

EDITORIAL COMMENT

Erectile Dysfunction

The New Harbinger for Major Adverse Cardiac Events in the Diabetic Patient*

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Erectile dysfunction (ED) was once thought of as a primarily psychological problem. Although this is true in some men, in the majority of men over the ages of 40 to 50 the problem is likely due to vascular disease, including the early stage of atherosclerosis, specifically endothelial dysfunction. If the blood vessels that supply blood to the corpora cavernosa of the penis cannot dilate in response to the appropriate signals, then an erection will not occur. Many of the risk factors for ED are the same as for other vascular diseases (such as coronary artery disease [CAD]) and include smoking, hypertension, dyslipidemia, diabetes, as well as lack of physical activity and obesity (1). Thus men with ED over the age of 40 commonly have some of these risk factors.

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A further development in the link between ED and cardiovascular disease has come from recent reports that ED might be a harbinger for major adverse cardiovascular events. Furthermore, ED remains a risk factor for developing these adverse cardiac events even after correcting for other known cardiovascular risk factors.

A classic study regarding this topic was published by Thompson et al. (2). As part of the Prostate Cancer Prevention Trial, men age 55 years or older who were part of a placebo group (n = 9,457) were evaluated at 3-month intervals for ED and cardiovascular disease. There were 4,247 men with no ED at study entry; 2,420 developed incident ED over 5 years. Incident ED (adjusted for other cardiovascular risk factors) was associated with a hazard ratio (HR) of 1.25 (95% confidence interval [CI] 1.02 to 1.53; p = 0.04) for subsequent cardiovascular events (including myocardial infarction, coronary revascularization,

cerebrovascular accident, transient ischemic attack, congestive heart failure, fatal cardiac arrest, or nonfatal cardiac arrhythmia requiring treatment). The adjusted HR was even higher (1.45; 95% CI 1.25 to 1.69; p < 0.001) for men with either incident or prevalent ED (i.e., had ED at study entry). The authors stated that incident ED “had an equal or greater effect on subsequent cardiovascular events of the same magnitude as a family history of myocardial infarction, cigarette smoking, or measures of hyperlipidemia” (2).

Blumentals et al. (3) studied the association between ED and myocardial infarction as part of a managed care database. There were 12,825 men with ED who were compared with an equal number without ED followed for almost 5 years. Those with ED had a 2-fold increased risk for acute myocardial infarction after adjusting for a number of confounding risk factors.

Both our group (4) and Montorsi et al. (5) showed that the prevalence of ED was high among men with known CAD. In the Montorsi et al. (5) study of 300 consecutive patients with acute chest pain and angiographically documented CAD, the prevalence of ED was 49%. Of 147 patients with both ED and CAD, the ED symptoms became clinically manifest before the CAD symptoms in 67% of patients, with a mean time interval between onset of ED and clinical symptoms of CAD of 39 months. Of note and relevant to the reports by Gazzaruso et al. (6) and Ma et al. (7) in this issue of the *Journal* is that in the Montorsi et al. (5) study all patients that had type 1 diabetes, ED, and CAD developed ED before symptoms of CAD.

The present issue of the *Journal* contains 2 complementary articles (6,7) that extend our knowledge of the link between ED and subsequent cardiovascular events. Gazzaruso et al. (6) recruited 291 type 2 diabetic males with silent CAD.

Those patients who developed major adverse cardiac events over the course of approximately 47 months were more likely to have ED (61.2%) versus those who did not (36.4%). On multivariate analysis, ED remained an important predictor of major adverse cardiac events. The authors point out that, although it is already known that diabetic patients have a high risk of cardiovascular disease, the risk is even higher in those diabetic patients that develop ED.

The article by Ma et al. (7) in this issue of the *Journal* studied a cohort of 2,306 diabetic men with no clinical evidence of CAD. At baseline 27% had ED. Over the course of approximately 4 years, the incidence of coronary heart disease was greater in men with ED (19.7/1,000 person-years) compared with those without ED (9.5/1,000 person-years). After adjustments for other covariates, age, duration of disease, antihypertensive agents, and albuminuria, ED remained an independent predictor of coronary heart disease (HR 1.58, 95% CI 1.08 to 2.30, p = 0.018).

Thus, both of these important studies suggest that in diabetic patients ED is a predictor of future cardiovascular events. Of course, this same statement might be true of a wider population of patients, as suggested by the other

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studies (1,3,5), but might be especially relevant to the diabetic population where ED is common, as is silent myocardial ischemia. Hence, physicians seeing diabetic patients should ask about ED and aggressively treat cardiovascular risk factors that these patients might have—including dyslipidemia and hypertension.

Why does ED seem to precede symptoms of CAD in patients with a vascular etiology for ED? Montorsi et al. (8) suggests that this phenomenon relates to the size or diameter 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 first compromise flow and cause ED compared with the same amount of plaque in the larger coronary artery causing angina. Another possibility, raised by Ma et al. (7), is that endothelium-dependent and endothelium-independent vasodilation are impaired in the diabetic patient before the onset of overt CAD. Impaired vasodilation without an anatomic atherosclerotic plaque narrowing the lumen of a penile artery is perhaps more likely to lead to ED than the same scenario in the coronary arteries leading to symptoms of angina.

Interesting features of the Gazzaruso et al. (6) study relate to the pharmacologic intervention received by the patients. In their study, statin use significantly reduced major adverse cardiac events. This observation is not unexpected. Recent large clinical trials such as the CARDS (Collaborative Atorvastatin Diabetes Study) trial showed that, even with a baseline low-density lipoprotein of approximately 117 mg/dl, 10 mg atorvastatin significantly reduced the incidence of nonfatal myocardial infarctions and strokes in diabetic patients (9). The surprising and somewhat hopeful new finding in the Gazzaruso et al. (6) study was the observation that there was a trend for phosphodiesterase type 5 (PDE5) inhibitor use to be associated with a lower rate of major adverse cardiac events (although this fell just short of being statistically significant). Gazzaruso et al. (6) reviews some of the potential mechanisms for a benefit of PDE5 inhibitors on the cardiovascular system, including an improvement in endothelial dysfunction. In addition, possible direct cardioprotective effects of the PDE5 inhibitors on ischemic/reperfused myocardium have now been described. Kukreja et al. (10,11) suggested that both sildenafil and vardenafil were capable of reducing myocardial infarct size in experimental animal models. Although sildenafil did not reduce anatomic myocardial infarct size in our rabbit model of 30 min of ischemia/reperfusion, it did have certain beneficial hemodynamic effects: reducing left ventricular end-diastolic pressure during ischemia, and reducing the ischemic bed's vascular resistance after ischemia/reperfusion (12). We did observe, in a rat model of coronary artery occlusion and reperfusion, a significant reduction in myocardial infarct size with the long-acting PDE5 antagonist tadalafil (13).

The pre-clinical results and findings of the study by Gazzaruso et al. (6) suggest the need for a long-term, randomized, placebo-controlled trial of PDE5 inhibitors in patients with risk factors for CAD in which end points are major adverse cardiac events. Although the PDE5 inhibitor sildenafil was initially studied as an antianginal agent and then went on to become approved for the treatment of ED and recently for pulmonary hypertension, study of the PDE5 inhibitors has come full circle. With evidence that PDE5 inhibitors improve endothelial function, slightly reduce blood pressure, and might have a primary cardioprotective effect, the time has come to study these agents systematically as potential therapies for the prevention of adverse cardiac events in patients with vascular risk factors.

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