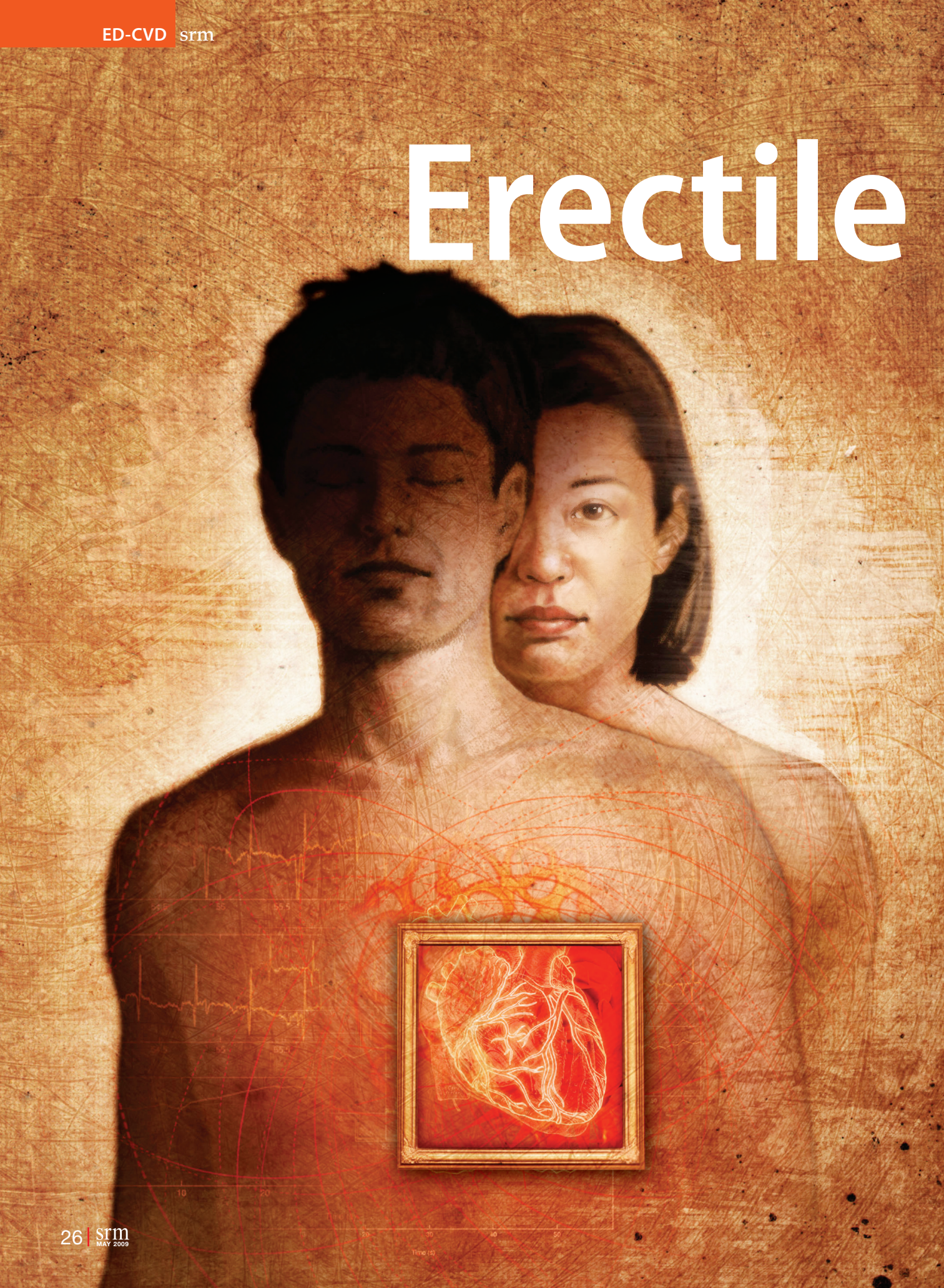
Erectile



dysfunction: A precursor to cardiovascular disease

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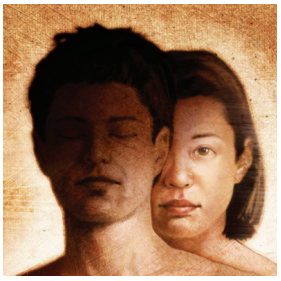
Erectile dysfunction (ED) is an early precursor to penile vasculature oxidative stress and vascular dysfunction[1] and has been suggested as a risk factor for the presence of occult cardiovascular disease (CVD).[1] ED can no longer be perceived as a secondary complication of its concomitant comorbid disease states—diabetes, CVD, hypertension, and dyslipidemia. Rather, it should be recognized in a new paradigm as an early manifestation of atherosclerosis and a potentially key precursor to vascular disease in more crucial arterial beds, such as the coronary and cerebrovascular circulation. Studies have shown that ED is an early manifestation of future cardiovascular (CVS) events—atherosclerosis, vascular impairment, and vascular disease of the coronary and cerebrovascular circulation. Early intervention in men with CVS risk factors results in fewer myocardial infarctions (MIs) or other CVD outcomes than in untreated men. Therefore, it is logical that early CVD treatment intervention in men who present with ED should be beneficial, and this should be an appropriate population for primary CVS prevention efforts.

ED and CVD: A "flagging" penis and a broken heart?

A prospective study of 1248 Dutch men free of CVD at baseline sought to determine the relationship between ED and impending CVD.[2] The answer to a single question from the International Continence Society male sex questionnaire—"Do you get erections?"—defined the severity of ED as follows: (a) no ED, normal erections; (b) moderate ED, erections with "reduced rigidity"; and (c) severe ED, no erections. At baseline, 258 patients (22.8%) had reduced erectile rigidity and 108 (8.7%) had severely



KEY POINT

A man with severe erectile dysfunction has a 1.5 to 2.5 increased risk of developing CVD, which is similar to a person who smokes or has diabetes.

reduced erectile rigidity. During an average of 6.3 years' follow-up, in a multiple variable Cox proportional hazards model, adjusting for age and CVD risk score, the hazard ratio (HR) for a CVS event was 1.6 (95% confidence interval [CI]: 1.2-2.3) for the reduced erectile rigidity group and 2.6 (95% CI: 1.3-5.2) for the severely reduced erectile rigidity group. Therefore, a man with severe ED has a 1.5 to 2.5 increased risk of developing CVD, which is similar to a person who smokes or has diabetes.

In this population-based study, a single question on erectile rigidity proved to be a precursor to the combined outcome of acute MI, stroke, and sudden death, independent of the risk factors used in the Framingham risk profile.

An analysis of Massachusetts Male Aging Study data revealed that the rate of incident ED increased as the quartile of 10-year coronary heart disease (CHD) risk increased. This implies that ED is a sensitive (although not necessarily specific) indicator of wider arterial insufficiency. If this could be further supported, erectile problems could call attention to coronary risk and contribute to CVD prevention efforts.[3]

Does ED precede CVD?

Additional studies have demonstrated that ED may predate the onset of cardiac symptoms in many men with coronary artery disease (CAD).[4] One study evaluated the rate of prior ED among a group of men who had had CAD. ED became evident prior to symptoms of ischemic heart disease in 65 of 200 men (32.5%). Some 65 of 96 men in this study (68%) complaining of ED developed angina or MI only after the ED problem.[4] In this study patients developed ED at a mean of 53.4 months prior to ischemic heart disease.[4] Furthermore, tests on men with vasculogenic ED (confirmed by hemodynamic testing) who did not respond to pharmacologic erection test (10 mcg prostaglandin E1) were more likely to have risk factors for cardiac disease and were more likely to have a positive exercise treadmill test (15.7%) than those who responded (0%).[5] Therefore, studies have suggested that some men with ED, even if they have no history of angina or acute MI, are more likely to develop evidence of myocardial ischemia during exercise treadmill testing and the ED may precede the onset of CAD by a lengthy period of time.[4]

Patients with ED who have a penile brachial pressure index ≤0.65 have a significantly greater risk of having an MI or cerebrovascular accident than do patients with higher scores. ED associated with a low penile brachial pressure index may signify a higher risk of future vascular events.[6] In one study of men aged 40 to 60 years with presumably vasculogenic ED, more than half of the men who had had an angiography reported experiencing ED before their cardiac diagnosis was made, 80% noted multiple CVS risk factors, and 28 of 50 had electrically positive graded exercise testing.[7]

Younger men are not immune

ED also occurs among younger men who do not have risk factors for CVD or atherosclerosis but may have structural and functional abnormalities in other vascular beds.[8] In a study of patients with ED and no CVD and no psychiatric causes for ED had a variety of vascular parameters measured, including: (1) coronary calcification, (2) aortic pulse wave velocity, (3) brachial and carotid artery diameters, intima-media thickness evaluations, compliance and distensibility, and (4) brachial artery endothelium–dependent and endothelium–independent vasodilation. Patients with ED were compared with matched controls. Framingham risk scores were not significantly different between the 2 groups. Subjects with ED had objective evidence of significant clinical and penile vascular disease. Lipid values, homocysteine levels, glucose and structural parameters were similar between the 2 groups, including calcium score and carotid and brachial artery compliance and distensibility. Brachial artery endothelium–dependent, flow-mediated vasodilation was significantly reduced in the ED patients compared with the controls, as was the maximal response to sublingual nitroglycerin (**FIGURE 1**). The measurement of brachial artery–dependent vasodilation assesses the ability of the endothelial vascular lining to induce vasodilation. This ability is thought to correlate with endothelial cell health. This study demonstrated that men with ED and no other clinical CVD signs or symptoms have a peripheral vascular abnormality in the nitric oxide–cGMP pathway as measured by brachial artery testing and vasodilation response to sublingual nitroglycerin. This suggests that this impair-

ment in the peripheral vascular system may result in ED as the first clinical sign of CVD.[8]

In studies of inflammatory markers as risk predictors for CVD, men with ED have elevated values of these markers compared with normal controls. A clinical study of men with and without ED used novel laboratory assays of endothelial cell activation to suggest that ED is a sentinel of early atherosclerotic disease.[9] This finding supports the concept that ED should prompt the clinician to search aggressively for vascular disease in men who might otherwise appear without risk. Also, preliminary studies reveal that fibrinogen (an independent, powerful predictor of vascular events) is elevated in men with ED. It is likely that this and other factors that cause endothelial dysfunction and/or predict vascular events (eg, homocysteine) will also prove to be predictors of ED.[10]

The earliest events in the generation of atherosclerosis—superoxide radical production and damage to arterial intima—are accelerated by risk factors such as hypertension and smoking, resulting in endothelial dysfunction. This has been noted in abnormal endothelium–dependent, flow–mediated vasodilation in the brachial arteries of patients with ED, indicating widespread endothelial dysfunction. The pathologic process of endothelial dysfunction occurs both in the coronary arteries as well as the penile arteries; this dysfunction is the earliest event in vascular ED.[11] Therefore, ED may be the earliest manifestation of vascular disease, and men with ED may be at increased risk of later developing clinically apparent arterial disease, including CAD. The onset of ED may reflect systemic arterial compromise and may be interpreted as a sign of subclinical coronary disease.[6,12]

Research indicates that ED may not only represent a way to discover men at increased CVS risk, but ED may itself be an independent signal of CVD.[10,13-16]

Is ED a precursor to CVS events in certain populations?

In their landmark 2005 report on more than 9400 men, Thompson et al[17] pose the following questions: "With the high prevalence of ED in aging men, do pharmacologic, lifestyle, or behavioral interventions that are cardioprotective also reduce or delay onset of ED? Could ED serve as a surrogate measure of treatment efficacy in preventive interventions for cardiac disease?" Today, 4 years later, these questions remain unanswered.

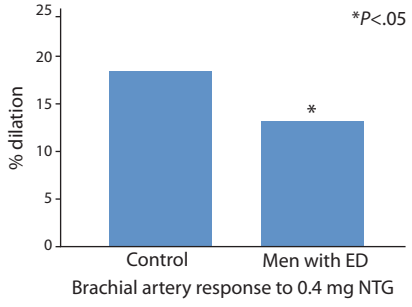
An analysis of the Prostate Cancer Prevention Trial studied the impact of incident ED on CVS events. Men aged 55 years or older were evaluated at 3-month intervals for ED and subsequent CVD (N=9475). There were 4247 men with no ED at baseline; of this group, 2420 developed incident ED (defined as the first report of ED of any grade) over the course of 5 years. Incident ED (adjusted for other CVS risk factors) was associated with an HR of 1.25 (95% CI: 1.04-1.53; *P*=.04) for subsequent CVS events—MI, coronary revascularization, cerebrovascular accident, transient ischemic attack, congestive heart failure, fatal cardiac arrest, or nonfatal cardiac arrhythmia. The adjusted HR was even higher (1.45; 95% CI: 1.25-1.69; *P*<.001) for men with either incident or prevalent ED at baseline. Based on these findings, the authors concluded that incident ED had an effect on subsequent CVS events that was greater than or equal to the effects of family history of MI, cigarette smoking, or measures of hyperlipidemia.[17]

ED and men with CAD and diabetes mellitus

In a 2006 study, Min et al[18] examined 221 men referred for a stress myocardial per-

FIGURE 1

Endothelium-independent vasodilation



ED, erectile dysfunction; NTG, nitroglycerin

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KEY POINT

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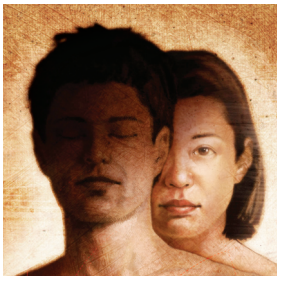

KEY POINT

All health care providers should begin inquiring about sexual function in patients with diabetes and aggressively treat CVS risk factors.

fusion single-photon emission computed tomography, a widely used, noninvasive imaging modality that allows diagnosis of coronary heart disease and stratification of CVS risk. The study's aim was to determine the relationship between ED and CHD in men referred for this noninvasive testing—clearly a group at risk for CVD. ED was present in 54.8% of the patients. More dramatically, patients with ED exhibited more severe CHD and left ventricular dysfunction than those without ED did. ED was associated with a shorter exercise time and a lower Duke treadmill score.

In another study of 300 consecutive patients with acute chest pain and angiographically documented CAD, the prevalence of ED was 49%. Of the 147 patients with both ED and CAD, 67% of patients experienced ED symptoms before CAD symptoms, with a mean time interval between onset of ED and clinical symptoms of CAD of 39 months.[19] Of note, all patients who had type 1 diabetes, ED, and CAD experienced ED before symptoms of CAD.[19]

Ma et al[20] studied 2306 diabetic men with no clinical evidence of CAD, 27% of whom had ED. Over the course of approximately 4 years, the incidence of CHD was greater in men with ED (19.7/1000 person-years) than in men without ED (9.5/1000 person-years). After adjustments for other covariates—including age, duration of disease, use of antihypertensive agents, and albuminuria—ED remained an independent predictor of CHD (HR, 1.58; 95% CI: 1.08-2.30; *P*=.018).

Because ED and silent CAD are prevalent among men with diabetes, all health care providers should begin inquiring about sexual function in patients with diabetes and aggressively treat CVS risk factors, including dyslipidemia and hypertension. Indeed, the Second Princeton Consensus Panel on sexual activity and cardiac risk published recommendations for the individual with established or suspected CAD related to estimated risk for CVS events.[21]

Those individuals of intermediate or indeterminate risk should receive further cardiac evaluation to delineate the presence and severity of coronary disease. (Intermediate or indeterminate risk are defined as no overt cardiac symptoms and 3 or more CVS risk factors, including sedentary lifestyle; moderate stable angina; recent MI [<6 weeks]; New York Heart Association Class II heart failure; prior stroke, transient ischemic attack, or history of peripheral vascular disease).

To evaluate both safety and efficacy of drug treatment, Nehra[22] reviewed the association between ED and its well-known concomitant comorbidities in the context of current knowledge of phosphodiesterase type 5 inhibitors. His analysis revealed compelling evidence for health care providers to address underlying CVS health concerns in men presenting with ED. His review suggests that the degree of ED strongly correlates with the severity of CVD and, indeed, that ED may be considered a sentinel marker for occult CVD. He has recommended that physicians screen ED patients for vascular disease. Furthermore, since ED often coexists with the comorbidities of diabetes, hypertension, or dyslipidemia, screening in the urologist's office should also include measurement of blood glucose, lipids, and blood pressure, with referral to a primary care or cardiology physician if these results are abnormal.

ED and the general population

What does the presence of ED suggest in the lower-risk male population? To this point, Inman et al[23] biennially screened a random sample of more than 1400 community-dwelling men who had regular sexual partners and no known CAD for the presence of ED over a 10-year period. Men were followed from the fourth screening round of the 1996 Olmsted County Urinary Symptoms and Health Status Among Men Study until the first occurrence of an incident cardiac event or the last study visit (December 31, 2005), whichever occurred earlier.

Men with ED at baseline were excluded from the analyses. Multivariate proportional hazard regression models were used to assess the association of ED with the covariates of age, diabetes, hypertension, smoking status, and body mass index (BMI). Unlike the Thompson study or others noted above, the participants in this study were not a highly select subset of the general male population or older than 55 years of age, but more representative of a normal (albeit predominantly Caucasian)

group of men. In addition, erectile function of the study participants was assessed by an externally validated questionnaire, the Brief Male Sexual Function Inventory.[24]

During the 10-year follow-up period, ED was modeled as a time-dependent covariate that allowed each patient's ED status to change over time, with results stratified by 10-year age periods and adjusted for diabetes, hypertension, smoking status, and BMI.[25]

Baseline prevalence of ED was 2% for 40-year-olds, 6% for 50-year-olds, 17% for 60-year-olds, and 39% for men aged 70 and older. New ED developed in 6.4% of patients at 2 years, with increases of approximately 5% in each subsequent 2-year interval over the 10-year follow-up period. Incident ED was more common in patients with both higher CVS risk and older age.[22]

Overall, new incident CAD developed in 11% of men over the 10-year follow-up period, with approximately 15% due to MI, 79% to angiographic anomalies, and 6% related to sudden death. The cumulative incidence of CAD was strongly influenced by patient age. CAD incidence densities per 1000 person-years for men without ED were 0.94 (aged 40-49), 5.09 (aged 50-59), 10.72 (aged 60-69), and 23.30 (aged 70+).

For men with ED, the incidence densities for CAD were 48.52 (aged 40 to 49), 27.15 (aged 50 to 59), 23.97 (aged 60 to 69), and 29.63 (aged 70+) (**FIGURE 2**).[23]

The meaning of these findings is highly significant. Although ED and CAD may be different manifestations of an underlying vascular pathology, when ED occurs in a man younger than age 60, it is associated with a marked increase in the risk of future cardiac events; in older men it has less prognostic value.

The importance of this study cannot be understated. Although ED had little relationship to the development of incident cardiac events in men aged 70 and older, it was associated with a nearly 50-fold increase in the 10-year incidence of cardiac events in men aged 49 years and younger. This raises the possibility of a "window of curability," whereby progression of cardiac disease might be slowed or halted by medical intervention. Younger men with ED could serve as the ideal populations for future studies of primary CVS risk prevention.

FIGURE 2

Effect of ED at baseline on subsequent CAD events

Age group (y)	ED at baseline* (CI)	No ED at baseline* (CI)
40-49	48.52 (1.23-269.26)	0.94 (0.02-5.21)
50-59	27.15 (7.40-69.56)	5.09 (3.38-7.36)
60-69	23.97 (11.49-44.10)	10.72 (7.62-14.66)
≥70	29.63 (19.17-43.75)	23.30 (17.18-30.89)

*Per 1000 person-years, by age group.
CAD, coronary artery disease; CI, confidence interval; ED, erectile dysfunction.

Inman BA, et al. Mayo Clin Proc. 2009;84:108-113.

ED and the general population of younger men

As stated, ED and CAD may be different manifestations of an underlying vascular pathology, and ED appears to precede symptoms of CAD in patients with a vascular etiology. This phenomenon relates to the caliber of the blood vessels.[1] For example, the penile artery has a diameter of 1 mm to 2 mm, whereas the proximal left anterior descending coronary artery is 3 mm to 4 mm in diameter. An equally sized atherosclerotic plaque burden in the smaller penile arteries would more likely compromise flow earlier, causing ED, compared to the same amount of plaque in the larger coronary artery causing angina. Another plausible explanation suggests greater impairment in arterial endothelial cell function with age.[9] The repetitive pulsations that the large central arteries are subjected to over their life span leads to fatigue and fracture of the elastic lamellae, resulting in increased arterial stiffness.[26] Ultimately, small arteries, such as the pudendal and penile arteries begin to degenerate and end-organ ischemia results. In the younger man with ED, impaired vasodilation of a penile artery is more likely to lead to ED, even in the absence of atherosclerotic plaque narrowing the lumen, than the same scenario in the coronary arteries leading to symptoms of angina.[1]

To answer Thompson's question, "Could erectile function serve as a surrogate measure of treatment efficacy of preventive interventions for cardiac disease?"[17] Inman suggests further studies of CVD prevention strategies in young men with ED. Only then can we fully comprehend and treat during a

KEY POINT

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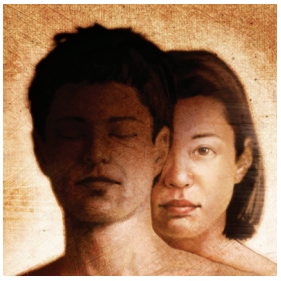

"window of curability" whereby future cardiac events in men might be prevented.

Conclusion

ED must no longer be viewed solely as a secondary complication of its concomitant comorbidities but, rather, as one of the earliest manifestations of atherosclerosis and as a precursor to systemic vascular disease. In several studies, onset of ED precedes CVS events from 3 to 7 years, thereby allowing a "window of curability" during which an individual's risk factors and lifestyle may be modified to prevent such a CVS event. Preventative efforts must therefore be focused both on early identification of ED in the general population and primary prevention of CVD once the diagnosis is established. ■

KEY POINT

Onset of ED precedes CVS events by 3 to 7 years, thereby allowing a "window of curability" to prevent CVS events.

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