

# Sex Differences in Risk for Coronary Heart Disease Mortality Associated With Diabetes and Established Coronary Heart Disease

Sundar Natarajan, MD, MSc; Youlian Liao, MD; Guichan Cao, MS; Stuart R. Lipsitz, ScD; Daniel L. McGee, PhD

**Background:** The sex-specific independent effect of diabetes mellitus and established coronary heart disease (CHD) on subsequent CHD mortality is not known.

**Methods:** This is an analysis of pooled data (n=5243) from the Framingham Heart Study and the Framingham Offspring Study with follow-up of 20 years. At baseline (1971-1975), 134 men and 95 women had diabetes, while 222 men and 129 women had CHD. Risk for CHD death was analyzed by proportional hazards models, adjusting for age, hypertension, serum cholesterol levels, smoking, and body mass index. The comparative effect of established CHD vs diabetes on the risk of CHD mortality was tested by testing the difference in log hazards.

**Results:** The adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for death from CHD were 2.1 (95%

CI, 1.3-3.3) in men with diabetes only, and 4.2 (95% CI, 3.2-5.6) in men with CHD only compared with men without diabetes or CHD. The HR for CHD death was 3.8 (95% CI, 2.2-6.6) in women with diabetes, and 1.9 (95% CI, 1.1-3.4) in women with CHD. The difference between the CHD and the diabetes log hazards was +0.73 (95% CI, 0.72-0.75) in men and -0.65 (95% CI, -0.68 to -0.63) in women.

**Conclusions:** In men, established CHD signifies a higher risk for CHD mortality than diabetes. This is reversed in women, with diabetes being associated with greater risk for CHD mortality. Current treatment recommendations for women with diabetes may need to be more aggressive to match CHD mortality risk.

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From the Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC (Dr Natarajan); the Center for Health Care Research (Dr Natarajan), Department of Medicine (Dr Natarajan), and Department of Biometry and Epidemiology (Drs Liao and Lipsitz and Ms Cao), Medical University of South Carolina, Charleston; and Department of Statistics, Florida State University, Tallahassee (Dr McGee). The authors have no relevant financial interest in this article.

**C**ORONARY HEART disease (CHD) remains the leading cause of mortality and morbidity in developed countries,<sup>1</sup> with approximately 30% dying of their first CHD event,<sup>2</sup> emphasizing the need for aggressive preventive strategies. Recent data indicate that individuals with diabetes (but without established CHD) have as high a risk for fatal CHD as persons with established CHD (but without diabetes).<sup>3</sup> Prior studies have shown that diabetes has greater impact on women's risk for CHD than on men.<sup>4</sup> National data indicate that men with diabetes have seen a slower decline in heart disease mortality than men without diabetes while women with diabetes have noted an increase in heart disease mortality,<sup>5</sup> emphasizing the need to further understand the sex-specific magnitude of risk associated with diabetes.

Guidelines from national organizations such as the American Diabetes Association<sup>6</sup> recommend aggressive management of other CHD risk factors in patients with diabetes, with the initiation

threshold and goals of treatment equivalent to the goals for patients with established CHD. Though diabetes has a greater effect on CHD mortality in women compared with men,<sup>7</sup> the magnitude of sex differences in CHD mortality in individuals with diabetes, particularly in comparison to an accepted marker of increased risk like established CHD, have not been elucidated. To determine this, evaluation of a population sample with both men and women in the study is needed. The specific aims of this investigation were (1) to evaluate the independent effect of diabetes and established CHD on subsequent CHD mortality and (2) to determine the differential sex-specific effects of diabetes on CHD mortality compared with established CHD.

## METHODS

### STUDY DESIGN AND STUDY SAMPLE

This analysis used public use cohort data involving participants from the Framingham Heart Study<sup>8</sup> or the Framingham Offspring

Study<sup>9</sup> who were 35 to 74 years old during 1970-1975. The examination at which the participants had their complete lipid profile determined was defined as the baseline. This corresponds to the first examination of the Framingham Offspring Study and the 11th examination for most in the Framingham Heart Study (others had it in the 10th or 12th examination).

## MEASUREMENTS

Coronary heart disease was defined as myocardial infarction, coronary insufficiency, or angina pectoris. The outcome measure was CHD mortality, which was ascertained by a panel of clinical investigators by reviewing records that included detailed history, clinical findings, electrocardiograms, autopsy reports, and death certificates.<sup>10</sup> Briefly, CHD death was categorized as either sudden or nonsudden death. Sudden death was defined as death within 1 hour from onset of symptoms where the death could not reasonably be attributed to some other non-CHD cause. Nonsudden death was diagnosed if the terminal episode lasted longer than 1 hour, the available documentation suggested CHD as the cause, and no other cause could be ascribed.

Participants were considered to have probable diabetes based on 2 casual plasma glucose levels greater than 150 mg/dL (8.3 mmol/L) or the use of hypoglycemic medications (insulin or oral hypoglycemic agents) in the Framingham Heart Study. These individuals then had their records reviewed (including glucose tolerance tests) by the investigators and a final diagnosis of diabetes was made based on corroborating evidence. A fasting plasma glucose level greater than 140 mg/dL (7.8 mmol/L) or the use of hypoglycemic agents defined diabetes in the Framingham Offspring Study.

Smoking status was obtained by self-report and participants were classified as current smokers (regular smoking in the year prior to the visit) and nonsmokers. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or taking anti-hypertensive medications.<sup>11</sup> Lipid measures included total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Height and weight were measured during each visit and body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

## STATISTICAL ANALYSIS

The analyses were performed separately by sex. Baseline characteristics were compared for the 4 CHD and diabetes groups: neither CHD nor diabetes, CHD only, diabetes only, and both CHD and diabetes. Life-table analysis was used to determine the cumulative CHD mortality rate and to produce CHD mortality curves for the 4 groups. Coronary heart disease mortality was adjusted for baseline age using the direct method and a log-rank test was used to test the differences in survival.

The independent effect of diabetes or established CHD on CHD mortality was determined using proportional hazards models.<sup>10</sup> All multivariate analyses were adjusted for age, hypertension, smoking, serum cholesterol (either total and HDL-C or LDL-C and HDL-C), and BMI. The risk of CHD death for the 3 CHD and diabetes groups (CHD alone, diabetes alone, and both CHD and diabetes) was evaluated using persons without diabetes or CHD as the reference. To determine the effect of CHD severity on subsequent CHD mortality, patients with CHD were classified into more severe (myocardial infarction) and less severe (coronary insufficiency or angina pectoris) categories and evaluated as independent variables, along with diabetes and other covariates, in a multivariate proportional hazards model.

Bootstrap resampling was used to compare the CHD and diabetes proportional hazards regression coefficients on the risk of death from CHD.<sup>12</sup> Two separate models were fit for each bootstrap sample. The first model contained CHD and all of the covariates while the second model contained diabetes and all of the covariates. The coefficients for CHD and diabetes were calculated for each bootstrap sample. One thousand bootstrap samples were drawn and we used the empirical distribution of these samples to calculate a 95% confidence interval (CI) for the difference in regression coefficients.

To further evaluate sex differences in the effect of diabetes and established CHD on CHD mortality, sex-diabetes, sex-CHD, diabetes-CHD interactions as well as the sex-diabetes-CHD interaction were tested in a hierarchical Cox model combining men and women. All analyses were performed using the Statistical Analysis System.<sup>13</sup>

## RESULTS

**Table 1** presents the baseline characteristics of the pooled sample. Of 5336 participants aged 35 to 74 years, 93 were not included in the analysis because of missing data. Among the 2494 men and 2749 women, 134 men and 95 women had diabetes, while 222 men and 129 women had CHD. Compared with women with CHD only, women with diabetes only had a higher proportion of smokers, higher BMI, were younger, and had similar blood pressures and lipid levels. Men with diabetes only were younger, had slightly higher BMI, similar proportion of smokers, lower total cholesterol and LDL-C levels, and similar blood pressure compared with men with CHD only. The distribution of the type of CHD differs in men and women, with fewer than half the prevalent CHD cases in men being classified as angina and about two thirds of CHD cases in women classified as angina.

The age-adjusted CHD mortality curves for men and women are displayed in the **Figure**. The CHD mortality for participants with both diabetes and CHD was substantially greater than other groups. The age-adjusted 20-year CHD mortality was 58% in men and 34% in women. Men with CHD alone had a significantly greater CHD mortality than men with diabetes alone (log-rank test,  $P < .001$ ), with CHD mortality of 44% and 23%, respectively, at 20 years. This was reversed in women, with diabetic women being at greater risk for CHD mortality than women with only CHD (log-rank test,  $P < .05$ ), with CHD mortality of 19% and 6%, respectively, at 20 years. Though men had higher overall cumulative CHD mortality than women, the age-adjusted CHD mortality rate for women with diabetes was higher than men without diabetes and approached the rate for men with diabetes.

To evaluate the risk of CHD mortality attributable to diabetes and/or established CHD, proportional hazards regression analyses adjusted for age and other covariates were undertaken (**Table 2**). After multivariate adjustment, the hazard ratio (HR) for CHD death in men with diabetes only was 2.1 (95% CI, 1.3-3.3) while it was 4.2 (95% CI, 3.2-5.6) in men with CHD only. In women, the corresponding HRs were 3.8 (95% CI, 2.2- 6.6) and 1.9 (95% CI, 1.1-3.4), respectively. The results were very similar when LDL-C instead of total cholesterol was included in the model.

**Table 1. Baseline Characteristics of the Study Sample\***

Variable	Men				Women			
	Diabetes		No Diabetes		Diabetes		No Diabetes	
	CHD	No CHD	CHD	No CHD	CHD	No CHD	CHD	No CHD
Participants, No. (%)	31 (1.2)	103 (4.1)	191 (7.7)	2169 (87.0)	20 (0.7)	75 (2.7)	109 (4.0)	2545 (92.6)
Age, y	62.6 ± 6.8	55 ± 10.2	59.4 ± 8.9	50.7 ± 10.1	62.7 ± 8.8	58.9 ± 10.1	64.4 ± 6.9	51.9 ± 10.3
BMI	27 ± 2.7	28.4 ± 4.3	26.8 ± 3.7	27 ± 3.5	29 ± 9	29.1 ± 6.3	26.9 ± 5.2	25.4 ± 4.4
Current smoking, %	48	47	46	47	45	37	16	38
Total cholesterol, mg/dL	226 ± 43	210 ± 47	223 ± 42	216 ± 39	234 ± 48	247 ± 48	252 ± 49	222 ± 44
HDL-C, mg/dL	39 ± 10	41 ± 11	41 ± 12	45 ± 13	48 ± 16	49 ± 13	54 ± 17	58 ± 16
LDL-C, mg/dL	145 ± 38	134 ± 33	147 ± 42	141 ± 35	140 ± 45	162 ± 44	166 ± 45	141 ± 40
Systolic BP, mm Hg	140 ± 23	143 ± 23	141 ± 20	133 ± 19	165 ± 31	149 ± 24	151 ± 25	130 ± 21
Diastolic BP, mm Hg	82 ± 13	86 ± 12	84 ± 11	84 ± 11	86 ± 17	85 ± 12	84 ± 11	80 ± 11
CHD categories, No. (%)†								
MI	19 (61.3)		96 (50.3)		5 (25)		27 (24.8)	
CI	5 (16.1)		12 (6.3)		1 (5)		10 (9.2)	
AP	7 (22.6)		83 (43.5)		14 (70)		72 (66.1)	

Abbreviations: AP, angina pectoris; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; CHD, coronary heart disease; CI, coronary insufficiency; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.02586.

\*Data are given as mean ± SD unless otherwise specified. Some of the percentages may not sum to 100 because of rounding.

To determine if the differential risk for CHD mortality in men and women is due to differences in severity of CHD, in the multivariate analysis, we separated CHD into 2 groups: myocardial infarction and angina pectoris/coronary insufficiency. In men, diabetes had an HR for CHD mortality of 1.7 (95% CI, 1.2-2.5), angina pectoris/coronary insufficiency had an HR of 3.2 (95% CI, 2.2-4.5), and myocardial infarction had an HR of 5.0 (95% CI, 3.6-6.9). In women, the corresponding HRs were 3.6 (95% CI, 2.2-5.9) for diabetes, 1.5 (95% CI, 0.9-2.7) for angina pectoris/coronary insufficiency, and 3.1 (95% CI, 1.2-7.6) for myocardial infarction. Thus, men with prior myocardial infarction or other forms of CHD were at a higher risk for CHD death than men with diabetes. In women, diabetes still conferred a higher risk than the 2 CHD groups.

To compare the magnitude of risk for CHD mortality in individuals with CHD with the magnitude of risk in individuals with diabetes, the difference in regression coefficients (equivalent to log hazard ratios) between CHD and diabetes was determined. The difference between the CHD coefficient and the diabetes coefficient in men was +0.73 (95% CI, 0.72-0.75). This indicates that, in men, established CHD has a greater magnitude of risk for CHD mortality than diabetes (HR, 2.08; 95% CI, 2.05-2.12). In contrast, the difference was -0.66 (95% CI, -0.68 to -0.63) in women, implying lower risk of CHD death from prior CHD than diabetes (HR, 0.52; 95% CI, 0.51-0.53).

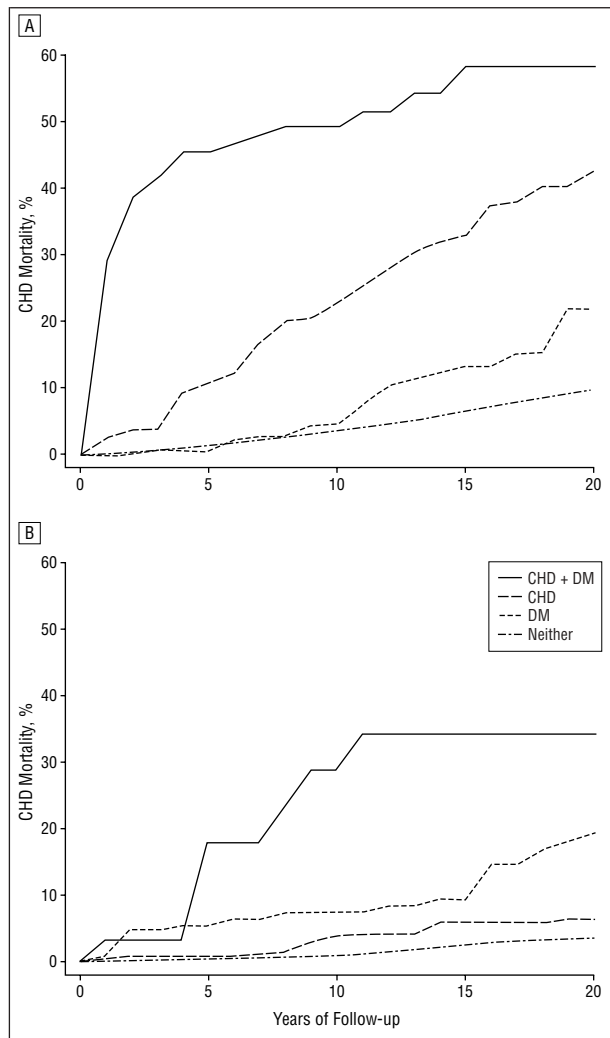
To further evaluate sex differences in the relationship between diabetes and CHD on CHD mortality, sex, diabetes, and CHD interactions were tested with men and women combined using hierarchical modeling principles. Because the sex-diabetes-CHD interaction ( $P = .96$ ) and the CHD-diabetes interaction ( $P = .31$ ) were not significant, they were not included in the final model. The sex-CHD interaction was associated with an HR of 0.50 (95% CI, 0.29-0.86), which indicates that the relative risk

for fatal CHD among women with CHD is significantly lower than the relative risk for men with CHD. In contrast, the sex-diabetes interaction was associated with an HR of 2.31 (95% CI, 1.26-4.23), indicating that the relative risk for CHD death in women with diabetes is higher than the relative risk for CHD death among men with diabetes.

#### COMMENT

The findings from this prospective, community-based study emphasize the magnitude of diabetes as a major risk factor for CHD mortality in men and women. These findings quantify sex differences in the risk for CHD mortality in individuals with diabetes by comparing it with established CHD. In men, while diabetes is an important risk factor for fatal CHD, established CHD is associated with a larger magnitude of risk. In women, the magnitude of the association is reversed and diabetes is a larger risk for fatal CHD than established CHD. In both men and women, individuals with both diabetes and CHD were at dramatically higher risk. Though it is well known that the CHD mortality rate in general is lower in women than in men of the same age, the age-adjusted CHD mortality rate in diabetic women is higher than in men without diabetes and approaches the mortality rate seen in men with diabetes.

The sex difference in the relative magnitude of risk for CHD mortality may be explained by several biological mechanisms. In our analysis, diabetic women without CHD were more likely to smoke, have lower HDL-C and lower LDL-C levels compared with nondiabetic women with CHD. However, even after adjusting for these and other risk factors, diabetes was associated with a significant increased risk for CHD mortality. Data from the Nurses' Health Study<sup>14</sup> indicate that at any level of other risk factors, women with diabetes are more likely to have



Age-adjusted cumulative coronary heart disease (CHD) mortality by CHD and diabetes mellitus (DM) status for men (A) and women (B).

cardiovascular events than women without diabetes. Women with diabetes have been shown to have lower HDL-C and higher triglyceride levels than men with diabetes.<sup>15</sup> Diabetes has been demonstrated to have greater adverse effects in women with regard to waist-to-hip ratio, LDL-C, HDL-C, LDL particle size, apolipoprotein B, apolipoprotein A<sub>1</sub>, and fibrinogen.<sup>16</sup> Compared with diabetic men, diabetic women may have greater levels of lipid peroxidation, independent of glycemic control.<sup>17</sup> In addition to the other CHD risk factors, excess circulating glucose may adversely affect the estrogen-related cardiovascular protection by decreasing vascular and platelet nitric oxide production,<sup>18</sup> thereby increasing vascular tone, platelet aggregation, and enhance vascular proliferation. While premenopausal nondiabetic women have greater endothelium-dependent vasodilation than nondiabetic men, premenopausal diabetic women have significant impairment of endothelial function, leading to endothelial dysfunction similar to diabetic men.<sup>19</sup> In addition to these markers of increased risk, since women have less severe coronary atherosclerosis and less collateral vessels than men,<sup>20</sup> they tend to sustain greater myocardial damage with coronary occlusion and thus diabe-

**Table 2. Rate of Fatal CHD and Its Relationship to Diabetes and Established CHD in Men and Women**

	CHD Deaths, No.	Rate/1000 Person-Years	Hazard Ratio (95% CI)	
			Age Adjusted	Multivariate*
<b>Men</b>				
Neither	172	4.5	1.0 (Reference)	1.0 (Reference)
CHD only	78	32.9	4.8 (3.6-6.3)	4.2 (3.2-5.6)
Diabetes only	19	12.1	2.2 (1.3-3.5)	2.1 (1.3-3.3)
Both diabetes and CHD	13	47.8	6.9 (3.9-12.3)	6.1 (3.4-10.9)
<b>Women</b>				
Neither	76	1.6	1.0 (Reference)	1.0 (Reference)
CHD only	14	8.3	2.3 (1.3-4.1)	1.9 (1.1-3.4)
Diabetes only	16	13.8	5.2 (3.0-9.0)	3.8 (2.2-6.6)
Both diabetes and CHD	7	31.7	9.2 (4.2-20.4)	5.4 (2.4-12.3)

Abbreviations: CHD, coronary heart disease; CI, confidence interval.

\*Adjusted for age, smoking, hypertension, total serum cholesterol, high-density lipoprotein cholesterol, and body mass index.

tes may impact women more than men, both for CHD morbidity and mortality.<sup>21,22</sup> For example, in the Framingham Study, 66% of CHD deaths in women occurred in those without prior angina.<sup>23</sup>

Because the weight of evidence indicates that diabetes and CHD have marked sex differences in subsequent CHD rates, it is crucial to analyze the data by sex.<sup>24</sup> This analytic approach is probably responsible for the differences between this study and the previous study,<sup>3</sup> which did not formally test for sex differences. Haffner et al,<sup>3</sup> combining Finnish men and women, compared the risk for fatal CHD in 890 diabetic individuals without prior myocardial infarction (48% female) with 69 nondiabetic individuals with prior myocardial infarction (26% female). They found an HR for fatal CHD of 1.2 (95% CI, 0.6-2.4) and inferred that the risk associated with diabetes and that associated with previous CHD were similar.

Though prior studies have shown a greater impact of diabetes in women compared with men, they have not determined the relative strength of the relationship compared with established CHD by sex.<sup>7,25,26</sup> Hu et al<sup>27</sup> evaluated the impact of diabetes and myocardial infarction on CHD mortality using self-reported data from the Nurses' Health Study (only women) with 20 years' follow-up. They reported a relative risk (RR) of 8.7 (95% CI, 7.4-10.3) associated with diabetes and an RR of 10.6 (95% CI, 8.1-13.8) with myocardial infarction. However, they did not directly compare the risks associated with diabetes and CHD using formal statistical procedures. Also, in a validation study of this cohort, only 68% of self-reported myocardial infarction cases were actually confirmed to have myocardial infarction.<sup>28</sup> In addition, all women did not have uniform assessment for diabetes and thus there may have been contamination of the nondiabetic reference group with undiagnosed diabetics,<sup>29</sup> which could have led to underestimation of relative risk among women with diabetes. In a report from the Physicians' Health Study (only US male physicians) using self-reported information on diabetes, CHD and risk factors, Lotufo et al<sup>30</sup> found

that a history of prevalent CHD was associated with greater relative risk of fatal CHD (RR, 5.4; 95% CI, 4.7-6.2) than prevalent diabetes (RR, 2.9; 95% CI, 2.3-3.7). Because the Nurses' Health Study and the Physicians' Health Study are 2 separate studies with very different study designs and populations, it is impossible to evaluate sex differences from them directly.

Our analysis found that men and women with both diabetes and CHD were at greatest risk for CHD death, which is consistent with other studies. Compared with individuals without CHD or diabetes at baseline, prior research has reported that women with both diabetes and CHD<sup>27</sup> had an RR for CHD mortality of 17.6 (95% CI, 10.5-29.4) while for men the RR was 12 (95% CI, 9.9-14.6).<sup>30</sup> Malmberg et al<sup>31</sup> found that prior diabetes in a patient recently hospitalized for unstable angina or non-Q-wave myocardial infarction was associated with a 2-year cardiovascular mortality rate of 9.3%, with greater adverse impact of diabetes in women compared with men. Miettinen et al<sup>32</sup> reported a high mortality rate in diabetic patients after their first myocardial infarction, with the difference being particularly high in women.

The results from this investigation should be interpreted while taking into account certain potential limitations. First, this community-based study comprised almost totally white participants and thus this same effect may not be seen in nonwhite persons. Second, information regarding family history of CHD, renal function, severity of diabetes, abdominal obesity, physical activity, homeostatic factors, inflammatory markers, other vascular risk factors, and socioeconomic status was not available. Therefore, we were unable to adjust for these potential confounders. Third, because angina is a less sensitive and specific symptom of coronary disease in women, a certain proportion of women reporting angina may be misclassified as having CHD. Even when severity of CHD was considered in the analysis, men with prior myocardial infarction or other forms of CHD were at a higher risk for CHD death than men with diabetes, while in women diabetes conferred a higher risk than the CHD groups. Finally, this study followed up participants over a 20-year period and these analyses have not accounted for differences in diagnostic criteria and treatment for diabetes and CHD over this period.

Despite these potential limitations, this analysis adds to the body of knowledge regarding the effect of diabetes on CHD mortality by quantifying the dramatic impact of diabetes in women after accounting for other known CHD risk factors. The findings from this study support aggressive management of diabetes to prevent CHD, particularly in women. While there may be a decrease in CHD events such as myocardial infarction with intensive glycemic control,<sup>33</sup> the benefits from aggressive treatment of hypertension,<sup>34</sup> dyslipidemia,<sup>35</sup> and platelet responsiveness<sup>36</sup> are unambiguous.

Of public health concern, estimates indicate that the number of persons with diabetes is likely to double in the first quarter of the 21st century with a corresponding increase in social and financial burden.<sup>37</sup> A recent cost-effectiveness analysis<sup>38</sup> found that treating dyslipidemia in diabetic patients without cardiovascular disease (\$5063-\$23 792 per year of life saved) was as cost-effective as treat-

ing nondiabetic patients with cardiovascular disease (\$8799-\$21 628 per year of life saved). Based on our data, since women are at higher risk, it is likely that treatment of women with diabetes will be even more cost-effective. Since the intensity of management of diabetic patients is based on their risk for CHD, and because women with diabetes may be at higher risk for CHD than women with established CHD, current guidelines for treatment of women with diabetes may need to be more aggressive.

In conclusion, this community-based prospective study identifies diabetes as worse than prior established CHD in risk for subsequent CHD mortality in women. In men, prior CHD has greater risk for subsequent fatal CHD than diabetes. This analysis should provide the impetus to further refine treatment guidelines to match the intensity of treatment to patients' risk for future CHD events.

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Corresponding author: Sundar Natarajan, MD, MSc, 423 E 23rd St, Room 11101-S, New York, NY 10010 (e-mail: [sundar.natarajan@med.nyu.edu](mailto:sundar.natarajan@med.nyu.edu)).

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