Erectile Dysfunction and Later Cardiovascular Disease in Men With Type 2 Diabetes

Prospective Cohort Study Based on the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) Trial

G. David Batty, PhD,*†‡ Qiang Li, MBIOSTAT,† Sébastien Czernichow, MD, PhD,†§ Bruce Neal, MD, PhD,† Sophia Zoungas, MD, PhD,†∥ Rachel Huxley, PhD,† Anushka Patel, MD, PhD,† Bastiaan E. de Galan, MD, PhD,†¶ Mark Woodward, PhD,†# Pavel Hamet, MD, PhD,** Stephen B. Harrap, MD, PhD,†† Neil Poulter, MD, PhD,‡‡ John Chalmers, MD, PhD,† on behalf of the ADVANCE Collaborative Group

Glasgow and London, United Kingdom; Sydney and Melbourne, Australia; Bobigny, France; Nijmegen, the Netherlands; New York, New York; and Montreal, Quebec, Canada

Objectives
The aim of this study was to examine the relationship between erectile problems in men and cardiovascular disease (CVD) mortality.

Background
Although there are plausible mechanisms linking erectile dysfunction (ED) with coronary heart disease (CHD) and stroke, studies are scarce.

Methods
In a cohort analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial population, 6,304 men age 55 to 88 years with type 2 diabetes participated in a baseline medical examination when inquiries were made about ED. Over 5 years of follow-up, during which study members attended repeat clinical examinations, the presence of fatal and nonfatal CVD outcomes, cognitive decline, and dementia was ascertained.

Results
After adjusting for a range of covariates, including existing illness, psychological health, and classic CVD risk factors, relative to those who were free of the condition, baseline ED was associated with an elevated risk of all CVD events (hazard ratio: 1.19; 95% confidence interval: 1.08 to 1.32), CHD (hazard ratio: 1.35; 95% confidence interval: 1.16 to 1.56), and cerebrovascular disease (hazard ratio: 1.36; 95% confidence interval: 1.11 to 1.67). Men who experienced ED at baseline and at 2-year follow-up had the highest risk for these outcomes.

Conclusions
In this cohort of men with type 2 diabetes, ED was associated with a range of CVD events. (J Am Coll Cardiol 2010; 56:1908–13) © 2010 by the American College of Cardiology Foundation
vascular (3–5). Thus, risk factors for erectile dysfunction (ED) (e.g., smoking, raised blood pressure, obesity) appear to be the same as those for cardiovascular disease (CVD) (3), and the occurrence of erectile dysfunction rises monotonically with a progressive clustering of these indexes.

Erectile dysfunction appears to be associated with increased risk for clinical events of CVD (6,7), coronary heart disease (CHD) (8–10), and stroke (9), but prospective cohort studies, which provide the best observational evidence of a relationship are very scarce. We address this paucity of evidence by using data from cohort analyses of a large, well-characterized, randomized controlled trial.

Methods

The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial, described in detail elsewhere (11), was designed to investigate the separate effects of routine blood pressure lowering and intensive blood glucose control on vascular outcomes in patients with existing type 2 diabetes. In brief, from 2001 to 2003, 12,877 men and women age 55 to 88 years with type 2 diabetes and histories of major macrovascular or microvascular disease, or at least 1 other cardiovascular risk factor, were recruited from 215 centers in 20 countries. After an initial “run-in” phase, 11,140 subjects (6,407 men) were randomized using a factorial design to perindopril-indapamide or placebo and to intensive blood glucose control on the basis of gliclazide modified release or to standard blood glucose control. The flow of patients through the study is depicted in Figure 1. For the purposes of the present study, data from the trial were analyzed on the basis of a prospective cohort study design, as we have done previously (12). Approval to conduct the trial was obtained from the ethics committee of each study center; all participants provided written informed consent.

Baseline examination. At study induction, participants responded to questionnaire inquiries and took part in a medical examination. Glycosylated hemoglobin, blood cholesterol (and fractions), blood pressure, resting heart rate, and serum creatinine were measured using standard protocols. Height and weight were used to derive body mass index (kg/m²). Nurses administered a series of questions regarding ethnicity, educational attainment, physical activity, alcohol intake, cigarette smoking habit, major chronic
disease, assistance with activities of daily living, medications used to control diabetes (e.g., gliclazide modified release, metformin) and related conditions (e.g., beta-blockers, thiazide). The presence of minor psychiatric disorders (anxiety and depression) was ascertained using the EQ-5D (13,14). Cognitive function was assessed using the Mini-Mental State Examination, on which low scores indicate impaired cognitive function was assessed using the Mini-Mental State Examination.Subjects with scores <24, or in whom the nurse suspected dementia, were referred to a medically qualified specialist for diagnosis of dementia according to Diagnostic and Statistical Manual of Mental Disorders criteria (16), if applicable. To maintain accurate self-reported information, those with either contemporaneous or prior diagnoses of dementia did not enter the study. Nurses also asked all male subjects whether they had ED (categorized as “yes” or “no”).

**Ascertainment of CVD, dementia, and cognitive impairment during follow-up.** Fatal and nonfatal CVD outcomes were ascertained using a variety of sources. Information on cause of death (certification, autopsy report, clinical notes) was scrutinized by the Endpoint Adjudication Committee and a coding made according to the 10th revision of the International Classification of Diseases (17). For nonfatal outcomes, when applicable, clinical notes, computed tomographic and magnetic resonance imaging reports (for suspected stroke), laboratory biomarkers (e.g., creatine kinase, troponins) and electrocardiographic reports (for suspected myocardial infarction) were used. A CHD event was denoted by death due to this condition (including sudden death), nonfatal myocardial infarction, silent myocardial infarction, coronary revascularization, or hospital admission for unstable angina (18). A cerebrovascular event was defined as a death due to this condition or nonfatal stroke, transient ischemic attack, or subarachnoid hemorrhage (18). The protocol used to identify dementia at follow-up was the same as that for baseline (described previously). Cognitive decline was defined as a reduction in Mini-Mental State Examination score of 3 or more points compared with baseline score.

**Statistical analyses.** Baseline data were missing for 103 men, resulting in an analytical sample of 6,304. Having first determined that the proportional hazards assumption had not been violated, Cox models were used to estimate hazard ratios, with accompanying 95% confidence intervals, to summarize the association between erectile function and the various health outcomes (19). Hazard ratios were first computed separately in the treatment and placebo groups. With no indication that treatment allocation modified the

### Table 1 Erectile Dysfunction and Baseline Characteristics in Men in the ADVANCE Trial (n = 6,304)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No (n = 3,146)</th>
<th>Yes (n = 3,158)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline examination (yrs)</td>
<td>64.8 ± 6.3</td>
<td>67.0 ± 6.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at completion of education (yrs)</td>
<td>19.8 ± 7.4</td>
<td>19.0 ± 7.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>7.4 ± 1.5</td>
<td>7.5 ± 1.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.2 ± 7.0</td>
<td>171.2 ± 7.3</td>
<td>0.843</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.8 ± 4.5</td>
<td>28.2 ± 4.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Total blood cholesterol (mmol/l)</td>
<td>5.0 ± 1.1</td>
<td>4.9 ± 1.1</td>
<td>0.002</td>
</tr>
<tr>
<td>High-density lipoprotein blood cholesterol (mmol/l)</td>
<td>1.19 ± 0.3</td>
<td>1.19 ± 0.3</td>
<td>0.634</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>143.8 ± 20.9</td>
<td>145.8 ± 21.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>81.6 ± 11.0</td>
<td>81.0 ± 10.7</td>
<td>0.026</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>73.4 ± 12.5</td>
<td>73.0 ± 12.4</td>
<td>0.283</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>91.9 ± 22.1</td>
<td>94.7 ± 26.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Cognitive function (MMSE score)</td>
<td>28.8 ± 1.7</td>
<td>28.5 ± 1.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Quality of life (EQ-5D score)</td>
<td>0.86 ± 0.2</td>
<td>0.82 ± 0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>7.5 ± 6.2</td>
<td>8.5 ± 6.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of occasions of exercise ≥15 min/week</td>
<td>4.0 ± 6.3</td>
<td>3.3 ± 5.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of alcoholic drinks/week</td>
<td>4.5 ± 9.7</td>
<td>5.0 ± 9.8</td>
<td>0.057</td>
</tr>
<tr>
<td>Caucasian/European ethnicity</td>
<td>1,852 (58.9%)</td>
<td>2,037 (64.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current cigarette smokers</td>
<td>604 (19.2%)</td>
<td>485 (15.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of metformin or beta-blockers</td>
<td>2,210 (70.2%)</td>
<td>2,227 (70.5%)</td>
<td>0.814</td>
</tr>
<tr>
<td>Require assistance with daily activities</td>
<td>67 (2.1%)</td>
<td>111 (3.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of major macrovascular disease</td>
<td>1,060 (33.7%)</td>
<td>1,267 (40.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of major microvascular disease</td>
<td>280 (8.9%)</td>
<td>385 (12.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of major diabetic disease</td>
<td>183 (5.8%)</td>
<td>267 (8.5%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD or as n (%). *A history of major macrovascular disease was defined as any of the following: stroke, myocardial infarction, hospital admission for transient ischemic attack, hospital admission for unstable angina, coronary revascularization, peripheral revascularization, or amputation secondary to vascular disease. †A history of major microvascular disease was defined as any of the following: macroleucominuria (urinary albumin/creatinine ratio > 300 μg/mg), proliferative diabetic retinopathy, retinal photocoagulation therapy, macular edema, or blindness in 1 eye thought to be caused by diabetes.

ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation; MMSE = Mini-Mental State Examination.
association of ED with the outcomes (p for interaction >0.10), data were pooled, and all analyses were adjusted for treatment.

In subgroup analyses of men who did not develop any of the outcomes of interest between baseline and follow-up at 24 months (n = 5,427), we examined the possibility that new erectile problems may be related to CVD and other outcomes. On the basis of the dichotomous questionnaire responses from baseline and 24-month follow-up, we therefore derived 4 groups: men without erectile dysfunction at either time point (referent group), men who had erectile problems at baseline but reported no such dysfunction at follow-up, men who developed erectile dysfunction between baseline and follow-up, and men who had ED at both baseline and follow-up (“unrelenting” erectile dysfunction). All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

**Results**

In Table 1, we show the baseline characteristics of study participants according to erectile dysfunction status. One-half of the men in the ADVANCE trial (3,158 of 6,304) reported ED at the baseline examination. With few exceptions, men with ED had less favorable levels of baseline CVD risk factors, morbidity, and drug use than those reporting no such problems. However, although statistically significant at conventional levels because of the large sample size, absolute differences in these characteristics between men with and without ED were generally modest in magnitude. Men with ED were older, were heavier, and had lower cognitive function. These men were also more likely to have chronic ill health as indexed by a range of baseline indexes. Although men with ED were also less likely to be physically active, contrarily, they were less likely to smoke and had lower total blood cholesterol, and diastolic blood pressure.

During a mean of 5 years of follow-up, there were 695 deaths from any cause, 1,579 fatal and nonfatal CVD events, 773 fatal and nonfatal CHD events, 411 fatal and nonfatal cerebrovascular disease events, 58 incident cases of dementia, and 1,013 cases of cognitive decline. In Table 2 we show the relation between ED and a range of health outcomes. Considering first the outcomes of total mortality, CVD, CHD, and cerebrovascular disease, it is unsurprising that, with both exposure and outcomes strongly age related, controlling for age had a marked attenuating effect on all the hazard ratios. In analysis adjusted for age and treatment group, relative to men who were free of erectile problems at baseline, those with ED had an elevated risk of between 34% and 53%. Adjusting for existing illness and medication led to some attenuation in these effects. Of the CVD risk factors, adding the psychological indexes (quality of life and cognitive function) to the multivariate model appeared to explain some of the effect of erectile problems on total mortality, all CVD events, and all CHD and
cerebrovascular events. After multiple adjustment for a range of baseline characteristics, some attenuation was again apparent, but with the exception of total mortality, gradients held at conventional levels of statistical significance. Erectile problems were associated with increased risk for both these outcomes, but most effect estimates were not statistically significant at conventional levels.

Finally, we examined the association of change in erectile function status between baseline and 24-month follow-up with the future risk for new events and deaths in a subsample of the population who remained free of these outcomes during this 2-year period (Table 3). For total mortality, CVD, CHD, and cerebrovascular disease, as anticipated, the highest rates were evident in men whose symptoms of ED persisted between baseline and follow-up 24 months later, although the confidence intervals for total mortality included unity. Similar patterns of association were apparent for dementia and cognitive decline, although the number of events for the former was very low.

**Discussion**

The main finding of this study was that ED was associated with total mortality, CVD, CHD, and cerebrovascular disease. Although controlling for the classic CVD risk factors (smoking, and raised blood pressure and blood cholesterol) had little impact on the magnitude of these gradients, marked attenuation was apparent when other covariates, such as existing illness, medication, and psychological distress, were added to the multivariate model. However, statistical significance at conventional levels was typically retained.

Prior studies. Our finding that ED apparently confers an increased risk for CHD is supported in the few other prospective cohort studies conducted, which were generally less well controlled than our own and, with few exceptions (9), markedly smaller in scale. To our knowledge, only 1 other study examined the role of erectile problems in the etiology of stroke (9), and that too found a positive association.

Plausible explanations. Potential noncausal explanations for the apparent impact of ED on these chronic CVD outcomes include bias and confounding. In the present study, dropout by the original study members was very low. We also adjusted for a very wide range of confounding variables, and these gradients, although attenuated, remained statistically significant at conventional levels. The effect that remained for ED in relation to the various outcomes is probably too large to be explained by residual confounding in this well-characterized study, but we of course cannot rule out the explanatory power of unmeasured or unknown covariates.

The absence of convincing alternative explanations for these associations raises the possibility of a real effect of ED on the outcomes herein. One obvious possibility is that ED results from peripheral neuropathy, that is, damage to nerves of the peripheral nervous system. Another option is that, given that the penis is an extensively vascularized organ, erections are, to a large degree, vascular events. With the penile (1 to 2 mm) arteries being substantially narrower than the coronary (3 to 4 mm), carotid (5 to 7 mm), and femoral (6 to 8 mm) arteries (20), as described, for the same quantity of atherosclerosis, erectile dysfunction may precede a similar vascular event in the heart.

**Study strengths and limitations.** Although the present study has a number of strengths, including the detailed range of covariates collected, the large sample size, repeat measurement of ED, and the fact that it is the first to examine links with dementia and cognitive function, it of course also has its limitations. Although it may be testimony to the robustness of the relation that a very simple question regarding erectile dysfunction was linked to CVD, we did not capture information on the severity of exposure by, for instance, using the International Index of Erectile Dysfunction (21). This would have allowed us to examine dose-response effects.

**Conclusions**

We demonstrated associations between ED and a range of CVD outcomes. However, rather than having a direct, independent effect on CVD, it is more likely that erectile dysfunction is a marker of CVD risk.

**Author Disclosures**

Dr. Batty is a Wellcome Trust Career Development Fellow (WBS U.1300.00.006.00012.01). Dr. Czernichow is supported by a fellowship from the Institut Servier and Assistance Publique-Hôpitaux de Paris. Dr. Neal has received
consultant fees from Pfizer, Roche, Takeda, and Pepsico; lecture fees from Amgen, AstraZeneca, GlaxoSmithKline, Pfizer, Roche, Sanofi-Aventis, Servier, and Tanabe; and research support from Johnson & Johnson, Merck Schering Plough, Servier, and United Healthcare Group. Dr. Zounigas has received honoraria for speaking engagements as well as travel expenses from Servier. Dr. Huxley holds a Career Development Award from the National Heart Foundation of Australia. Dr. Patel has received grants from Servier, Sanofi-Aventis, Dr. Reddy’s laboratories, and Pfizer; lecture fees from Servier, Sanofi-Aventis, Pfizer, Abbott, and AstraZeneca; and travel grants from Pfizer, Servier, and Dr. Reddy’s laboratories. Dr. Hamet is a consultant for Servier, Bellow Health, Pfizer, Bristol-Myers Squibb, Eli Lilly, Cybiocare, BioK; speaker fees from Merck Frosst, Bristol-Myers Squibb, Servier, Novartis, Sanofi-Aventis, Bayer, and AstraZeneca; grants from CIHR, CFI, Canada Research Center, Pfizer, and Genome Canada/Quebec; and is the CEO of Programix Inc. Medipharmagen. Dr. Harrap has received honoraria from Servier. Dr. Poulter has received research grants from Pfizer, Servier, Memorum, and Novartis. Dr. Chalmers has received research grants from Servier. All other authors have reported that they have no relationships to disclose.

Reprint requests and correspondence: Dr. G. David Batty, UCL Epidemiology and Public Health, 1-19 Torrington Place, London WC1E 6BT, United Kingdom. E-mail: david.batty@ucl.ac.uk.

REFERENCES


Key Words: coronary heart disease • epidemiology • erectile dysfunction • stroke.