

Erectile Dysfunction as a Predictor of Cardiovascular Events and Death in Diabetic Patients With Angiographically Proven Asymptomatic Coronary Artery Disease

A Potential Protective Role for Statins and 5-Phosphodiesterase Inhibitors

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Objectives	We sought to investigate whether erectile dysfunction (ED) is a predictor of future cardiovascular events and death in diabetic patients with silent coronary artery disease (CAD) and whether there are predictors of cardiovascular events and death among CAD diabetic patients with ED.
Background	Case-control studies showed that ED is associated with CAD in diabetic patients, but no prospective study is available.
Methods	Type 2 diabetic men (n = 291) with silent CAD angiographically documented were recruited. Erectile dysfunction was assessed by the International Index Erectile Function-5 questionnaire.
Results	During a follow-up period of 47.2 ± 21.8 months (range 4 to 82 months), 49 patients experienced major adverse cardiac events (MACE). The difference in ED prevalence between patients with and those without MACE was significant (61.2% vs. 36.4%; $p = 0.001$). Cox regression analysis showed that ED predicted MACE (hazard ratio [HR] 2.1; 95% confidence interval [CI] 1.6 to 2.6; $p < 0.001$). Among patients with CAD and ED, the Kaplan-Meier method showed that the statin (Mantel log-rank test: 3.921; $p = 0.048$) and 5-phosphodiesterase (5-PDE) inhibitor use (Mantel log-rank test: 4.608; $p = 0.032$) were associated with a lower rate of MACE. Cox regression analysis showed that statin use (HR 0.66; 95% CI 0.46 to 0.97; $p = 0.036$) reduced MACE. Treatment with 5-PDE inhibitors did not enter the model, but its p value was very near to the significant level (HR 0.68; 95% CI 0.46 to 1.01; $p = 0.056$).
Conclusions	Our data first show that ED is a powerful predictor of cardiovascular morbidity and mortality in diabetic patients with silent CAD and that the treatment with statins and 5-PDE inhibitors might reduce the occurrence of MACE among CAD diabetic patients with ED. (J Am Coll Cardiol 2008;51:2040-4) © 2008 by the American College of Cardiology Foundation

Several epidemiological studies showed that erectile dysfunction (ED) is associated with coronary artery disease (CAD) in both diabetic and nondiabetic subjects (1-3). Only 1 longitudinal report documented an association

between ED and CAD in the general population: in the placebo arm of the Prostate Cancer Prevention Trial, Thompson et al. (4) observed that prevalent and incident ED preceded coronary events. No prospective study is

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available in diabetic patients. We aimed at assessing whether ED is a predictor of cardiovascular events and death in diabetic patients with silent CAD and whether there are predictors of cardiovascular morbidity and mortality in CAD diabetic patients with ED.

Methods

A total of 317 consecutive male type 2 diabetic patients with type 1 silent CAD (according to Braunwald) angiographically documented were enrolled between November 1998 and February 2006. Some of the patients (97 subjects) were the same as in our previous report (3). The study population included patients who were diagnosed with silent CAD according to the American Diabetes Association (ADA) guidelines (5). An exercise stress testing was performed in diabetic patients with conditions and/or risk factors suggested by the aforementioned guidelines (5). In patients with any condition that did not permit maximal exercise testing (such as severe obesity, foot wound, and so on) a dipyridamole stress testing was performed. When an exercise electrocardiogram (ECG) test was highly positive, the suspicion of CAD was considered strong. In patients with a positive exercise ECG test, exercise stress thallium scintigraphy was performed. Procedures for stress testing and scintigraphy and criteria to consider stress testing as positive or highly positive were reported elsewhere (6,7). In patients with a highly positive exercise ECG or a positive scintigraphy or a positive dipyridamole stress testing, a diagnostic coronary angiography was recommended. Angiography was performed as previously described (2). A coronary lesion was considered significant when a stenosis $\geq 50\%$ of the lumen was documented. We used the same exclusion criteria as reported in our previous studies (3,6,7). The study was approved by the ethics committee. All patients gave their informed consent both to perform each test and to participate in the study.

As in our previous studies (2,3,6,7), diabetes was diagnosed according to ADA criteria and hypertension was diagnosed according to European Society of Hypertension/European Society of Cardiology criteria. Patients with albumin excretion rate (AER) < 30 mg/day were considered normoalbuminuric; patients with an albumin excretion rate between 30 and 299 mg/day were considered microalbuminuric. Patients were considered smokers if current smokers or ex-smokers. A family history of CAD was considered positive in the presence of a documented myocardial ischemia or infarction in a first-degree relative. Body mass index was calculated by the following formula: kg/m^2 . Autonomic function was assessed as previously reported (7).

Venous blood samples were taken from subjects after fasting for 12 h. Cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured by an automatic analyzer HITACHI 737 (Tokyo, Japan). High-density lipoprotein cholesterol was calculated by the Friedewald's formula. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HPLC) (Bio-rad, Richmond, California). The albumin excretion rate was measured by nephelometry (Beckmann, Milan, Italy).

ED assessment. Presence and degree of ED were assessed by the validated International Index Erectile Function-5 (IIEF-5) questionnaire (8). Erectile dysfunction was con-

sidered present when the IIEF-5 score was ≤ 21 (8). Only patients who filled in the questionnaire in the year before the detection of CAD were enrolled.

Follow-up. Among 317 patients, 15 (4.7%) were lost at follow-up and 11 (3.5%) were excluded from the study because they had restenosis after percutaneous transluminal coronary angioplasty within 6 months. Of the 15 patients lost at follow-up, 5 had ED, whereas 7 of the 11 patients excluded from the study had ED. So, 291 patients with complete follow-up data were included in the study. The CAD was treated as judged appropriate by the cardiologists on the basis of angiographic CAD severity. Of 291 patients, 176 underwent coronary bypass, 48 coronary angioplasty, and 67 were treated with pharmacological therapy alone. Follow-up included periodic control visits in the outpatient diabetes clinic (every 3 to 4 months) and in the outpatient cardiology unit (every 6 to 12 months). At the beginning and during the follow-up, all patients were treated aggressively with the purpose of reducing every cardiovascular risk factor according to the current guidelines. So, appropriate lifestyle changes were suggested and pharmacological treatments, including statins, antihypertensive and antidiabetic drugs, antiplatelet agents, and antianginal drugs, were prescribed. In particular, according to current guidelines, most patients were treated at baseline with angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers (84.5%) and statins (61.5%). These percentages did not change significantly during the follow-up.

The end point was the occurrence of major adverse cardiac events (MACE). The following were considered to be MACE: CAD death, sudden death, nonfatal myocardial infarction, death due to congestive heart failure, unstable angina, need for repeat revascularization (aside from restenosis), stroke or transient ischemic attack (TIA), and symptomatic peripheral artery disease (PAD) documented by angiography. Myocardial infarction was diagnosed on the basis of clinical symptoms, ECG changes, and cardiac enzyme elevations. Unstable angina was defined as a hospital stay because of an episode of prolonged chest pain at rest associated with ischemic changes but no rise in biomarkers. Transient ischemic attack was defined by physician diagnosis of any sudden focal neurological deficit that cleared definitively within 24 h.

Any information regarding potential MACE was validated by source data, including hospital record forms, death certificates, and other documents. Periodic contacts with general practitioner and telephone interviews were undertaken to evaluate the occurrence of MACE.

Statistical analysis. We assessed differences in normal variables by the Student *t* test and differences in non-normal

Abbreviations and Acronyms

- 5-PDE** = 5-phosphodiesterase
- CAD** = coronary artery disease
- CI** = confidence interval
- ECG** = electrocardiogram
- ED** = erectile dysfunction
- HR** = hazard ratio
- IIEF-5** = International Index Erectile Function-5
- MACE** = major adverse cardiac events

