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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 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.

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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 ≥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) (Biorad, 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 considered 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.

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

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

variables by the Mann-Whitney *U* test. The Pearson chi-square test was used for frequency comparison. Survival curves were estimated by the Kaplan-Meier test and compared by the Mantel log-rank test. The effect of several variables on the occurrence of MACE was tested by the stepwise Cox regression analysis. Before the analysis, lipid parameters were adjusted for body mass index, smoking, statin use, presence of hypertension, and microalbuminuria by an analysis of covariance. The following variables were tested: age, diabetes duration, hypertension, family history of CAD, smoking, microalbuminuria, glycated hemoglobin, body mass index, cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, ED, and autonomic dysfunction. Variables were dichotomized as previously reported (3). Hazard ratios (HR) with a 95% confidence interval (CI) were computed to identify significant predictors of MACE. A p value <0.05 was considered statistically significant.

Results

Table 1 shows the features of the whole study population at baseline and of the patients stratified by the presence/absence of ED and MACE.

Occurrence of MACE. The follow-up period duration was defined as the period of time up to the occurrence of the first MACE or up to the last information obtained. Mean follow-up period was 47.2 ± 21.8 months (range 4 to 82 months). During the follow-up period 49 patients had MACE: Table 1 reports MACE distribution. Patients with ED experienced a significantly greater incidence of MACE as compared with patients without ED.

Potential impact of pharmacological treatment on the occurrence of MACE. The potential impact of several classes of drugs on the occurrence of MACE was evaluated. In particular, no difference in the percentage of patients treated with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, insulin, diabetes oral agents, diuretics, calcium-channel blockers, or platelet antiaggregants at baseline was found between patients with and without ED or between patients with and without MACE (data not shown). No difference in the percentage of patients treated with statins was observed between patients with and without ED (60.2% vs. 62.4%; p = 0.697). Nevertheless, the percentages of patients treated with statins was signifi-

Table 1 Biological and Clinical Features of the Whole Study Population With Silent CAD at Baseline, of Patients With and Without ED, and of Patients With and Without MACE

	All	ED	No ED	p Value*	MACE	No MACE	p Value†
n	291	118	173		49	242	
Age (yrs)	54.8 ± 7.3	54.2 ± 7.2	55.1 ± 7.4	0.307	54.5 ± 7.7	54.8 ± 7.2	0.764
Duration of diabetes (yrs)	8.2 ± 5.8	9.4 ± 5.5	7.3 ± 5.8	0.003	7.6 ± 5.1	8.3 ± 5.9	0.454
BMI	27.5 ± 3.9	27.6 ± 4.5	27.4 ± 3.5	0.581	27.4 ± 4.2	27.5 ± 3.8	0.936
HbA1c (%)	7.3 ± 1.1	7.3 ± 1.0	7.3 ± 1.2	0.584	7.6 ± 1.0	7.2 ± 1.1	0.069
Cholesterol (mg/dl)	209.6 ± 29.1	209.7 ± 27.3	209.4 ± 30.3	0.953	211.5 ± 28.6	209.2 ± 29.2	0.615
LDL (mg/dl)	134.5 ± 28.0	134.0 ± 26.3	134.9 ± 29.2	0.799	138.6 ± 25.5	133.7 ± 28.5	0.262
HDL (mg/dl)	43.6 ± 9.5	43.9 ± 8.3	43.4 ± 10.2	0.689	43.2 ± 10.4	43.7 ± 9.3	0.706
Triglycerides (mg/dl)	157.0 ± 57.5	158.8 ± 56.2	155.8 ± 58.5	0.660	148.4 ± 54.2	158.8 ± 58.1	0.251
Multivessel disease (%)	43.6	38.1	47.4		40.8	44.2	
Bivessel disease (%)	32.6	38.1	28.9	0.200	30.6	33.0	0.680
Monovessel disease (%)	23.7	23.8	23.7		28.6	22.8	
Microalbuminuria (%)	55.7	72.8	43.9	<0.001	85.7	49.6	<0.001
Smokers (%)	65.3	67.8	63.6	0.458	65.3	65.3	0.998
Family history of CAD (%)	44.7	44.1	45.1	0.863	46.9	44.2	0.726
Hypertension (%)	59.1	63.6	56.1	0.202	61.2	58.7	0.740
Autonomic neuropathy (%)	17.2	24.6	12.1	0.005	36.7	13.2	<0.001
ED (%)	40.5	100	0		61.2	36.4	0.001
Total MACE (%)	14.3	25.4	11.0	0.001	100	0	
MACE distribution (n)							
Total events and deaths	49	30	19		49	0	
CAD deaths	3	1	2		3	0	
Sudden deaths	2	1	1		2	0	
Nonfatal MI	14	8	6		14	0	
Deaths due to CHF	1	1	0		1	0	
Unstable angina	8	6	2		8	0	
Repeat revascularization	3	2	1		3	0	
Stroke or TIA	16	10	6		16	0	
Peripheral artery disease	2	1	1		2	0	

*Erectile dysfunction (ED) versus no ED. †Major adverse cardiac events (MACE) versus no MACE.
BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; HbA1c = glycated hemoglobin; TIA = transient ischemic attack.

cantly lower in patients with than in those without MACE (40.8% vs. 65.7%; p = 0.001).

Multivariate analysis. The Kaplan-Meier method showed that ED was associated with a higher rate of MACE (log-rank test: 41.847; p < 0.001) (Fig. 1). Univariate logistic regression showed an association between ED and MACE: HR 2.8; 95% CI 1.5 to 5.2; p = 0.002. A multivariate Cox regression analysis showed that ED was the only predictor of MACE: HR 2.1; 95% CI 1.6 to 2.6; p < 0.001.

Subgroup analysis. To identify possible predictors of MACE in ED patients, the analysis of this subgroup was performed. Table 2 shows features of ED patients with and without MACE. Also in this subgroup, the potential impact of the aforementioned classes of drugs on the reported occurrence of MACE was evaluated, but no difference was found between patients with and without MACE. The percentage of patients treated with statins was significantly lower among ED patients with than among those without MACE (33.3% vs. 69.3%; p = 0.0005). Among the 118 ED patients, 37.3% were treated with 5-phosphodiesterase (5-PDE) inhibitors at baseline. Interestingly, the percentage of ED patients treated with 5-PDE inhibitors was significantly lower among patients with than among those without MACE (20.0% vs. 43.2%; p = 0.0234).

The Kaplan-Meier method showed that, among ED patients, microalbuminuria (log-rank test: 6.087; p = 0.014) was associated with a higher rate of MACE, whereas statin (log-rank test: 3.921; p = 0.048) and 5-PDE inhibitor use (log-rank test: 4.608; p = 0.032) were associated with a lower rate of MACE. Figure 2 shows the Kaplan-Meier curve according to 5-PDE inhibitor use. Univariate logistic regression showed an association of MACE with statin (HR 0.2; 95% CI 0.1 to 0.5; p = 0.001) and 5-PDE inhibitor use (HR 0.3; 95% CI 0.1 to 0.9; p = 0.028).

A Cox regression analysis showed that predictors of MACE were microalbuminuria (HR 1.56; 95% CI 1.02 to 2.36; p = 0.036) and statin use (HR 0.66; 95% CI 0.46 to 0.97; p = 0.036); 5-PDE inhibitor use did not enter the

Table 2 Biological and Clinical Features of ED Patients With and Without MACE

	MACE	No MACE	p Value
n	30	88	
Age (yrs)	54.5 ± 7.7	54.2 ± 7.0	0.823
Duration of diabetes (yrs)	8.0 ± 5.3	9.8 ± 5.6	0.131
BMI	27.7 ± 4.7	27.6 ± 4.4	0.934
HbA1c (%)	7.2 ± 1.0	7.4 ± 1.1	0.659
Cholesterol (mg/dl)	210.2 ± 30.0	209.5 ± 26.5	0.916
LDL (mg/dl)	136.4 ± 24.6	133.2 ± 27.0	0.574
HDL (mg/dl)	42.6 ± 9.5	44.3 ± 7.9	0.352
Triglycerides (mg/dl)	155.5 ± 57.8	159.9 ± 55.9	0.711
Multivessel disease (%)	40.0	37.5	
Bivessel disease (%)	26.7	37.0	0.224
Monovessel disease (%)	33.3	20.5	
Microalbuminuria (%)	90.0	67.1	0.015
Smokers (%)	66.7	68.2	0.878
Family history of CAD (%)	46.7	43.2	0.739
Hypertension (%)	70.0	61.4	0.396
Autonomic neuropathy (%)	46.7	17.1	0.001
Total MACE (%)	100	0	

HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; other abbreviations as in Table 1.

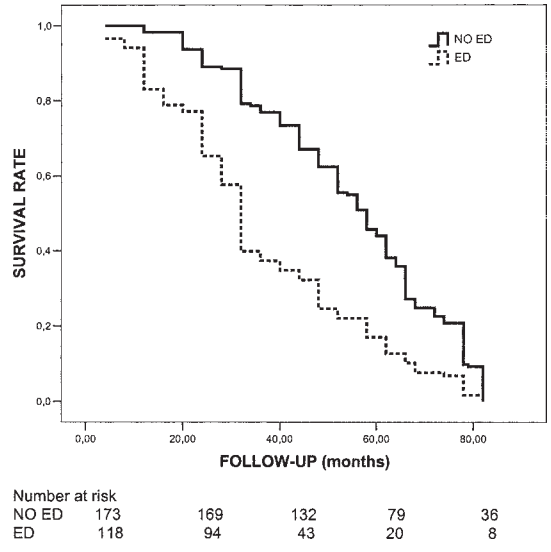

Figure 1 Kaplan-Meier Analysis in Diabetic Patients With Silent Coronary Artery Disease

Event-free survival estimate according to presence/absence of erectile dysfunction (ED).

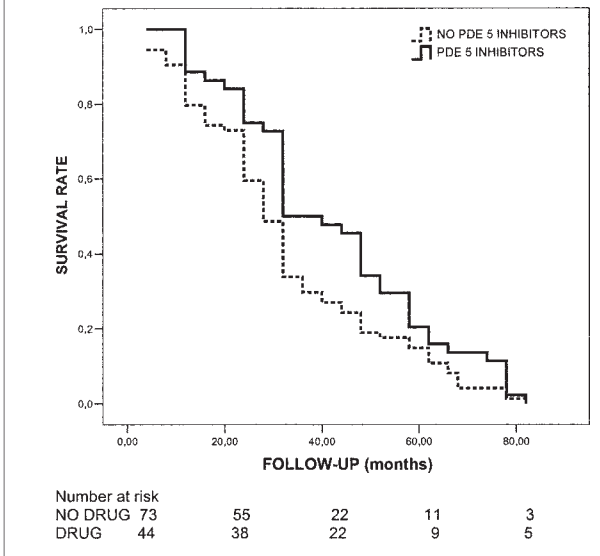

Figure 2 Kaplan-Meier Analysis in Diabetic Patients With Silent CAD and ED

Event-free survival estimate according to the use of 5-phosphodiesterase (5-PDE) inhibitors. CAD = coronary artery disease; ED = erectile dysfunction.

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).

Discussion

No study investigated the impact of ED on cardiovascular morbidity and mortality in a population at very high cardiovascular risk with a high prevalence of ED like diabetic patients with CAD. The finding that ED is a powerful predictor of MACE in our population might be of clinical interest. Indeed, our study suggests that, although all diabetic patients are at high cardiovascular risk, those with ED might be at particularly very high risk. This might imply that, in diabetic patients with ED, specific and aggressive programs to prevent cardiovascular events should be performed. Thus it is intriguing to understand how to reduce the cardiovascular risk in ED patients. We found that the use of statins could protect against the occurrence of MACE in ED patients. This might owe both to high-density lipoprotein cholesterol reduction and to the so-called pleiotropic effects attributed to statins (9). Among these pleiotropic effects there is the improvement in endothelial dysfunction (9), which seems to be the link between ED and atherothrombosis (1).

Another original finding is that PDE-5 inhibitors might protect against the development of MACE in CAD diabetic patients with ED. Both Kaplan-Meier and univariate analysis show an association between PDE-5 inhibitor use and lower risk of MACE, although in multivariate analysis PDE-5 inhibitor use does not attain statistical significance. The relatively small subgroup of ED patients and the fact that our study is not interventional might explain this result, even if the p value was very near to the significance level. Anyway, PDE-5 inhibitors might really reduce the cardiovascular risk for several reasons. Indeed, these drugs were born as antianginals, and they are able to improve endothelial dysfunction (10,11). Furthermore, recent studies demonstrated that 5-PDE inhibitors can have several cardioprotective effects and they seem to provide potential pathophysiological mechanisms by which these drugs might reduce the cardiovascular risk (10,11). So, our findings could not be surprising and, if confirmed by specific intervention studies, they might imply that in patients with stable CAD PDE-5 inhibitors not only are not contraindicated but might even play a major role in the prevention of cardiovascular events.

Conclusions

In conclusion, our study shows that ED is a powerful predictor of MACE in diabetic patients at very high cardiovascular risk, namely with CAD angiographically proven. Additional studies should confirm our findings in other populations. Among diabetic patients with silent CAD and ED, statins and PDE-5 inhibitors might reduce cardiovascular morbidity and mortality.

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