris	
History of myocardial infarction (two to six weeks prior)	
Left ventricular dysfunction (NYHA class II)	
Noncardiac sequelae of atherosclerotic disease	Deferment of sexual activity indicated until cardiovascular condition has stabilized or cardiovascular specialist has issued clearance to resume sexual activity
<b>High</b>	
Unstable or refractory angina pectoris	
Uncontrolled hypertension	
Congestive heart failure (NYHA class III or IV)	
Recent myocardial infarction (less than two weeks prior)	
Malignant arrhythmias (left ventricular dysfunction)	
Obstructive hypertrophic cardiomyopathy	

ED = Erectile dysfunction; NYHA = New York Heart Association

Seven of the eight major CVD risk factors identified by the first conference were reaffirmed by the second. The second conference, however, added family history of premature CAD, which is now recognized as a very strong risk factor for future cardiac events, and eliminated obesity, which is not as well validated as a CVD risk factor (Table 1).<sup>23,24</sup>

Both conference panels concluded that the vast majority of patients with CVD are at low risk for a cardiovascular event related to sexual activity or ED treatment.<sup>23,24</sup> These patients may initiate or resume sexual activity and receive treatment for sexual dysfunction. Patients at high risk should avoid sexual activity until their CVD is stabilized, and patients at indeterminate risk require further evaluation to enable classification as high or low risk (Table 2, Figure).<sup>23–25</sup>

## Optimizing Treatment Adherence

Patient education plays a vital role in optimizing patient adherence to ED treatment. Patients need to be instructed to take the PDE-5 inhibitors sufficiently in advance of planned sexual activity (about an hour for sildenafil or vardenafil or two hours for tadalafil) and that the drugs are not aphrodisiacs—sexual stimulation is necessary for their efficacy.<sup>19–21,26</sup> Patients taking sildenafil or vardenafil should be advised that taking the drugs with a high-fat meal may slow absorption; tadalafil absorption is not affected by food.<sup>20–22</sup> If the patient and his partner have not been intimate for awhile, he should allow at least eight attempts before deciding that the treatment has failed and then speak with his physician about the possibility of increasing the dose.<sup>26</sup>

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