Prognostic utility of erectile dysfunction for cardiovascular disease in younger men and those with diabetes

Erectile dysfunction (ED) is defined as the inability to reach or maintain an erection sufficient for satisfactory sexual performance. The fact that ED often coexists with hypertension, hyperlipidemia, and diabetes provides support for a vasculogenic etiology of ED. Beyond its association with vascular risk factors, vasculogenic ED has been recently recognized as a predictor of future cardiovascular events, most strikingly in men in their third, fourth, fifth, and sixth decades. Consequently, the identification of vasculogenic ED in the younger man has potentially significant prognostic import.

Here, we provide evidence that vasculogenic ED precedes coronary heart disease in younger and middle-aged men. Pathophysiologic links between vasculogenic ED and cardiovascular disease (CVD) are explained, and the role of vascular markers is discussed with a focus on those that may enhance the predictive value of vasculogenic ED for CVD. Finally, we provide guidance for evaluation of vasculogenic ED.
of the overall multifaceted process of male sexual function.\textsuperscript{1} This de-emphasized intercourse as the sine qua non of sexual life and gave equal importance to other aspects of male sexual behavior. Sigal et al\textsuperscript{5} studied data on men 20 years and older collected via The National Health and Nutrition Examination Survey. Data included medical histories in which specific queries were made regarding sexual function. Erectile dysfunction was reported by nearly 1 in 5 respondents. Hispanic men were more likely to report ED (OR, 1.89), after controlling for other factors. The prevalence of ED increased substantially with advanced age, and 77.5% of men \( \geq 75 \) years old were affected.

ED can be categorized as organic or psychogenic. In general, organic ED is characterized by a gradual onset. Erectile rigidity may be weakened, duration may be shortened, or both. These changes are evident under most or all circumstances, be it with the morning erection, nocturnal erection, or sexually stimulated erection. The most common type of organic ED is vasculogenic ED. Situational ED, such as that occurring with a partner but not with morning erections or masturbatory behavior, is usually considered psychogenic in origin.\textsuperscript{6}

**ED and CVD risk factors often coexist**

A number of studies have documented associations between ED and established CVD risk factors. Data from the National Health and Nutrition Examination Survey (National Health and Nutrition Examination Survey) revealed several risk factors that were independently associated with ED, including diabetes mellitus (OR, 2.69), obesity (OR, 1.60), current smoking (OR, 1.74), and hypertension (OR, 1.56).\textsuperscript{3} Furthermore, Seftel et al\textsuperscript{2} quantified the prevalence of diagnosed hypertension, hyperlipidemia, diabetes mellitus, and depression in male health plan members with ED, using a nationally representative managed care claims database that covered 51 US health plans and 28 million lives from 1995 through 2002. Of 87,163 patients with ED, only 32\% had no comorbid diagnosis of hypertension, hyperlipidemia, diabetes mellitus, or depression.\textsuperscript{2} In a sample of nearly 4000 Canadian men (40-88 years) seen by primary care clinicians, 49.4\% had ED based on the International Index of Erectile Function (IIEF).\textsuperscript{7} The presence of CVD or diabetes increased the probability of ED after adjustment for other factors. Among men without CVD or diabetes, the calculated 10-year Framingham coronary risk (OR, 1.03 per 1\% increase) and fasting glucose level (OR, 1.14 per 18 mg/dL increase) were independently and significantly associated with ED. ED was also independently and significantly associated with undiagnosed hyperglycemia (OR, 1.46), impaired fasting glucose (OR, 1.26), and presence of the metabolic syndrome (OR, 1.45).\textsuperscript{7, 8} This evidence suggests that ED shares etiologic links with established CVD risk factors and supports ED as a potential observable marker for CVD risk.

**ED precedes and predicts clinical CVD**

A number of studies support the presence of vasculogenic ED as a predictor of subsequent CVD. In the Prostate Cancer Prevention Trial, men >55 years of age were evaluated for CVD and ED every 3 months between 1994 and 2003. In a multivariate analysis of data from 9457 men randomized to the placebo group, incident ED (defined as the first report of ED of any grade in men who did not have ED at baseline) was associated with a hazard ratio (HR) of 1.27 (\( P = .02 \)) for subsequent cardiovascular events.\textsuperscript{8} The predictive strength of ED for cardiovascular events was similar to that of age (5-year increase; HR, 1.31) and family history of myocardial infarction (HR, 1.36) and stronger than that of body mass index (5-U increase; HR, 1.14). Parenthetically, men with either incident or prevalent ED (ie, ED at study entry) had a HR for cardiovascular events of 1.45 (\( P < .001 \)). In a substudy of 1549 men with CVD who participated in the ONTARGET and TRANSCEND trials, men with ED (compared to those without ED) were twice as likely to suffer death from all causes (11.3\% vs 5.6\%) and 1.6 times more likely to suffer the composite of cardiovascular death, heart attack, stroke, or heart failure hospitalization (16.2\% vs 10.3\%) during follow-up (median, 53-54 months).\textsuperscript{9}

Imaging studies are consistent with the aforementioned findings. Jackson and Padley\textsuperscript{10} studied 20 nondiabetic men with ED and no cardiac symptoms. Eleven men had coronary artery calcium scores >50 and angiographic coronary artery disease (CAD), but only 2 had abnormal exercise electrocardiograms. Four men had calcium scores of 6 to 17 and single plaque disease on computed tomography (CT), and the remaining 5 had normal cardiac CT studies. These data suggest that ED may be a predictor of subclinical, non–flow-limiting CAD that is not detectable using exercise electrocardiography. Min et al\textsuperscript{11} studied 221 men referred for stress myocardial perfusion single-photon emission CT, a technique commonly used to diagnose and stratify CVD. They found that men with ED exhibited more severe coronary heart disease (based on myocardial perfusion single-photon emission CT summed stress score >8) than men without ED (43\% vs 17\%, respectively). Left ventricular dysfunction (ie, left ventricular ejection fraction <50\%) was also significantly more common among men with ED (24\% vs 11\%).

Montorsi et al\textsuperscript{12} divided 285 patients with CAD into 3 age-matched groups: acute coronary syndrome (ACS) and 1-vessel disease, ACS and 2- or 3-vessel disease, and chronic coronary syndrome.\textsuperscript{12} A control group was composed of 95 patients with suspected CAD but normal coronary arteries based on angiography. ED prevalence differed across subsets of patients with CAD and was...
related both to coronary clinical presentation and extent of CAD. In logistic regression analysis, age (OR, 1.1), multivessel vs single-vessel coronary disease (OR, 2.53), and chronic coronary syndrome vs ACS (OR, 2.32) were independent, significant predictors of ED. In patients with established CAD, ED preceded CAD by an average of 2 to 3 years. These findings support the assertion that ED is a harbinger of cardiovascular events and is related to the severity of CAD.

The “artery size hypothesis” may help explain the temporal relationship between onset of ED symptoms and clinically evident CVD. The hypothesis asserts that a larger vessel can better tolerate the same amount of plaque compared with a smaller one. The penile artery has a diameter of 1 to 2 mm, whereas the proximal left anterior descending coronary artery is 3 to 4 mm in diameter. Thus, reduced blood flow and symptoms (ie, ED) may result from a small atherosclerotic plaque burden in the narrower penile arteries, whereas a larger plaque burden would be required for obstruction and symptoms (ie, angina) in the larger coronary artery. Although this hypothesis is plausible, data supporting parallel development of plaques in penile and coronary arteries are lacking, and alternative explanations should be evaluated.

**Erectile dysfunction is a particularly powerful predictor of cardiovascular events in the younger- and middle-aged man**

Three recent studies have evaluated the effect of age on the relationship between ED and cardiovascular risk. Inman et al studied a random sample of more than 1400 community-dwelling men who had regular sexual partners and no known CAD. Over a 10-year follow-up period, the men were biennially screened for the presence of ED. Incidence densities of CAD were calculated after age stratification and adjusted for potential confounders by time-dependent Cox proportional hazards models. Prevalences of ED were 2%, 6%, 17%, and 39% for men 40 to 49 years, 50 to 59 years, 60 to 69 years, and ≥70 years of age, respectively. The CAD incidence densities per 1000 person-years for men without ED were 0.94 (40–49 years old), 5.09 (50–59 years old), 10.72 (60–69 years old), and 23.30 (≥70 years old). For men with ED, CAD incidence densities increased to 48.52 (40–49 years old), 27.15 (50–59 years old), 23.97 (60–69 years old), and 29.63 (≥70 years old) (Figure). These data suggest that ED in younger men is associated with a marked increase in the risk of future cardiac events, whereas in older men, the prognostic importance of ED is diminished.

Chew et al analyzed hospital morbidity data and death registrations in a retrospective cohort study of 1660 men with ED. They used a standardized incidence rate ratio to compare the incidence of atherosclerotic cardiovascular events subsequent to the manifestation of ED in this cohort to that in the general male population. Men with ED had a significantly higher incidence of atherosclerotic cardiovascular events than was observed in the general population (standardized incidence rate ratio, 2.2). The incidence of atherosclerotic cardiovascular events in men 20 to 29 and 30 to 39 years of age with ED was more than 7 times the incidence in the same age groups in the general population. A marked weakening of the relationship between ED and cardiovascular events was observed with increasing age (P < .0001), and incidence rate ratios were not statistically significant in men 70 years and older.

Most recently, Riedner et al performed a case-control study involving 242 men (mean age, 58 years) referred for elective coronary angiography. One hundred fourteen men had significant CAD, defined by stenosis of 50% or greater in ≥1 of the major epicardial vessels or their branches. The remaining men (n = 128) had no significant CAD. Men <60 years with CAD were significantly more likely to have ED than those without CAD (P = .009). However, CAD was not associated with increased likelihood of ED in men ≥60 years (P = .5). In a statistical model that controlled for the effects of cardiovascular risk factors, testosterone, and C-reactive protein, the probability of CAD was 2.3 times higher in men <60 years of age with ED versus those without ED (P = .04). There was no association between ED and probability of CAD in men ≥60 years (P = .3). These studies support ED as a powerful indicator of
cardiovascular risk in men in their third, fourth, fifth, and sixth decades and suggest that ED screening is a valuable means of identifying young and middle-aged men who are candidates for cardiovascular risk assessment and medical intervention.

**Erectile dysfunction, diabetes, and CVD: an evolving picture**

Although published prevalence estimates differ, the literature suggests that ED is highly prevalent among men with diabetes. In a recent study of 611 consecutive men (35-70 years of age) regularly attending diabetes clinics, 60% had some degree of ED based on the IIEF-5 (mild, 9%; mild to moderate, 11.2%; moderate, 16.9%; and severe, 22.9%). Men with higher (vs lower) glycated hemoglobin levels were more likely to have ED, as were men who reported lower (vs higher) levels of physical activity.

Gazzaruso et al were among the first to prospectively evaluate ED as a predictor of cardiovascular morbidity and mortality in men with type 2 diabetes mellitus (DM2) and silent CAD. During a mean follow-up period of 47 months, 49 of the 291 patients experienced a major adverse cardiac event (MACE). The prevalence of ED was significantly greater in patients with MACE (61.2%) than in those without (36.4%), and a Cox regression analysis showed that ED was a significant predictor of MACE (HR, 2.40) in this population. Ma et al studied a consecutive cohort of 2306 men with DM2 and no clinical evidence of CVD over a mean follow-up of 4 years. The incidence of coronary events was higher among the 616 men with ED at baseline than in those without (19.7 vs 9.5 per 1000 person-years), and ED remained an independent, significant predictor for coronary events after adjustment for confounding factors.

In a cohort analysis of the ADVANCE population, more than 6300 men (mean age, 66 years) with DM2 participated in a baseline medical examination that included inquiries about ED. The incidences of fatal and nonfatal CVD outcomes were ascertained over a 5-year follow-up period. After adjustment for classic CVD risk factors, baseline ED was associated with significantly increased risk for all CVD events (HR, 1.19), coronary heart disease (HR, 1.35), and cerebrovascular disease (HR, 1.36). These findings reinforce the assertion that symptoms of ED should be independently sought to identify high-risk subjects for comprehensive cardiovascular assessment. Although it is not known whether ED has stronger predictive power for CVD in diabetics than in non-diabetics, the literature clearly supports greater cardiovascular risk among diabetics with ED than those without. Thus, all men with DM2 and new-onset ED should undergo thorough cardiovascular risk evaluation.

**Endothelial dysfunction: the pathophysiologic link between ED and CVD?**

Hypertension, diabetes, dyslipidemia, obesity, and smoking all have detrimental effects on endothelial function, and adequate endothelial function is required for maintenance of vascular health. The endothelium regulates vascular tone, coagulation, and inflammation throughout the vascular tree, primarily via production of nitric oxide (NO). Endothelial NO possesses antiatherogenic, antithrombotic, and anti-inflammatory properties and promotes vasodilation of the vascular smooth muscle. The endothelium also protects the vessel wall from infiltration by circulating low-density lipoprotein cholesterol and chylotriglyceride. Given these functions, it is not surprising that endothelial dysfunction is associated with atherosclerosis and is an independent predictor of cardiovascular events.

Penile erection also relies on a healthy endothelium and involves 3 synergistic and simultaneous processes: increased penile arterial inflow mediated neurologically and hormonally, relaxation of the cavernosal smooth muscle, and restriction of the venous outflow. Research has shown that adequate arterial vasodilatation and sinusoidal smooth muscle relaxation are dependent on normal functioning of the vascular endothelium and the cavernosal endothelium, respectively. Apolipoprotein E-deficient [Apo E (−/−)] mice fed a high-cholesterol diet, a model of atherosclerosis, demonstrate significantly impaired endothelial function in the aorta and in blood vessels of the corpus cavernosum, as well as impairment of NO production in the corpora cavernosa. Of note, inhibition of the renin-angiotensin system (RAS) lowered blood pressure, improved penile endothelial function, and restored NO production in these mice. RAS inhibition also reduced the amount of lipid peroxides and restored expression of endothelial nitric oxide synthase in the corpora cavernosa tissue.

Consistent with these findings, angiotensin receptor blockade restored erectile function in aged rats to levels similar to those observed in young animals. Several human studies have tested the hypothesis that patients with ED and no clinical CVD have systemic endothelial dysfunction, of which ED is the first clinical manifestation (Table I). Despite differences in the patient populations and methods used to evaluate erectile and endothelial functions, results consistently showed an attenuation of peripheral, endothelium-dependent vasodilation in patients with ED when compared to controls. These findings are similar to those reported by De Angelis et al in diabetic men with and without ED. These investigators reported increased thrombomodulin and cell adhesion molecules, enhancement of coagulation activation, reduced fibrinolysis, and
attenuated reductions in blood pressure and platelet aggregation in response to L-arginine in diabetic men with ED versus those without ED. In sum, studies in laboratory animals and humans suggest that endothelial dysfunction is rarely limited to the penile vasculature, and that ED and CVD represent different manifestations of a common underlying vascular disorder. Furthermore, it appears that RAS activity contributes to the endothelial dysfunction that precedes clinical CVD and ED.

Does addition of ED to traditional cardiovascular risk factors improve CVD prediction?

The ability of ED to improve CVD prediction beyond traditional risk factors is a topic of debate. In a population-based study of 1248 men (mean age, 61 y) who were free from CVD at baseline, Schouten et al used a single, multiple-choice question to determine presence and severity of ED. Their data revealed that 22.8% had reduced erectile rigidity and 8.7% had severely reduced erectile rigidity. During an average of 6.3 years of follow-up, reduced erectile rigidity (compared with normal erections) was associated with a HR of 1.6 for cardiovascular events (acute myocardial infarction, stroke, or sudden death), after adjustment for age and Framingham Risk Score (FRS). Severely reduced erectile rigidity was associated with a HR of 2.6. Thus, in this population-based study, the presence of ED was a predictor of cardiovascular events independent of Framingham risk factors.

In a recent, prospective, population-based study of 1,709 men followed for a mean of 15 years, Araujo et al examined the association of ED with all-cause mortality

Table I. Studies addressing endothelial function in men with erectile dysfunction and no symptoms of cardiovascular disease

<table>
<thead>
<tr>
<th></th>
<th>Yavuzgil et al</th>
<th>Kaya et al</th>
<th>Kaiser et al</th>
<th>Chiurlia et al</th>
</tr>
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<tbody>
<tr>
<td>Patients, n</td>
<td>36</td>
<td>32</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Age, y</td>
<td>54 ± 9</td>
<td>55 ± 10</td>
<td>46 ± 2</td>
<td>51 ± 6.7</td>
</tr>
<tr>
<td>Test for ED</td>
<td>NA</td>
<td>NA</td>
<td>IIEF-5 (ED &gt;22)</td>
<td>IIEF-5 (ED &gt;22)</td>
</tr>
<tr>
<td>IIEF score</td>
<td>14.8 ± 3.5</td>
<td>9.1 ± 3.1</td>
<td>13.7 ± 1.2</td>
<td>12.7 ± 1.5</td>
</tr>
<tr>
<td>Penile Doppler PSV (cm/s)</td>
<td>NA</td>
<td>NA</td>
<td>28 ± 3</td>
<td>27.5 ± 3.5</td>
</tr>
<tr>
<td>Test for endothelium</td>
<td>BAFMD (upper arm)</td>
<td>BAFMD (forearm)</td>
<td>BAFMD (wrist)</td>
<td>BAFMD (forearm)</td>
</tr>
<tr>
<td>BAFMD, %</td>
<td>3.2 ± 3</td>
<td>6.0 ± 4</td>
<td>1.3 ± 0.3</td>
<td>2.3 ± 1.8</td>
</tr>
<tr>
<td>Post-NTG 0.4 mg/isosorbide dinitrate 5 mg sublingually, %</td>
<td>12.1 ± 6</td>
<td>12.8 ± 4.2</td>
<td>13 ± 1.4</td>
<td>8.36 ± 3.3</td>
</tr>
</tbody>
</table>

Adapted with permission from Eur Urol. 2006;50:727.

Table II. Can erectile dysfunction be used to reclassify Framingham risk?

<table>
<thead>
<tr>
<th>10-y CVD probability after inclusion of ED</th>
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<tbody>
<tr>
<td>&lt;5%</td>
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<tr>
<td>5 to &lt;10%</td>
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<tr>
<td>10 to &lt;20%</td>
</tr>
<tr>
<td>≥20%</td>
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<tr>
<td>Total</td>
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Among subjects who developed CVD within 10 years, 9 were reclassified to higher risk. Adapted with permission from J Am Coll Cardiol. 2010;55(4):350-356.
and cause-specific mortality. After adjustment for age; body mass index; alcohol consumption; physical activity; cigarette smoking; self-assessed health; and self-reported heart disease, hypertension, and diabetes, ED was associated with hazard ratios of 1.26 and 1.43 for all-cause and CVD mortality, respectively.44 These findings suggest that the association between ED and all-cause mortality is primarily driven by CVD mortality. In a subsequent analysis of the 1,057 men with complete risk factor data who were free of CVD and diabetes at baseline, Araujo et al evaluated whether ED predicts CVD beyond traditional risk factors.43 After adjustment for age and traditional CVD risk factors, ED was associated with increased incidence of CVD events (HR, 1.41). Addition of ED to the FRS, after adjustment for age, yielded a reclassification of 17 (11%) of 155 men who had CVD events within 10 years (Table II).43

In sum, the evidence strongly suggests that vasculogenic ED is a sign of future CVD events and has potential to alter the 10-year predictive capacity of the FRS. This may be especially true in the younger population, in whom the FRS is traditionally under-predictive of both 10-year and lifetime risk.45

### The future: ED, CVD, and prognostic markers of systemic vascular disease

Based on established relationships between endothelial dysfunction and CVD, as well as the potential bidirectional association between endothelial dysfunction and inflammation, pro-inflammatory markers have received considerable recent attention with respect to cardiovascular risk assessment.46,47 It has also come to light that most of these markers are up-regulated in men with ED, irrespective of the etiology of ED. For instance, among a wide range of proinflammatory and endothelial-prothrombotic markers, the combination of fibrinogen <225 mg/dL with interleukin-6 (IL-6) <1.24 pg/mL showed a very good negative predictive value for ED (91.7% [ie, very few false negative results]).48 Levels of high-sensitivity C-reactive protein (hsCRP) are significantly higher in men with ultrasonographically documented arteriogenic ED compared to subjects with normal penile arterial function.49 Furthermore, recent studies showed that improvement or normalization of sexual activity is associated with a favorable effect on markers of penile and peripheral endothelial function and pro-inflammatory biomarkers (hsCRP, IL-6).50,51 A routine measurement of these biomarkers, although useful, is not yet indicated.

Emerging independent markers of vasculogenic ED presence and severity include endothelial cell-derived factors that either participate in the regulation of corporal muscle tone (nitric oxide, endothelin-1, angiotensin II, C natriuretic peptide, asymmetric dimethyl-arginine) or indicate increased endothelial cell activation (intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-Selectin) and damage or repair (endothelin-1, monocyte oxidative activity, endothelial microparticles, endothelial progenitor cells).46

Tests that measure the atherosclerotic burden either in the coronary circulation (i.e., coronary calcium score by electron-beam computed tomography), coronary computed tomography angiography (CCTA), or in extracoronary vessels (ie, ankle brachial index, carotid intima-media thickness), along with functional arterial indices (flow-mediated dilatation) or mixed (functional and structural) arterial indices (aortic stiffness) are also considered surrogate markers of CVD.46 ED has been associated with several of the above-mentioned indices of atherosclerotic burden (Table III).38,53,54 Because ED represents an independent marker for cardiovascular events47 it would be clinically useful to identify potential
biomarkers that would predict future CVD events in the ED population. The biomarkers of generalized vascular disease discussed above are such candidates and, based on their predictive ability in various populations, they are expected to be predictive of CVD events in ED patients. For example, 2-year data from the Coronary CT Angiography Evaluation For Clinical Outcomes International Multicenter registry (n = 15,223) suggested that, among patients without known CAD, CCTA measures of both non-obstructive and obstructive CAD aided stratification of risk for major adverse cardiac events. However, with the exception of arterial stiffness (indirect support through pulse pressure data), relevant studies supporting the predictive value of the above-mentioned indices for cardiovascular events in ED patients have not been performed. Thus, routine use of these tests is not indicated at present.

Conclusion
The literature reviewed here unequivocally supports ED as a predictor of cardiovascular events. Because ED is a particularly strong predictor of CVD in younger and middle-aged men, identification of ED represents an important first step toward CVD risk detection and reduction. Although further studies are required to determine whether ED is a stronger predictor of CVD in diabetic than in non-diabetic patients, several studies indicate that diabetic men with ED are at greater cardiovascular risk than those without. Thus, we encourage physicians to inquire about ED symptoms in all men >50 years of age with cardiovascular risk factors, and in all men with DM2. Although not all men with ED are at increased cardiovascular risk, it is the clinician’s obligation to characterize cardiovascular risk through aggressive workup and diagnostics and to initiate intensive risk factor management in appropriate patients. Early identification of at-risk men has the potential to lower healthcare costs and improve outcomes. Additional studies are needed to determine whether change in erectile function can serve as a surrogate measure of treatment efficacy in preventive interventions for cardiac disease.

Potential conflicts of interest
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