Erectile Dysfunction and Cardiovascular Disease: Efficacy and Safety of Phosphodiesterase Type 5 Inhibitors in Men With Both Conditions

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Risk factors for cardiovascular disease and erectile dysfunction (ED) are similar, as might be expected given their shared etiologic and pathophysiologic origins. It is now generally accepted that most cases of ED result from a vascular disturbance of the endothelium. Recent epidemiological studies have documented a strong association between ED and comorbid conditions such as hypertension, diabetes mellitus, and dyslipidemia. Phosphodiesterase type 5 (PDE5) inhibitors are recommended as first-line therapy for erection problems of all etiologies and severities. The efficacy and safety of PDE5 inhibitors in the general ED population is well documented and has been extensively reviewed. To examine the association between ED and vascular disorders in the context of current knowledge regarding PDE5 inhibitors, an electronic search was performed of articles published from January 2002 through April 2008 using the PubMed, EMBASE, and MEDLINE databases. Although preference was given to randomized, blinded, controlled clinical trials, data from retrospective studies were also reviewed when appropriate. This analysis revealed that the clinical evidence linking ED to future cardiovascular events is compelling, presenting physicians with a unique interventional opportunity to address underlying cardiovascular health concerns in men presenting with ED. In most studies, PDE5 inhibitors were shown to effectively and safely improve erectile function regardless of cause, severity, or presence of comorbid conditions, including hypertension, diabetes mellitus, and dyslipidemia.


BPH = benign prostatic hyperplasia; CAD = coronary artery disease; CI = confidence interval; CVD = cardiovascular disease; ED = erectile dysfunction; EF = ejection fraction; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; IEF = International Index of Erectile Function; LDL-C = low-density lipoprotein cholesterol; LUTS = lower urinary tract symptom; NHANES = National Health and Nutrition Examination Survey; PDE5 = phosphodiesterase type 5; PE = premature ejaculation; PVD = peripheral vascular disease; SEP = sexual encounter profile; TC = total cholesterol

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The clinical diagnosis and treatment paradigm of erectile dysfunction (ED) has evolved considerably during the past 2 decades. Before the late 1990s, ED was typically treated by urologists, with surgery as the first recourse. Increased understanding of the male erectile process and the introduction in the late 1990s of safe, effective, oral pharmacological treatments have revolutionized the management of ED, providing an attractive alternative to patients who would have been previously considered candidates for surgery. In addition, direct-to-consumer advertising increased awareness of these treatment options. As a result of these developments, diagnosis and management of ED shifted to the primary care setting, and it was soon realized that ED often occurs in the context of common diseases managed by primary care physicians, such as diabetes mellitus and hypertension. Although preclinical studies had suggested such a correlation at the level of the endothelium, only recently have clinical studies provided robust data that ED is a sentinel symptom in patients with occult vascular diseases, in particular cardiovascular disease (CVD). Comorbidities commonly observed in men with ED, including hypertension, dyslipidemia, and diabetes mellitus, may be implicated in the etiology of ED in some of these patients. However, growing evidence indicates that ED may actually precede the advent of these conditions in many men with ED. This has been shown in landmark clinical trials and retrospective analyses and is also recognized by the consensus panel of experts of the Second Princeton Consensus on Sexual Dysfunction and Cardiac Risk Guidelines for Sexual Medicine.

Cardiovascular disease remains a source of considerable morbidity and mortality despite advances in prevention, diagnosis, and treatment. New global and regional projections of mortality and burden of disease from 2002 to 2030 have identified ischemic heart disease and cerebrovascular disease as the first and second most common causes of death in the world in 2002, respectively; these 2 conditions will remain the leading causes of death in the year 2030. This review explores the association between ED and vascular disorders in the context of the current literature regarding phosphodiesterase type 5 (PDE5) inhibitor therapy. The PubMed, EMBASE, and MEDLINE databases were searched for articles published from January 2002 through April 2008 using the following search terms: erectile dysfunction and vascular disease, erectile dysfunction and hypertension, erectile dysfunction and cardiovascular disease, erectile dysfunction and dyslipidemia, erectile dysfunction and diabetes mellitus, and erectile dysfunction clinical trials, as well as the same terms together with either sildenafil, tadalafil, or vardenafil.
**PREVALENCE AND ASSOCIATED RISK FACTORS/COMORBIDITIES**

Up to 30 million men in the United States and an estimated 150 million men worldwide are affected by ED.\(^{1,11,12}\) Independent risk factors for both ED and CVD are well recognized and include age, smoking, diabetes mellitus, hypertension, dyslipidemia, depression, obesity, and a sedentary lifestyle.\(^{13-15}\) Compelling evidence exists that the most common underlying mechanism is vascular and that CVD and ED share etiologies as well as pathophysiology, with endothelial dysfunction as the common denominator.\(^{3,16}\) Degree of ED strongly correlates with severity of CVD, and recent studies suggest that ED may be considered a sentinel marker in patients with occult CVD.\(^{3,4,17}\) The increased number of patients with CVD risk factors is paralleled by the worldwide increase in the prevalence of ED.\(^{12,18-20}\)

**Hypertension**

Hypertension is a highly prevalent condition, affecting an estimated 65 million US adults between 1999 and 2004.\(^{21}\) It is frequently associated with ED and often contributes to its etiology (ie, hypertension-related arterial stenotic lesions).\(^{1,22}\) It is present in 38% to 42% of men with ED,\(^{1,23,24}\) and approximately 35% of men with hypertension have some degree of ED.\(^{25}\)

The Third National Health and Nutrition Examination Survey (NHANES III) reported an increased prevalence of hypertension in the United States.\(^{26}\) Because hypertension is known to have a shared etiology with ED, the prevalence of ED associated with hypertension is also expected to increase. According to both the NHANES 1999-2000 and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, up to 30% of men with hypertension are unaware of their underlying disease. Therefore, screening men more carefully for hypertension in the primary care setting will not only help identify this condition but may also provide a unique opportunity to uncover underlying ED.\(^{2,13,27}\) Men already diagnosed as having hypertension should also be closely screened for clinical signs of underlying ED.

**Dyslipidemia**

Dyslipidemia constitutes a vascular risk factor with considerable impact on ED, and both conditions are important concerns for clinicians.\(^{28}\) Data from the NHANES 1999-2000 indicate that more than 91 million US men have mean lipid values outside the optimal ranges specified by the National Cholesterol Education Program Adult Treatment Panel III.\(^{14}\) The prevalence of concurrent ED and dyslipidemia in men is also notable. According to a survey by Seftel et al,\(^{23}\) up to 42.4% of men with ED also had hyperlipidemia. In a cohort of 1519 healthy men (mean ± SD age, 42.9±7.9 years), elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were associated with moderate to severe ED (\(P=.04\) and \(P=.02\), respectively). Elevated serum lipid levels were the most important risk factors for ED in that healthy population.\(^{29}\)

In a smaller study of 215 men with ED and 100 without ED, the prevalence of hyperlipidemia was 70.6% in men with ED vs 52.0% in men without ED (\(P=.06\)). The high-density lipoprotein cholesterol (HDL-C) and TC/HDL-C ratio (\(P=.011\) and \(P<.001\), respectively) were predictors of ED in that population.\(^{30}\) In another study, elevated levels of LDL-C were found as well in 114 (74.0%) of 154 elderly men with ED.\(^{31}\) In a retrospective study involving 988 men (aged 46-81 years), Eaton et al\(^{32}\) found that men with poor to very poor erectile function had twice the odds of an elevated TC/HDL-C ratio (\(P=.02\)) compared with men with good and very good erectile function. Thus, aggressive treatment of both ED and dyslipidemia may result in a decrease in cardiovascular events and improvement in erectile function.\(^{28}\)

**Diabetes Mellitus**

Erectile dysfunction is one of the most common complications of diabetes mellitus. Depending on the severity and duration of diabetes, the prevalence of ED ranges from 20% to 85%.\(^{13,33,34}\) According to the American Diabetes Association’s National Diabetes Fact Sheet, 18.2 million people in the United States had diabetes in 2002. With a projected increase in the number of patients with diabetes to 29 million by 2050, a corresponding increase in those with ED is also expected.\(^{35}\) The survey by Seftel et al\(^{35}\) indicated that 20.2% of men with ED also had diabetes; the Massachusetts Male Aging Study (MMAS) showed a 28% age-adjusted prevalence of ED in men with diabetes compared with 10% in men without diabetes, ie, a 3-fold increased risk.\(^{36}\) Prevalence of ED is higher in men with diabetes who are older than 50 years, nearly double that in age-matched men without diabetes (45.8% vs 24.1%). In
addition, an increase in the relative risk of ED was associated with increased duration of diabetes.\textsuperscript{34} Erectile dysfunction is known to occur at an earlier age in men with diabetes than in those without it.\textsuperscript{35} In some cases, ED may be a manifestation of previously undiagnosed diabetes mellitus, which highlights the importance of screening patients with ED for diabetes-related risk factors.

**OTHER NONCARDIOVASCULAR COMORBIDITIES**

Other comorbidities or risk factors commonly associated with ED include depression, smoking, premature ejaculation (PE), lower urinary tract symptoms (LUTSs) secondary to benign prostatic hyperplasia (BPH), and other causes of urinary flow obstruction such as overactive bladder. The variables that best define PE and the consequences of errors of inclusion and exclusion in the diagnosis of PE have recently been reviewed.\textsuperscript{37} In 3 different surveys of men with ED,\textsuperscript{23,38,39} depression was reported by 11%\textsuperscript{23} and premature ejaculation by approximately 30%\textsuperscript{38} or 60%\textsuperscript{39} of respondents.

Several studies have documented a strong association between LUTSs and ED. LUTSs and BPH, reported in up to 72% of men with ED,\textsuperscript{40,41} are independent risk factors for each other and share both noncardiovascular (eg, age, mental disorders) and cardiovascular (eg, obesity, hypertension, diabetes mellitus) risk factors.\textsuperscript{42,43} A common pathophysiological link between ED and LUTSs means that treatment of one condition could influence the other. Although recent studies have shown that PDE5 inhibitors had beneficial effects on LUTSs/BPH,\textsuperscript{44-46} trials to elucidate whether PDE5 inhibitors could play a role in the treatment of LUTSs/BPH are ongoing.\textsuperscript{47} The use of PDE5 inhibitors in combination with \(\alpha\)-adrenergic blockers for treating both ED and LUTSs/BPH simultaneously is another ongoing avenue of research.\textsuperscript{48} None of the available PDE5 inhibitors is currently indicated for the treatment of LUTSs/BPH.\textsuperscript{49-51}

**ED AS A VASCULAR DISEASE: CLINICAL IMPLICATIONS**

It is now generally accepted that most cases of ED result from a vascular disturbance of the endothelium.\textsuperscript{2} Vascular smooth muscle cells are relaxed and dilated by cyclic guanosine monophosphate, which is regulated by the release of nitric oxide from the endothelium in response to stimuli such as increased shear stress during increased blood flow and muscarinic receptor stimulation.\textsuperscript{2,52} Endothelial dysfunction disrupts nitric oxide production, in turn preventing the relaxation and vasodilation of vascular tissue lining the arterioles.\textsuperscript{2,53} Thus, endothelial dysfunction serves as a marker of peripheral vascular disease (PVD) before vascular disease becomes clinically evident.\textsuperscript{54,55} Erectile dysfunction may be a sentinel marker of endothelial dysfunction, the common link between the vascular diseases observed in patients with ED and ED itself.\textsuperscript{3,4,6}

Several studies have documented the underlying disturbance in the endothelium. Kaiser et al\textsuperscript{16} investigated whether patients with vascular ED and no other underlying clinical CVD had structural and functional abnormalities of other vascular beds. Results of their study revealed that these patients had peripheral vascular defects associated with endothelium-dependent and -independent vasodilation. These defects were apparent before the development of overt functional or structural systemic vascular disease and were independent of other traditional vascular risk factors.

In the clinical setting, however, the apparent absence of overt cardiovascular risk factors in patients with ED may prevent the physician from assessing their overall cardiovascular risk. Patients with ED who have clinical signs and symptoms of vascular disease comorbidities (eg, high blood pressure, abnormal lipid profile, elevated glycemic parameters, abnormal cardiovascular biomarkers) and are therefore taking multiple medications are likely to be followed up by their physicians for these comorbidities. However, patients with ED who do not have these overt clinical indicators most likely will not be assessed for the presence of endothelial dysfunction that may be associated with subclinical vascular abnormalities.\textsuperscript{16}

Results of one study in particular revealed alarming trends regarding the association between ED and subsequent CVD. In a retrospective analysis of data from 9457 men, Thompson et al\textsuperscript{7} found that ED was a strong marker of future cardiovascular events and posed a risk equivalent to or greater than smoking, dyslipidemia, or a family history of myocardial infarction.\textsuperscript{7} Study participants included men who did not have a history of chronic heart failure, myocardial infarction, angina, transient ischemic attack, arrhythmia, or stroke. As a result, the population was healthier, more active, and better educated than the general population at risk of CVD. Incident ED was defined as the first report of ED of any grade. Proportional hazards regression models were used to evaluate the observed association between ED and CVD. The study showed a statistically significant association between incident ED and subsequent angina after covariate adjustment (\(P=.04\)), whereas risk of stroke was suggestive (\(P=.06\)). Incident ED was associated with an adjusted hazard ratio of 1.25 (95% confidence interval [CI],1.02-1.53; \(P=.04\)) for subsequent cardiovascular events (myocardial infarction, stroke, angina, or chronic heart failure). The unadjusted risk of an incident cardiovascular event among men without ED at study entry was 0.015 per person-year vs 0.024 per person-year for those with ED. Therefore, the presence of ED provides a unique opportunity for primary prevention in all.
A retroductive cross-sectional study of 12,825 men with ED and PVD also suggested that ED may be a marker for PVD, with risk becoming more definitive with increasing age. PVD also suggested that ED may be a marker for PVD, older and had a higher frequency of ED and microvascular CI, 7.4-11.7 person-years). Men who developed CAD were 14.3-25.2 person-years vs 9.5 per 1000 person-years; 95% confidence intervals (95% CI).

ED prevalence was higher in men with clinical evidence of CVD, 26.7% of whom had ED at baseline, the incidence of CAD events was shown to be higher in men with than in those without ED (19.7 per 1000 person-years; 95% CI, 14.3-25.2 person-years vs 9.5 per 1000 person-years; 95% CI, 7.4-11.7 person-years). Men who developed CAD were older and had a higher frequency of ED and microvascular complications.

Men with diabetes are prone to develop cardiovascular complications. The risk association between ED and new-onset CAD has been documented in a recent study by Ma et al., which strongly suggested that ED is a surrogate marker for future CAD. In a prospective analysis of a large cohort of 2306 men with no clinical evidence of CVD, 26.7% of whom had ED at baseline, the incidence of CAD events was shown to be higher in men with than in those without ED (19.7 per 1000 person-years; 95% CI, 14.3-25.2 person-years vs 9.5 per 1000 person-years; 95% CI, 7.4-11.7 person-years). Men who developed CAD were older and had a higher frequency of ED and microvascular complications.

A retrospective cohort study of 12,825 men with ED and PVD also suggested that ED may be a marker for PVD, with risk becoming more definitive with increasing age. Therefore, despite the absence of cardiovascular risk factors in patients with ED, the presence of underlying peripheral vascular disorders can be recognized.

Erectile dysfunction has also been strongly correlated with CAD. Montorsi et al. studied 300 consecutive patients with acute chest pain and CAD documented by angiography using a semistructured interview to evaluate medical and sexual histories. Results showed that 49% of patients with CAD also had ED. In addition, in almost 70% of cases, ED symptoms preceded CAD symptoms.

Another study in 40 patients with ischemic heart disease showed a statistically significant correlation between erectile function and the number of coronary vessels involved in ischemia. Patients with 1-vessel disease had more (P<.04) and firmer (P<.007) erections than men with 2- or 3-vessel disease.

Despite the aforementioned correlation between ED and CAD, patients with ED without clinically identified CAD seldom have concomitant symptoms of CAD, whereas patients with CAD have been known frequently to have symptoms of ED. In another study, ED was shown to be highly correlated with silent myocardial ischemia and CAD in men with uncomplicated type 2 diabetes. Interestingly, although apolipoprotein(a) polymorphism, smoking, microalbuminuria, HDL-C, and LDL-C were significantly associated with silent CAD in this study, ED appeared to be the most efficient predictor of covert CVD.

**STANDARD OF CARE IN ED MANAGEMENT**

When managing patients with ED, clinicians should pursue a comprehensive treatment approach that targets not only the primary condition (ED) but also ED-associated comorbidities. The recent American Urological Association guidelines recommend oral PDE5 inhibitors as first-line therapy for ED unless contraindicated. Phosphodiesterase type 5 inhibitors are contraindicated in patients who are actively using nitrates for their cardiac condition. Patients who are not currently using nitrates but who have been prescribed nitrates in the past should be reevaluated by a cardiologist. Risk stratification should be performed as outlined by the second Princeton consensus panel of experts; if deemed to be at minimal risk, the patient may be introduced to the use of PDE5 inhibitors.

The clinical efficacy of PDE5 inhibitor therapy (sildenafil, tadalafil, and vardenafil) in the general ED population has been extensively evaluated in clinical trials and is well documented. The efficacy of PDE5 inhibitors has also been shown in patients with ED and concomitant hypertension, diabetes, and/or hyperlipidemia or dyslipidemia. Efficacy was evaluated in clinical trials using the International Index of Erectile Function (IIEF), total score; ejection fraction (EF) domain score values; specific questions, such as IIEF question 3 (ability to achieve erection) and IIEF question 4 (ability to maintain an erection); and diary questions, such as Sexual Encounter Profile (SEP) questions (ie, SEP2 [penetration], SEP3 [maintenance of erection sufficient for successful intercourse]), the general assessment question, and the general evaluation question. Following is an overview of PDE5 inhibitor efficacy and safety data from clinical trials in men with ED for a number of comorbid conditions.

**HYPERTENSION**

Because hypertension and ED frequently coexist, it is not uncommon for men to be taking a PDE5 inhibitor and an antihypertensive agent concomitantly. Both classes of agents act as vasodilators; however, their vasodilatory mechanisms are somewhat different. The efficacy and safety of PDE5 inhibitors have been evaluated in men with ED taking concomitant antihypertensive medication in pla-
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FIGURE. Erectile function and return to normal rates after PDE5 inhibitor use in men with erectile dysfunction and hypertension (top), erectile dysfunction and diabetes (middle), and hyperlipidemia/dyslipidemia (bottom). Numbers inside bars represent medication doses in milligrams. B = baseline; CG = comorbid group; IIEF = International Index of Erectile Function; P = placebo; PDE5 = phosphodiesterase type 5; RG = reference group; S = sildenafil; T = tadalafil; V = vardenafil.

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the 20-mg dose \((P<.001,\ vs\ placebo)\). Parameters that were different in these 2 studies include study duration of 12 or 26 weeks in the vardenafil study vs 12 weeks in the tadalafil study, a placebo success rate of 27% with vardenafil vs 31% with tadalafil, and a duration of ED of 6 months or greater in patients in the vardenafil study vs 3 months in those in the tadalafil study. More importantly, the tadalafil and sildenafil studies included a subset of hypertensive patients with ED (29.0% and 29.8%, respectively), whereas all the patients in the vardenafil study had concomitant hypertension. None of the efficacy parameters used in the sildenafil study were used in the tadalafil or vardenafil studies.

Antihypertensive medications do not seem to have any clinically relevant impact on the effectiveness and safety of the PDE5 inhibitors or vice versa. Treatment-emergent adverse events have been shown to be similar in patients who are taking antihypertensive agents and those who are not, and no clinically relevant changes in blood pressure were observed even in patients taking 2 or more antihypertensive agents. The PDE5 inhibitors were equally effective, regardless of the type of antihypertensive agent; comparable improvements in erectile function were observed in the presence of \(\beta\)-blockers, diuretics, calcium channel blockers, or angiotensin-converting enzyme inhibitors. However, caution is advised when PDE5 inhibitors are coadministered with \(\alpha\)-blockers because both agents are vasodilators with blood pressure–lowering effects. In some patients, concomitant use of these drugs may result in a substantial drop in blood pressure.

**Diabetes Mellitus**

Several studies have evaluated the efficacy and safety of PDE5 inhibitors in patients with ED and type 1 or 2 diabetes (Table; Figure, middle). The sildenafil studies showed improvement in erectile function primarily on the basis of responses to IIEF question 3 and question 4, whereas the vardenafil and tadalafil studies used IIEF-EF, SEP2, and SEP3 to measure improvement.

The effect of diabetes, poor glycemic control, and long-term complications on the efficacy of PDE5 inhibitors was evaluated in a number of clinical trials, and the key results of these trials are summarized here. Sildenafil improved erectile function vs placebo \((P=.0001)\) in patients with type 1 diabetes regardless of hemoglobin A\(_1c\) (HbA\(_1c\)) levels and degree of disease progression. The efficacy of sildenafil was demonstrated in men with type 2 diabetes, independently of HbA\(_1c\) concentration and diabetes complications. Significant correlation was observed between severity of ED and duration of type 2 diabetes, inadequate metabolic control, and presence of 1 or more diabetes-related complications \((P<.05\ for\ each)\), all of which affected the efficacy of sildenafil. However, global efficacy and overall patient satisfaction remained high. Levels of HbA\(_1c\) at baseline did not appear to influence tadalafil response in men with type 1 or 2 diabetes. Responses to tadalafil were similar in men with ED who did and did not have diabetes, regardless of HbA\(_1c\) levels, diabetes therapy, or previous use of another PDE5 inhibitor (sildenafil), as shown in a retrospective analysis. Vardenafil effectively increased rates of successful intercourse at all levels of ED severity and at different levels of HbA\(_1c\) in men with type 1 or 2 diabetes.

**Hyperlipidemia or Dyslipidemia**

A number of clinical studies with PDE5 inhibitors have shown significant improvement of erectile function in men with ED and hyperlipidemia (Table; Figure, bottom). More specific details regarding these trials are depicted in the Table.

Neither sildenafil nor tadalafil has been prospectively evaluated in an exclusively dyslipidemic patient population. The Reliability-Vardenafil for Erectile Dysfunction (RELY) I study showed that 10 mg of vardenafil was highly successful as a first-dose therapy in patients with or without specific comorbidities, including a subgroup of patients with ED and dyslipidemia. Success rates were evaluated by responses to SEP2 and SEP3. In 2 studies designed to evaluate the efficacy of tadalafil and vardenafil, subgroup analysis revealed similar improvements in erectile function in men with ED who had and did
not have hyperlipidemia/dyslipidemia. No such analysis has been identified in studies with sildenafil.

In a recently conducted 12-week prospective, randomized, double-blind, placebo-controlled trial, the efficacy and safety of on-demand, flexible-dose vardenafil (10 mg, titrated to 5 mg or 20 mg on the basis of efficacy and safety) were evaluated in a population of men with ED and dyslipidemia who were all receiving stable statin therapy.28 The differential effect of vardenafil vs placebo in this patient population was assessed using 3 primary efficacy measurements (SEP2, SEP3, IIEF-EF domain scores). During the study treatment period, the adjusted mean success rates in patients who took vardenafil were 79% for SEP 2 and 67% for SEP 3. Patients receiving placebo had a 52% SEP2 and a 34% SEP3 success rate. All comparisons were statistically significant (P<.001). The adjusted mean IIEF-EF domain score for week 12 using the last observation carried forward method was 21.99 for patients taking vardenafil vs 14.83 for patients taking placebo (P<.001). No significant safety issues were identified in this study.

CONCLUSION

Erectile dysfunction and CVD, especially CAD, share the same risk factors: smoking, high blood pressure, high cholesterol, and diabetes. These 2 conditions also share the same pathophysiology, mediated by endothelial dysfunction. Thus, ED may be an important risk marker of silent vascular disease in men with no cardiac symptoms, providing physicians with a unique opportunity to uncover and address underlying CAD in patients who present with ED. It is recommended that physicians screen these patients for vascular disease. Because ED is often associated with comorbid conditions such as diabetes, hypertension, or dyslipidemia, screening should also include measurements of blood glucose, lipids, and blood pressure.4

The safety and efficacy of the 3 currently available PDE5 inhibitors (sildenafil, tadalafil, and vardenafil) have been evaluated extensively in patients with ED and concomitant CVD, hypertension, dyslipidemia, or diabetes with or without additional risk factors. Overall, these studies have shown similar efficacy for the 3 agents, resulting in significant improvement of erectile function in patients with any of these comorbid conditions. Their safety profile was also similar. No adverse effect on cardiac contraction, ventricular repolarization, or ischemic threshold was noted, and there was no evidence of increased cardiovascular risk from using any of these agents. However, because ED is known to be a harbinger of cardiovascular events in some men, the presence of ED should prompt investigation and intervention for cardiovascular risk factors.

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