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Erectile Dysfunction and the "Window of Curability": A Harbinger of Cardiovascular Events

In their landmark 2005 report of more than 9400 men, Thompson et al[1] posed the following questions: "With the high prevalence of erectile dysfunction in aging men, do pharmacologic, lifestyle, or behavioral interventions that are cardioprotective also reduce or delay onset of erectile dysfunction? Could erectile dysfunction serve as a surrogate measure of treatment efficacy in preventive interventions for cardiac disease?" Today, 4 years later, these questions remain unanswered.

In the Thompson et al study, as part of the Prostate Cancer Prevention Trial, men aged 55 years and older who were part of a placebo group (n=9457) were evaluated at 3-month intervals for erectile dysfunction (ED) and subsequent cardiovascular disease. At study entry, 4247 men did not have ED; during the course of 5 years, 2420 of these men developed incident ED (defined as the first report of ED of any grade). Incident ED (adjusted for other cardiovascular risk factors) was associated with a hazard ratio (HR) of 1.25 (95% confidence interval [CI], 1.04-1.53; P=.04) for subsequent cardiovascular events, including myocardial infarction, 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 ED or prevalent ED (ie, ED at study entry). Therefore, the authors were able to conclude that, in terms of an association with subsequent cardiovascular events, incident ED had an effect equal to or greater than family history of myocardial infarction, cigarette smoking, or hyperlipidemia.[1]

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That study lends further support to the theory that ED is predominantly a disease of vascular origin with endothelial cell dysfunction as the unifying link. Studies of men with diabetes have also supported this concept and in fact suggest that ED is a predictor of future cardiovascular events in this group. Gazzaruso et al[2] recruited 291 men with type 2 diabetes mellitus who had silent coronary artery disease (CAD) and found that those who developed major adverse cardiac events during the course of approximately 4 years were more likely to have ED (61.2%) than those who did not (36.4%). Through further multivariate analysis, ED remained an important predictor of adverse cardiac events, and although diabetic men have a high risk of cardiovascular disease, the risk is even higher in those who develop ED. In addition, in that study, statin use significantly reduced major cardiovascular events. Moreover, the use of phosphodiesterase type 5 (PDE5) inhibitor drugs was associated with a lower risk of adverse cardiac events, although multivariate analysis showed no statistical significance. The former observation is expected given the findings of recent large clinical trials such as the Collaborative Atorvastatin Diabetes Study (CARDS)[3] and Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER),[4] each showing a reduction in nonfatal myocardial infarctions and strokes with 10 mg of atorvastatin and 20 mg of rosuvastatin, respectively, in specific populations (those with diabetes in the former and those with elevated highly sensitive C-reactive protein levels in the latter).

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Ma et al[5] studied 2306 diabetic men with no clinical evidence of CAD, 27% of whom had ED. During the course of approximately 4 years, the incidence of coronary heart disease was greater in men with ED (19.7 per 1000 person-years) than in men without ED (9.5 per 1000 person-years). After adjustments for other covariables, including age, duration of disease, antihypertensive agents, and

albuminuria, ED remained an independent predictor of coronary heart disease (HR, 1.58; 95% CI, 1.08-2.30; *P*=.018).

Therefore, because ED and silent CAD are prevalent in the diabetic population, all health care professionals in primary care should inquire about sexual function in the diabetic patient and aggressively treat cardiovascular risk factors including dyslipidemia and hypertension. Indeed, the Second Princeton Consensus Panel[6] on sexual activity and cardiac risk published recommendations for initiating or resuming sexual activity and for managing sexual dysfunction in patients with cardiovascular disease. Given that most patients are at low risk, they can be encouraged to initiate or resume sexual activity and can be treated for sexual dysfunction (including ED). The consensus panel characterized some patients as having intermediate or indeterminate risk; this subset includes patients with the following:

- No overt cardiac symptoms including angina but 3 or more cardiovascular risk factors including sedentary lifestyle (but excluding sex)
- Moderate stable angina
- Recent myocardial infarction more than 2 weeks but less than 6 weeks before evaluation
- New York Heart Association class II heart failure with left ventricular ejection fraction less than 40%
- Noncardiac manifestations of atherosclerotic disease such as prior stroke or transient ischemic attack or history of peripheral arterial disease

According to the Second Princeton Consensus Panel, these patients with intermediate or indeterminate risk should receive further cardiac evaluation (such as stress testing, particularly those with sedentary lifestyle) to delineate the presence and severity of coronary disease before initiation of oral PDE5 therapy for ED.

In this issue of *Mayo Clinic Proceedings*, Nehra[7] reviews the association between ED and its well-known concomitant comorbidities in the context of the current knowledge of PDE5 inhibitors to evaluate both the safety and the efficacy of drug treatment. His analysis revealed compelling evidence for primary care physicians to address underlying cardiovascular health concerns in men presenting with ED. Nehra's review suggests that the degree of ED strongly correlates with the severity of cardiovascular disease and indeed that ED may be considered a sentinel marker for occult cardiovascular disease. It is recommended that physicians screen the ED patient for vascular disease, and since ED often coexists with the comorbidities of diabetes, hypertension, or dyslipidemia, screening in the urologist's office should also include measurements of blood glucose, lipids, and blood pressure, with likely referral to a primary care physician or cardiologist if results are abnormal.

What about the nondiabetic population? What does the presence of ED suggest in the lower-risk male population not yet studied? To address this issue, Inman et al[8] in this issue of *Mayo Clinic Proceedings* biennially screened during a 10-year period a random sample of 1402 community-dwelling men for the presence of ED; study participants had regular sexual partners and no known CAD. Men were followed up from the fourth screening round (1996) of the Olmsted County Study of Urinary Symptoms and Health Status Among Men until the first occurrence of an incident cardiac event or the last study visit (on or before December 31, 2005). Men with ED at study onset were excluded from the analyses. Multivariate proportional hazard regression models were used to assess the association of the covariables of age, diabetes, hypertension, smoking status, and body mass index with ED. Unlike the Thompson et al study or the other studies mentioned earlier, the participants of this study were neither a highly selected subset of the general male population nor exclusively older than 55 years; they were more representative of the overall male population (albeit predominantly white). In addition, erectile function of the study participants was assessed by an externally validated questionnaire, the Brief Male Sexual Function Inventory,[9] a self-report questionnaire consisting of 11 items rated on a scale of 0 to 4, with higher scores representing better sexual function.

ED was modeled as a time-dependent covariable 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 body mass index. Baseline prevalence of ED was 2% for men aged 40 years, 6% for men aged 50 years, 17% for men aged 60 years, and 39% for men older than age 70 years. New ED developed in 6% of the study population at 2 years of follow-up with increases of approximately 5% in each subsequent 2-year interval. Incident ED was more common in patients with cardiovascular risk and older age.[8]

Overall, new-onset CAD developed in 11% of men during the 10-year period, with approximately 15% experiencing myocardial infarction, 79% having angiographic anomalies, and 6% experiencing 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 (age 40-49 years), 5.09 (age 50-59 years), 10.72 (age 60-69 years), and 23.30 (age ≥70 years). For men with ED, the incidence densities for CAD were 48.52 (age 40-49 years), 27.15 (age 50-59 years), 23.97 (age 60-69 years), and 29.63 (age ≥70 years).[8]

The meaning of these findings is important. Although ED and CAD may be different manifestations of an underlying vascular pathology, when ED occurs in a younger man (<60 years), it is associated with a marked increase in

the risk of future cardiac events, whereas in older men it has less prognostic value. The importance of the study by Inman et al cannot be overstated. Although ED had little relationship to the impact on the development of incident cardiac events in men aged 70 years and older, it was associated with a nearly 50-fold increase in the 10-year incidence in men 49 years and younger. This raises the possibility of a "window of curability," in which progression of cardiac disease might be slowed or halted by medical intervention. Younger men with ED could provide the ideal populations for future studies of primary cardiovascular risk prevention.

Why younger than older men? 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. Montorsi et al[11] suggest that this phenomenon relates to the caliber of the blood vessels. For example, 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. An equally sized atherosclerotic plaque burden in the smaller penile arteries would more likely compromise flow earlier and cause ED compared with the same amount of plaque in the larger coronary artery causing angina. In another plausible explanation, Inman et al[8] suggest greater impairment in arterial endothelial cell function with age. The repetitive pulsations that the large central arteries are subjected to over their life span lead to fatigue and fracture of the elastic lamellae, resulting in increased stiffness.[12] Ultimately, small arteries such as the pudendal and penile arteries begin to degenerate, and end-organ ischemia results. In younger men 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.[5]

To answer the question by Thompson:[1] "Could erectile dysfunction serve as a surrogate measure of treatment efficacy in preventive interventions for cardiac disease?" Inman et al and Nehra suggest that further studies of cardiovascular disease prevention strategies in young men with ED are needed. Only then can we fully comprehend and make the most of a "window of curability" in which future cardiac events might be prevented.

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