Erectile Dysfunction and Subsequent Cardiovascular Disease

Ian M. Thompson, MD; Catherine M. Tangen, DrPH; Phyllis J. Goodman, MS; Jeffrey L. Probstfield, MD; Carol M. Moinpour, PhD; Charles A. Coltman, MD

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ABSTRACT

Context The risk factors for cardiovascular disease and erectile dysfunction are similar.
Objective To examine the association of erectile dysfunction and subsequent cardiovascular disease.
Design, Setting, and Participants Men aged 55 years or older who were randomized to the placebo group (n = 9457) in the Prostate Cancer Prevention Trial at 221 US centers were evaluated every 3 months for cardiovascular disease and erectile dysfunction between 1994 and 2003. Proportional hazards regression models were used to evaluate the association of erectile dysfunction and cardiovascular disease. In an adjusted model, covariates included age, body mass index, blood pressure, serum lipids, diabetes, family history of myocardial infarction, race, smoking history, physical activity, and quality of life.
Main Outcome Measures Erectile dysfunction and cardiovascular disease.
Results Of the 9457 men randomized to placebo, 8063 (85%) had no cardiovascular disease at study entry; of these men, 3816 (47%) had erectile dysfunction at study entry. Among the 4247 men without erectile dysfunction at study entry, 2420 men (57%) reported incident erectile dysfunction after 5 years. After adjustment, incident erectile dysfunction was associated with a hazard ratio of 1.25 (95% confidence interval [CI], 1.02-1.53; *P* = .04) for subsequent cardiovascular events during study follow-up. For men with either incident or prevalent erectile dysfunction, the hazard ratio was 1.45 (95% CI, 1.25-1.69; *P*<.001). For subsequent cardiovascular events, the unadjusted risk of an incident cardiovascular event was 0.015 per person-year among men without erectile dysfunction at study entry and was 0.024 per person-year for men with erectile dysfunction at study entry. This association was in the range of risk associated with current smoking or a family history of myocardial infarction.
Conclusions Erectile dysfunction is a harbinger of cardiovascular clinical events in some men. Erectile dysfunction should prompt investigation and intervention for cardiovascular risk factors.

METHODS

More than 10 million men in the United States are affected by erectile dysfunction, with an estimated 100 million men affected worldwide.[1,2] The risk of erectile dysfunction is related to many factors, including age, smoking, diabetes, heart disease, depression, and hypertension.[3,4] Because cardiovascular disease and erectile dysfunction share etiologies as well as pathophysiology (endothelial dysfunction) and because of evidence that degree of erectile dysfunction correlates with severity of cardiovascular disease, it has been postulated that erectile dysfunction is a sentinel symptom in patients with occult cardiovascular disease.[5]To examine this hypothesis, we studied a cohort of men who were assessed prospectively for both of these diseases over the course of 7 years.
This analysis is based on data from the Prostate Cancer Prevention Trial, a prospective, blinded, randomized controlled trial designed to examine the hypothesis that administration of finasteride would reduce the prevalence of prostate cancer over a period of 7 years.[6] Beginning in 1994, 18 882 men were randomly assigned to receive either placebo or finasteride, 5 mg/d. Eligible men were aged 55 years or older, had a prostate-specific antigen level of less than 3.0 ng/mL, had normal digital rectal examination findings, and had no history of prostate cancer. There were no eligibility requirements related to sexual function or cardiovascular disease, but at least a 10-year life expectancy was required. During a 3-month

placebo run-in, men who reported an increase of more than 2 toxicity grades from baseline for sexual functioning were ineligible for randomization. During 7 years of treatment, men were followed up annually with prostate-specific antigen measurement and digital rectal examination. Biannual visits included an update on general health issues, a compliance assessment based on the number of tablets of study medication taken, and queries regarding adverse effects. Three-month telephone calls between clinic visits queried men regarding interval adverse effects and medical events, including cardiovascular events. All participants provided written informed consent and the study was approved by the institutional review boards of the participating institutions.

Because of potential sexual adverse effects of finasteride, study coordinators specifically asked participants about 3 issues: erectile dysfunction, decrease in libido, and decreased volume of ejaculate. Erectile dysfunction was graded as follows: grade 0, absent; grade 1, decrease in normal function but ability to achieve vaginal penetration with difficulty; or grade 3, no erections. Additionally, participants completed a yearly survey[4] addressing sexual problems and activities. For example, the survey included questions such as “Over the previous 4 weeks, how much of a problem was it to get or keep an erection?” (not a problem [grade 0], a bit of a problem or somewhat of a problem [grade 1], or very much of a problem [grade 3]). An end-point review committee evaluated all nonprostate primary cancers and all deaths. Deaths were categorized as due to prostate cancer, other primary cancer, a cardiovascular event, or other causes.

As a component of the study safety monitoring, cardiovascular complications were also evaluated. These outcomes were identified using definitions from *International Classification of Diseases, Ninth Revision*codes for cardiovascular disease, cerebrovascular disease, and sudden death. Nonfatal cardiovascular events were reported by participants or study investigators and were not confirmed by physician notes nor centrally reviewed. For this study, we defined cardiovascular disease as any of the following events: myocardial infarction or surgical treatment of coronary artery disease including coronary artery bypass graft or angioplasty, angina, cerebrovascular accident, transient ischemic attack, congestive heart failure graded at a minimum of mild, fatal cardiac arrest, or nonfatal cardiac arrhythmia defined as a minimum of an arrhythmia requiring treatment. The date of cardiovascular event was recorded as the date of clinic visit or telephone call when first reported.

For this analysis, we examined only the cohort of men in the study's placebo group. Men with a history of congestive heart failure, myocardial infarction, angina, transient ischemic attack, arrhythmia, or stroke were excluded to evaluate incident cardiovascular disease. Incident erectile dysfunction was defined as the first report of erectile dysfunction of any grade. Men with erectile dysfunction of any grade at study entry were excluded from analyses that evaluated the association of incident erectile dysfunction with cardiovascular events. For analyses of incident or prevalent erectile dysfunction, men with erectile dysfunction at study entry were also included.

A proportional hazards regression model was used to evaluate the association of erectile dysfunction with cardiovascular disease. A separate model was fit to each of the 6 cardiovascular events (angina, myocardial infarction, cerebrovascular accident, transient ischemic attack, congestive heart failure, or cardiac arrhythmia), then an additional outcome was created (cardiovascular event) to evaluate the global cardiovascular hypothesis and was defined as the first occurrence of any of these cardiovascular end points. Time to death from any cause was also assessed.

To evaluate the association of incident erectile dysfunction with cardiovascular disease, a time-dependent model was used to model the exposure of erectile dysfunction. A time-dependent covariate takes into account that all patients start with no erectile dysfunction but that some individuals will develop erectile dysfunction during the course of the study. This method accounts for both occurrence and chronology of erectile dysfunction. For incident or prevalent erectile dysfunction analyses, men with erectile dysfunction at baseline start with an erectile dysfunction indicator coded as “yes” at time 0 in contrast with those who are coded as having incident erectile dysfunction at the time it is first reported during the study. Erectile dysfunction must have been reported in at least 1 contact (typically, 3 months) prior to the reporting of the cardiovascular event to be considered a preceding event.

Two models were fit for each type of cardiovascular event: unadjusted and covariate-adjusted. For the unadjusted model, only the time-dependent covariate of erectile dysfunction is included. For the covariate-adjusted model, we also include a number of potential confounders. The following covariates were assessed at study entry: age, body mass index,

systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, history of diabetes, parent or sibling with a history of myocardial infarction, race (white vs other), current smoking, current use of antihypertensive medication, physical activity (moderate or very active vs sedentary or light), and global, self-reported health status (excellent or very good vs fair or poor).[4] Race was determined in the Prostate Cancer Prevention Trial because of the increased risk of prostate cancer among African American men. Race was self-selected from a prespecified list. Only 1 category could be chosen. All covariates are included in most of the adjusted models. However, for models fit to the outcome of time to congestive heart failure, no covariate adjustment was performed because of the low event rate. For some models with modest event rates, a smaller subset of covariates was included based on identification from a stepwise model.

Interval from erectile dysfunction to first cardiovascular event was calculated using the Kaplan-Meier method. For this analysis, only men with incident erectile dysfunction who had not experienced an incident cardiovascular event prior to developing erectile dysfunction were included, and the time to cardiovascular event was defined as the time between initial report of erectile dysfunction and first cardiovascular event. Men without anevent were censored at their last assessment date, with a maximum follow-up time for all participants of 7 years ± 90 days. SAS statistical software, version 9.0 (SAS Institute Inc, Cary, NC) was used for all analyses. $P \leq .05$ was considered statistically significant.

RESULTS

Of 9457 eligible men randomized to the study placebo group, 8063 (85%) had no cardiovascular disease at study entry. Of these men, 3816 (47%) reported some level of erectile dysfunction at study entry and were excluded from analyses that assess the association of incident erectile dysfunction with cardiovascular events. Among the 4247 men with no erectile dysfunction at study entry, 2420 (57%) reported incident erectile dysfunction after 5 years, and this increased to 65% at 7 years. Table 1 describes these men with and without erectile dysfunction at study entry. In general, this clinical trial recruited a higher proportion of white men and men who were healthier, more active, and better educated relative to the general population at risk of cardiovascular disease.[4] Seventy-six percent of men participated in all 7 years of the study.

Table 1. Characteristics at Study Entry by Erectile Dysfunction Status for Men With No History of Cardiovascular Disease Events*

Table 2. Relationship of Incident ED and Incident Cardiovascular Disease Without and With Adjustment for Covarates.

Table 2. shows the relationship between the first report of erectile dysfunction and subsequent cardiovascular disease with and without adjustment for covariates. Incident erectile dysfunction was statistically significantly associated with subsequent angina, myocardial infarction, and stroke. With covariate adjustment, risk of angina remained statistically significant (*P* = .04) while risk of stroke was suggestive (*P* = .06; Table 2). Men with incident erectile dysfunction had a significantly increased risk of myocardial infarction or angina relative to men without a report of erectile dysfunction after adjusting for potential confounders (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.06-1.76; *P* = .02). Because only 11% of the men who had a myocardial infarction also had previously reported angina, there was little overlap of these 2 events.

Table 3. Relationship of Incident or Prevalent (Baseline) ED and Incident Cardiovascular Disease Without and With Adjustment for Covarates.

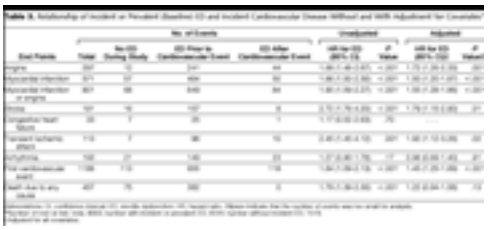
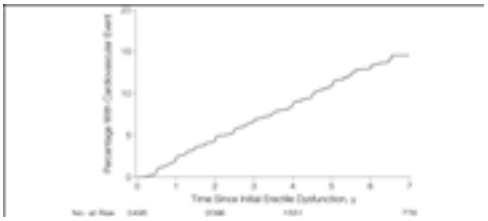


Table 3 shows the association of incident or prevalent erectile dysfunction with incident cardiovascular disease. These analyses also include men who reported erectile dysfunction at the time of study randomization, thus nearly doubling the population analyzed. The results are similar to **Table 2**, but the HRs tend to be larger. The largest effect was seen with transient ischemic attack, with an HR for prevalent or incident erectile dysfunction of 1.92 (95% CI, 1.12-3.26; *P* = .02). The adjusted HR for any cardiovascular event was 1.45 (95% CI, 1.25-1.69; *P*<.001).

It is probable that incident and prevalent erectile dysfunction in study participants was multifactorial. Since decreased libido due to androgen deficiency may have occurred in some men with erectile dysfunction, we evaluated whether the association of erectile dysfunction with cardiovascular disease differed if men with erectile dysfunction and decreased libido were excluded from the analysis. We thus excluded men who had reported a significant reduction in libido prior to reporting any erectile dysfunction, then evaluated the association of incident erectile dysfunction with first report of cardiovascular disease. A significant reduction in libido was defined as grade 3 or 4 (moderate to severe decrease in desire for sexual activity and moderate effect on frequency of intercourse, or no desire for sexual activity and no intercourse). Only 1% of men in the placebo group reported a significant decrease in libido prior to incident erectile dysfunction and, as a result, this subset analysis was virtually identical to that found in Table 2 for any cardiovascular event (unadjusted HR for erectile dysfunction, 1.47; 95% CI, 1.22-1.78; *P*<.001; adjusted HR, 1.28; 95% CI, 1.03-1.57; *P* = .04). The Figure provides estimates of incident cardiovascular disease in men who developed incident erectile dysfunction during the study and prior to any cardiovascular event. One year after initial report of erectile dysfunction, 2% of the men had experienced an initial cardiovascular event while, by 5 years, 11% had had cardiovascular events. Because of the

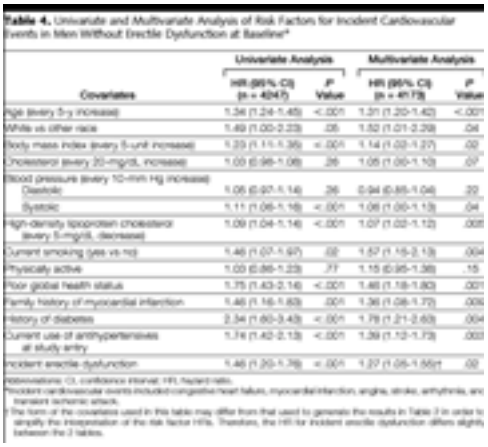
changing number of men at risk of cardiovascular end points in the 2 groups (erectile dysfunction vs no erectile dysfunction) over time, the HRs reported in Tables 2, 3, and 4 are a more valid expression of the differential risk in the groups. Nonetheless, it is possible to contrast the 2 groups by comparing the number of events per person-year exposed. The unadjusted risk of an incident cardiovascular event among men without erectile dysfunction at study entry was 0.015 per person-yearcompared with 0.024 per person-year for those with erectile dysfunction.

Figure, Time to Any Cardiovascular Event From Initial Report of Erectile Dysfunction for Those With Incident Erectile Dysfunction and No Previous Cardiovascular Event.
At risk, n = 2495; number of cardiovascular events, 255; 5-year estimate of cardiovascular events,11%.



To place the association of erectile dysfunction and cardiovascular disease into perspective with traditional risk factors for cardiovascular disease, we conducted a multivariate assessment of these risk factors and incident cardiovascular events for participants without erectile dysfunction at baseline (Table 4). These data demonstrate that incident erectile dysfunction 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.

Table 4. Univariate and Multivariate Analysis of Risk Factors for Incident Cardiovascular Events in Men Without Erectile Dysfunction at Baseline*



COMMENT

Cardiovascular disease is the leading cause of death in the United States, accounting for nearly 40% of all deaths. In men, 50% of deaths due to coronary heart disease occur in men without a history of the disease.7Compelling data now allow the identification of risk factors for cardiovascular disease that can be modified with pharmacologic and behavioral interventions.8- 14 Identification of a predictive symptom or finding could allow even earlier intervention, possibly further reducing morbidity and mortality due to the disease.15 This

would be especially useful for men who do not have regular medical assessments or who are inadequately assessed or treated for cardiovascular disease risk factors.

The association between erectile dysfunction and cardiovascular disease has previously been recognized.[16]Patients with cardiovascular disease frequently describe preexisting erectile dysfunction.[17] Risk factors for both disease processes include obesity, tobacco use, physical inactivity, diabetes, hypertension, and hyperlipidemia.[18] These patients must be clearly distinguished from those who have neither cardiovascular disease nor cardiovascular risk factors and have a defect in the peripheral vascular generating nitric oxide-3′-5′-cyclic guanosine monophosphate system in smooth muscle that is independent of other systemic vascular disease.[19]

It has been suggested, but never demonstrated, that early treatment of coronary heart disease risk factors may reduce the later risk of erectile dysfunction.[20] Furthermore, it has been hypothesized that erectile dysfunction is a harbinger of cardiovascular disease.[21,22] In a study of men with diabetes with vs without erectile dysfunction, erectile dysfunction was the most efficient predictor of coronary artery disease.[23] A large-scale study of 25 650 men found a 75% increased risk of peripheral vascular disease in men with preexisting erectile dysfunction.[24]

Although the link between erectile dysfunction and cardiovascular disease has been previously documented, convincing evidence of the direction and magnitude of the effect has not been available. The Prostate Cancer Prevention Trial provided an opportunity to assess the relationship between erectile dysfunction and subsequent cardiovascular disease in a prospective study. Because the study drug had a risk of sexual adverse effects, we queried study participants regularly regarding sexual function. Additionally, monitoring of cardiovascular events was a prespecified element of the study. Our analysis of men in the placebo group of this study demonstrates the substantial association between incident as well as prevalent erectile dysfunction and subsequent cardiovascular disease, including angina, myocardial infarction, stroke, and transient ischemic attack. Previous studies have suggested this association but have not prospectively monitored a group of asymptomatic, healthy men for development of erectile dysfunction and then for subsequent cardiovascular events.

Although it may seem surprising that 47% of men reported some degree of erectile dysfunction at study entry and that 57% of men without erectile dysfunction reported this symptom after 5 years, the high prevalence of erectile dysfunction has been previously reported. In a population of men aged 40 to 70 years, the mean probability of impotence was 52%, and the rate tripled between ages 40 and 70 years.[25]

A limitation of this analysis was that only 1 of the 2 patient-reported sexual function measures was validated, the Sexual Problems Scale,[26] while the sexual activity measure was developed for purposes of the trial. For this analysis, we used the participant report of erectile dysfunction from the validated measure, the Sexual Problems Scale. In 1992, when this study was developed, measures such as the International Index of Erectile Function were not yet developed. Such measures would have provided a greater measure of accuracy in the degree of erectile dysfunction as well as other domains related to sexual function, such as orgasm and libido.[27,28] Nevertheless, a comparison of the International Index of Erectile Function with a single-question measure of erectile dysfunction similar to that used in this study found good correlation between the 2 instruments in the classification of men with and without erectile dysfunction.[29]

A second study limitation was that data on medications that may cause erectile dysfunction or that are used to treat erectile dysfunction were not consistently collected. Data on use of medications for treating hypertension were collected at baseline (Table 1), but we did not have information on men who started taking antihypertensive agents (or other agents that could cause erectile dysfunction) during the course of the study. We also did not routinely collect information on use of medications to treat erectile dysfunction, such as sildenafil. Although it is possible that agents used for the treatment of erectile dysfunction may have increased the risk of cardiovascular events, a pooled analysis of studies of sildenafil found no increased risk of myocardial infarction or cardiovascular death with this agent.[30]

The implications of this study are substantial. With the availability of effective pharmacotherapy, an increasing number of men are seeking care for erectile dysfunction. It is estimated that more than 600 000 men aged 40 to 69 years in the United States develop erectile dysfunction annually.[3] Our data suggest that the older men in this group have about a 2-fold greater risk of cardiovascular disease than men without erectile dysfunction. With 70% to 89% of sudden cardiac deaths occurring in men and with many men not having regular

physical examinations, this analysis suggests that the initial presentation of a man with erectile dysfunction should prompt the evaluating physician to screen for standard cardiovascular risk factors[8,9] and, as appropriate, initiate cardioprotective interventions.[7]
Several questions arise from our findings. Since erectile dysfunction is such a predictor of cardiovascular disease in asymptomatic men, what evaluation should be prompted by this symptom? The Princeton Consensus Panel Guidelines on management of sexual dysfunction suggest that patients are at low risk of cardiovascular disease if they are asymptomatic and have 3 or fewer cardiovascular disease risk factors, as long as hypertension is controlled.[31] The inference is that no cardiovascular workup is necessary for these men. A specialized cardiovascular evaluation is suggested for men with more than 3 cardiovascular disease risk factors (excluding age and sex) in asymptomatic individuals.[31] Two additional questions arise. 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? Also, could erectile function serve as a surrogate measure of treatment efficacy in preventive interventions for cardiac disease?
Our data provide the first evidence, to our knowledge, of a strong association between erectile dysfunction and subsequent development of clinical cardiovascular events. Acknowledging this association over a 5-year period and the high prevalence of vasculogenic/atherogenic etiologies in men of this age, the presenting symptom of erectile dysfunction should prompt an assessment of cardiovascular risk factors and vigorous interventions as appropriate. While a full cardiovascular evaluation is not necessary in response to findings of erectile dysfunction in asymptomatic patients, such findings should prompt diligent observation of at-risk men and reinforces the need for intervention for cardiovascular risk factors.

ARTICLE INFORMATION

Corresponding Author: Ian M. Thompson, MD, Department of Urology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78229 (thompsoni@uthscsa.edu).
Author Contributions: Dr Tangen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Thompson, Tangen, Goodman, Coltman.
Acquisition of data: Thompson, Goodman, Probstfield.
Analysis and interpretation of data: Thompson, Tangen, Goodman, Probstfield, Moinpour.
Drafting of the manuscript: Thompson, Tangen, Probstfield, Moinpour.
Critical revision of the manuscript for important intellectual content: Thompson, Tangen, Goodman, Probstfield, Coltman.
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