Is Diabetes Mellitus a Cardiovascular Disease Risk Equivalent for Fatal Stroke in Women?

Data From the Women’s Pooling Project

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Background and Purpose—Diabetes mellitus is an independent risk factor for stroke and is associated with a 1.8- to 6-fold increased risk compared with nondiabetic subjects. Recent guidelines have classified diabetes as a coronary heart disease risk equivalent. Whether diabetes is a cardiovascular disease risk equivalent for stroke is not established.

Methods—Data were pooled from 9 prospective epidemiological studies in the United States. We followed up 27,269 women (8.5% diabetic, 2.9% with prior myocardial infarction, 2.3% with prior stroke) for an average of 8.3 years, during which 238 stroke deaths were observed.

Results—Both diabetic subjects without cardiovascular disease and nondiabetic subjects with history of prior stroke had a significantly increased risk of 10-year stroke mortality compared with nondiabetic subjects without prior cardiovascular disease (hazard ratio [HR], 6.77; 95% confidence interval [CI], 4.56 to 10.05; HR, 3.37; 95% CI, 2.38 to 4.77). History of prior myocardial infarction was not associated with long-term stroke mortality (HR, 0.66; 95% CI, 0.27 to 1.61). After adjustment for risk factors, diabetic subjects had similar risk compared with subjects with a history of prior stroke (HR, 1.29; P=0.43).

Conclusions—Diabetic subjects without cardiovascular disease have a fatal stroke risk similar to that of nondiabetic subjects with a history of prior stroke and similar risk factor profile. This suggests that diabetes mellitus may be classified as a stroke risk equivalent and may warrant more aggressive treatment strategies in the future prevention of stroke. (Stroke. 2003;34:2812-2816.)

Key Words: cardiovascular diseases ■ diabetes mellitus ■ epidemiology ■ stroke ■ women

An estimated 17 million Americans have diabetes mellitus, and the incidence of diabetes and its cardiovascular complications is projected to rise in the next 20 to 30 years. Diabetes mellitus accelerates the clinical course of atherosclerosis and increases both cardiovascular morbidity and mortality. The higher prevalence of atherosclerosis in diabetics has been associated with hyperglycemia, insulin resistance, and dyslipoproteinemia.

Coronary heart disease (CHD) mortality is increased 2- to 4-fold in the diabetic population. In a recent study, Haffner et al compared diabetic subjects without prior CHD and non-diabetic subjects with established CHD and found a similar increase in CHD mortality in both groups. Such results prompted the classification of diabetes as a CHD risk equivalent in recent treatment guidelines that advocated aggressive antiatherosclerosis management of diabetic patients. Although the increase in CHD mortality has been well studied, fewer prospective studies have examined stroke mortality in the diabetic population. Diabetes has been shown to be a strong independent risk factor for stroke and is associated with a 1.8- to 6-fold increased risk of stroke. However, whether diabetes is a stroke risk equivalent for stroke mortality remains unknown.

The objective of this study was to examine the long-term stroke mortality risk in diabetic and nondiabetic women with and without prior myocardial infarction (MI) or stroke. We hypothesized that stroke mortality was similarly increased in diabetic subjects without prior cardiovascular disease (CVD) compared with nondiabetic subjects with history of prior stroke.

Methods

The Women’s Pooling Project is a prospective study that combines data from the following 9 long-term epidemiological studies based in the United States: Atherosclerosis Risk in Communities Study (ARIC), Charleston Heart Study, Evans County Study, Framingham Heart Study (original and offspring cohorts), National Health Examination Follow-up Study (NHEFS), Rancho Bernardo Study, San Antonio Heart Study, and the Tecumseh Community Health Study. Details of sampling procedures, study designs, and methods for each of the respective studies have been described. The study was approved by the appropriate institutional review board.
Subjects
The study included women ≥30 years of age at initial examination. Subjects missing data on diabetic status, previous MI, or previous stroke at baseline were excluded from analysis. Prevalent diabetes mellitus was defined as a combination of treatment with diabetic medications and glucose parameters in all cohorts except Evans County, which used self-reported history. Subjects with type I and type II diabetes mellitus were included in the study; disease subtype was not specified. The Framingham original cohort included subjects with fasting glucose >8.27 mmol/L (149 mg/dL), whereas a fasting glucose >7.71 mmol/L (139 mg/dL) or a 2-hour postload serum glucose >11.1 mmol/L (199 mg/dL) was used in all other cohorts in accordance with the 1985 World Health Organization (WHO) criteria for diabetes.7 Further indicators of disease severity, including duration, degree of glycemic control, and associated renal function, were not identified in the pooled database.

Previous MI included self-reported history, ECG criteria (all cohorts except NHEFS), and study panel review of historical and medical evidence (Evans County, Framingham original and offspring cohorts, Rancho Bernardo). Previous stroke was based on self-reported history in all cohorts except Evans County and Framingham original and offspring cohorts, in which a combination of history and review of medical records was used.

Subjects were separated into subgroups according to CVD history and diabetic status: nondiabetic subjects with no history of MI or stroke (no CVD, no diabetes), nondiabetic subjects with history of previous MI and no previous stroke (previous MI, no diabetes), nondiabetic subjects with history of stroke and no previous MI (previous stroke, no diabetes), diabetic subjects with history of stroke and no previous MI (diabetes, previous stroke), and diabetic subjects with history of previous MI, stroke, or diabetes were examined separately from the main analysis.

Measurements
Subject variables measured at baseline included total cholesterol, blood pressure (BP), body mass index (BMI), smoking status, use of BP medications, and education. Both systolic and diastolic BPs were recorded as the average of the last 2 readings unless only 1 reading was available. BMI (kg/m²) was calculated from the raw data for height and weight, and smoking status was stratified into current and noncurrent cigarette smokers. Educational status was dichotomized into non–high school graduate versus high school graduate.

Main Outcomes
Completion of follow-up was >97% for all cohorts. Mortality data were based on version 9 of the International Classification of Diseases (ICD) except in the Charleston, Evans County, and Framingham original and offspring cohorts, which were based on version 8.8 Primary outcome was stroke mortality, which included both hemorrhagic (ICD-9 codes 430 through 432; ICD-8 code 431) and nonhemorrhagic strokes (ICD-9 codes 433 through 438; ICD-8 codes 432 through 438). Additional outcome included CHD mortality (ICD-9 code 429.2; ICD-8 code 410; and codes 410 to 414 for both versions). Because of the potential misclassification of risk between baseline measurement and outcome, only events (death resulting from stroke or otherwise) that occurred within 10 years of baseline examination were included.

Statistical Analysis
Baseline measurements were compared between subgroups by use of 2-tailed Student’s $t$ tests for continuous variables and Pearson’s $\chi^2$ tests for dichotomous variables. Results were expressed as mean±SD or percentages, respectively.

The 10-year stroke mortality rates were calculated and age adjusted to the overall study population. Cox proportional-hazards regression was used to calculate stroke and CHD mortality HRs, with the no CVD, no diabetes subgroup serving as the reference population. Separate models were first constructed for each comparison, and then a single multivariable model was used to include all subjects and test for interactions between explanatory variables.

Stroke mortality was compared between the previous stroke and diabetes groups using Cox regression. All models used age as the time axis with left truncation for entry age, and events occurring >10 years after baseline examination were censored at 10 years. Cox regression models were adjusted for age and then repeated with adjustment for age, total cholesterol, BMI, systolic and diastolic BPs, BP medication use, smoking and educational status, and race. All calculations were done with SAS version 8.2.

Results
The study included a total of 27 269 women (16% black, 5% Hispanic). At baseline, 8.6% of women had diabetes mellitus, 2.9% had a history of previous MI, and 2.3% had a history of previous stroke. During a mean follow-up of 8.3±2.1 years, a total of 238 stroke deaths and 547 CHD deaths were observed.

Clinical characteristics for study subjects at baseline are shown by subgroup in Table 1. Diabetes was more prevalent among blacks and Hispanics and was associated with older age and higher total cholesterol, BMI, and systolic BP. Both

### TABLE 1. Clinical Characteristics of Subgroups

<table>
<thead>
<tr>
<th></th>
<th>No CVD, No Diabetes</th>
<th>Previous MI</th>
<th>Previous Stroke</th>
<th>Diabetes, Previous Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>23 876</td>
<td>567</td>
<td>432</td>
<td>2091</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.7±1.2</td>
<td>6.4±1.3†</td>
<td>6.2±1.2†</td>
<td>5.9±1.3*</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>128±24</td>
<td>144±28†</td>
<td>148±35†</td>
<td>137±26†</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78±13</td>
<td>84±14†</td>
<td>86±17†</td>
<td>79±13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±5</td>
<td>27±6*†</td>
<td>27±6†</td>
<td>30±7*</td>
</tr>
<tr>
<td>Age, y</td>
<td>51±11</td>
<td>61±9†</td>
<td>61±9†</td>
<td>56±9*</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>8.4±2.0</td>
<td>8.2±2.5†</td>
<td>7.8±2.7†</td>
<td>7.4±2.3*</td>
</tr>
<tr>
<td>Blacks, %</td>
<td>14</td>
<td>13†</td>
<td>16†</td>
<td>31*</td>
</tr>
<tr>
<td>Hispanics, %</td>
<td>5</td>
<td>2†</td>
<td>2†</td>
<td>10*</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>29</td>
<td>27†</td>
<td>30†</td>
<td>23*</td>
</tr>
<tr>
<td>BP medications, %</td>
<td>15</td>
<td>32†</td>
<td>39*</td>
<td>41*</td>
</tr>
<tr>
<td>High school graduate, %</td>
<td>31</td>
<td>46*</td>
<td>50*</td>
<td>49*</td>
</tr>
</tbody>
</table>

* $P<0.05$ comparing each subgroup to no CVD, no diabetes subgroup.  † $P<0.05$ comparing each subgroup to diabetes subgroup.

8.27 mmol/L (199 mg/dL) was used in all other cohorts in accordance with the 1985 World Health Organization (WHO) criteria for diabetes.
history of previous MI and stroke were associated with older age and higher total cholesterol, BMI, and systolic and diastolic BPs.

Age-adjusted 10-year stroke mortality rates and HRs are shown in Table 2. Stroke mortality rates showed trends similar to the survival estimates. In reference to the no diabetes, no CVD subgroup, subjects with previous stroke showed a 6.77-fold increased risk of fatal stroke (95% confidence interval [CI], 4.56 to 10.05), whereas diabetic subjects had a 3.37-fold increased risk (95% CI, 2.38 to 4.77). Subjects with both diabetes and previous stroke had a 7.82-fold increased risk (95% CI, 3.81 to 16.06). Subjects with previous MI had the highest risk for CHD death relative to the reference group (HR, 0.66; 95% CI, 0.27 to 1.61).

When CHD mortality was examined, subjects with previous MI had the highest risk for CHD death relative to the reference group (HR, 4.06; 95% CI, 3.12 to 5.28) compared with all other subgroups (previous stroke: HR, 2.37; 95% CI, 1.59 to 3.55; diabetes: HR, 2.99; 95% CI, 2.35 to 3.78; diabetes, previous stroke: HR, 3.89; 95% CI, 2.00 to 7.57; diabetes, previous MI: HR, 10.56; 95% CI, 6.95 to 16.02, all age-adjusted).

Adjustment for risk factors attenuated the stroke risk in diabetic and nondiabetic subjects with previous stroke, although general trends were preserved for both fatal stroke and CHD. When analyzed in a single multivariable Cox regression model, there was an interaction between diabetes and previous stroke that suggested that the combination of conditions carried a slightly increased fatal stroke risk over the individual conditions; however, the risks were not additive or multiplicative (P=0.04 age-adjusted, P=0.22 multivariable adjusted).

The Figure compares stroke mortality between subjects with previous stroke and diabetic subjects. Subjects with previous stroke had an increased risk compared with diabetic subjects (HR, 2.17; P<0.01), although this difference was nonsignificant after adjustment for risk factors (HR, 1.29; P=0.43), suggesting that both diabetes and previous stroke conferred a similar risk for fatal stroke.

**Discussion**

The principal finding of this study was that diabetes mellitus and history of previous stroke significantly increased the risk of fatal stroke compared with women with no history of CVD or diabetes. After adjustment for traditional risk factors, the stroke mortality risk in diabetics was similar to that in nondiabetic subjects with prior stroke. In contrast, previous MI did not significantly predict long-term stroke mortality.

Our findings are consistent with previous studies that have shown diabetes to be an independent risk factor for stroke. The relative risk of fatal stroke in prospective studies has ranged from 1.8 to 6.0 in women.10–13 However, most previous studies did not include subjects ≥74 years of age and were limited in power. Because diabetes and stroke incidence in the population most likely to have diabetes or experience fatal stroke.

The association between previous MI and stroke risk is poorly established. Stroke risk has been shown to be higher in the acute period after MI (incidence, 0.7% to 4.7% within 2 weeks of infarction) and decreases with time.15 Long-term incidence rates in subjects with previous MI have been found to be low at 1% to 1.5% per year,15,16 although incidence rates were higher in elderly subjects (2.5% per 6 months).14 One study showed no significant differences in stroke risk between subjects with and without previous MI over 1 year (P=0.29).17 However, other independent risk factors such as
low left ventricular ejection fraction may significantly increase stroke risk after MI in certain subgroups. Our study found no significant association between previous MI and long-term fatal stroke risk and supports the overall low stroke risk shown by other studies. The lack of association between previous MI and stroke mortality may have been due to a competing risk effect because subjects with previous MI had a high risk of fatal CHD compared with other subgroups.

Several studies have compared the cardiovascular risk in subjects with diabetes mellitus and established CVD and have led to the classification of diabetes as a CHD risk equivalent in the recent Adult Treatment Panel III guidelines. Haffner et al noted similar CHD mortality risk between diabetic subjects without prior MI and nondiabetic subjects with prior MI. Our CHD mortality data are more consistent with several other studies indicating a slightly higher risk in nondiabetic subjects with established CVD compared with diabetics without CVD.

Few studies have examined the CVD risk equivalency of diabetes in stroke mortality. Malmberg et al showed that diabetic subjects without prior CVD had a relative risk for fatal/nonfatal stroke similar to nondiabetic subjects with established CVD after hospitalization for unstable angina or non–Q-wave MI (relative risk of 1.47 [95% CI, 1.07 to 2.03] versus 1.40 [95% CI, 0.80 to 2.43]). However, the inclusion criteria in this particular study may have resulted in a population at higher risk compared with those in our study. Another study examined carotid artery intima-media wall thickness and found that it was slightly increased in diabetic subjects without clinical CHD compared with nondiabetic subjects with symptomatic CHD. This difference was statistically insignificant, suggesting that diabetic subjects had extensive atherosclerosis in the carotid artery that was similar in degree to nondiabetic subjects with CHD. Although this study was not designed to assess clinical outcomes, these findings lend support to our results because carotid artery intima-media wall thickness has been shown to be a significant predictor of incident stroke. 

Kuller et al showed that diabetic subjects without subclinical CVD had similar fatal and nonfatal stroke incidence compared with subjects with impaired fasting glucose tolerance and prevalent subclinical CVD (relative risk, 2.5; 95% CI, 1.3 to 4.8; relative risk, 2.3; 95% CI, 1.4 to 3.8, respectively). Although this study was focused on subclinical CVD and thus examined different risk groups, it demonstrated trends similar to those in our study. Previous studies were limited in power compared with our study, and none were able to examine subjects with previous MI and previous stroke separately. Our study suggests that stroke risk varies by CVD subgroup (previous MI versus previous stroke), and we showed that diabetics carried similar adjusted fatal stroke risk compared with subjects with previous stroke, the CVD subgroup at highest risk for fatal stroke.

Our findings may have treatment implications for the prevention of stroke in diabetics. Our data support the classification of diabetes as a high-risk group and suggest that diabetics be treated as aggressively as subjects with a history of prior stroke. In addition to increased stroke mortality, diabetic subjects have worse outcomes associated with stroke, including higher rates of stroke-related dementia and stroke recurrence, compared with nondiabetic subjects, making stroke prevention more crucial in this population. Tight BP control in diabetic subjects has been shown to reduce fatal and nonfatal stroke risk by 44%, and the use of an angiotensin-converting enzyme inhibitor may decrease stroke risk up to 33% compared with other BP regimens. The American Diabetes Association recently recommended the use of aspirin in the secondary prevention of CVD in diabetic subjects and considered use in the primary prevention in diabetic subjects at high risk. Our findings may warrant trials for the use of antplatelet therapy in the primary prevention of stroke in diabetics without prior CVD. The role of HMG CoA reductase inhibitors in stroke prevention is less well established, although recent secondary prevention trials suggest a possible decrease in the risk of nonhemorrhagic strokes with pravastatin in both diabetic and nondiabetic subjects.

Our study has several limitations. Previous stroke was based on self-report, and fatal stroke outcomes relied on ICD codes, which may have led to misclassification of risk. Some studies have shown a threshold of cardiovascular risk with increased duration of diabetes. Because we were not able to adjust for time since diagnosis of diabetes, the diabetic population in our study may have been at higher risk if study entry occurred late in the course of the disease. We were unable to differentiate type I from type II diabetes in this analysis, and the inclusion of a small percentage of type I diabetes mellitus patients may have elevated risk in the diabetic population. However, this effect would be minimal because of the low prevalence of type I compared with type II diabetes in the general population (5% versus 95% of diagnosed cases in 1995). Further misclassification of diabetes could have occurred in pooling data from different studies because of the variable definitions within each cohort, although data from secondary analyses examining separate definitions of diabetes were not materially different, indicating our definition is robust. Use of the 1985 WHO fasting glucose parameters for diabetes may have excluded diabetics defined by the revised criteria from the diabetic subgroup. However, this would have biased our results to the null by including potentially high-risk subjects in the nondiabetic subgroup. Most of the subjects were recruited before the widespread use of thrombolytic therapy in the management of acute MI. We may have underestimated hemorrhagic stroke as a complication after acute MI, although the overall complication rate is low and most cases of stroke after acute MI are of ischemic rather than hemorrhagic origin. Finally, we were not able to adjust for type of antihypertensive medication, type of cholesterol-lowering medication, and use of aspirin, all of which have been shown to influence stroke risk in nondiabetic and diabetic subjects.

In summary, we showed that women with diabetes mellitus and no prevalent CVD had a 3-fold–increased fatal stroke risk compared with nondiabetic women without CVD. Although stroke mortality was highest among women with prior stroke, our findings suggest that for similar risk factor profiles, diabetes carries a fatal stroke risk similar to that of a history of prior stroke.
Future studies should confirm stroke risk in diabetics without prior CVD and prediabetic states compared with established cerebrovascular disease. In consideration of the recent classification of diabetic subjects without CHD as a CHD risk equivalent and to treat diabetic patients with aggressive preventive strategies in the future.

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References

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