Cardiovascular Events in Diabetic and Nondiabetic Adults With or Without History of Myocardial Infarction

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For the Atherosclerosis Risk in Communities (ARIC) Study Investigators

Background—Whether diabetic patients without a history of myocardial infarction (MI) have the same risk of coronary heart disease (CHD) events as nondiabetic patients with a history of MI remains controversial. We compared risks of CHD and stroke events and mortality from cardiovascular disease (CVD) in diabetic and nondiabetic men and women with and without a history of MI.

Methods and Results—We followed a total of 13 790 African American and white men and women ages 45 to 64 years who participated in the Atherosclerosis Risk in Communities study, beginning in 1987 to 1989. There were 634 fatal CHD or nonfatal MI events, 312 fatal or nonfatal strokes, and 358 deaths from CVD during an average of 9 years of follow-up (125 998 person-years). After adjustment for age, sex, race, Atherosclerosis Risk in Communities field center, and multiple baseline risk factors, patients who had a history of MI without diabetes at baseline had 1.9 times the risk of fatal CHD or nonfatal MI (95% CI, 1.35 to 2.56; P<.001) compared with diabetic patients without a prior history of MI. The nondiabetic patients with MI also had 1.8 times the risk of CVD mortality compared with diabetic patients without MI (95% CI, 1.22 to 2.72; P=.003). However, stroke risk was similar between diabetic patients without MI and nondiabetic patients with MI (RR, 1.05; 95% CI, 0.61 to 1.79; P=.87). We also observed that nondiabetic patients with MI had a carotid artery wall thickness similar to diabetic patients without MI (P=.77).

Conclusions—Diabetic patients without MI had lower risk of CHD events and mortality from CVD compared with nondiabetic patients with MI, but stroke risk was similar between these 2 groups. (Circulation. 2004;109:855-860.)

Key Words: diabetes mellitus • myocardial infarction • stroke • cardiovascular diseases

Type 2 diabetes is a significant risk factor for coronary heart disease (CHD) and stroke.1–4 Prospective studies have shown that persons with type 2 diabetes have twice the risk of incident CHD and ischemic stroke2–4 and 2 to 4 times the risk of CHD and stroke mortality compared with their counterparts without diabetes.5 After myocardial infarction (MI), diabetic persons have a higher risk of recurrent MI, fatal CHD, and stroke mortality than do nondiabetic persons.6,7 CHD is the leading cause of death in patients with type 2 diabetes,8 and life expectancy in the middle-aged patients is reduced by 5 to 10 years.9 Haffner and colleagues10,11 have suggested that diabetic persons have a risk of cardiovascular events similar to patients with previous MI. For example, in the Insulin Resistance Atherosclerosis Study, diabetic persons who were free from MI had a similar atherosclerosis progression in the carotid artery as nondiabetic patients with MI.10 Furthermore, a Finnish population-based study reported that people with type 2 diabetes without MI had similar or even higher rates of incident CHD and stroke and mortality from cardiovascular disease (CVD) compared with nondiabetic patients with MI.11 Results from the placebo arm of the Heart Outcomes Prevention Evaluation (HOPE) study suggested similarly that the rate of a CVD event was comparable for people with diabetes and those with a prior history of CVD.12 In contrast, a recent Scottish population-based study showed that type 2 diabetic persons without MI had a 64% lower risk of CVD mortality compared with nondiabetic MI patients.13 A similar result also was observed in an Australian population-based study.14 Because of the high risk and poor outcome of CHD in diabetic patients, recent national cholesterol guidelines recommend treating diabetic patients as if they had CHD.15,16 We investigated in the Atherosclerosis Risk in Communities (ARIC) study whether, as Haffner and colleagues have suggested, diabetic persons without prior MI have an equivalent risk of incident CHD and stroke and mortality from CVD as nondiabetic persons with a history of MI. We also assessed the mean carotid artery intima-media thickness in diabetic and nondiabetic men and women with and without a history of MI.
Methods

Study Population
The ARIC study is a population-based cohort study to investigate the etiology of atherosclerosis in a biracial population from 4 United States communities: Forsyth County, NC; Jackson, Miss; Washington County, Md; and the northwest suburbs of Minneapolis, Minn. The study population comprises 15792 men and women, ages 45 to 64 years, recruited in 1987 to 1989. All participants from Jackson and 12% of participants from Forsyth County were African American, whereas most participants from the other 2 communities were white (99%). The complete study design, sampling strategy, and examination techniques have been reported previously.17

Measurements
All participants signed informed consent and completed a home interview and a clinical examination. The home interview included assessment of participants’ health habits, demographic characteristics, and medical histories. The clinical examination included a physical examination, blood pressure measurement, blood tests, anthropometrics, a 12-lead ECG, and a B-mode ultrasound examination of the carotid artery.

All participants were asked to fast for 12 hours before the clinical examination. Body weight and height were measured with a calibrated scale and a vertical metal rule, respectively, and body mass index (BMI, kg/m2) was calculated as weight in kilograms divided by height in meters squared. Seated blood pressure was measured after 5 minutes of rest using a random-zero sphygmomanometer, and the average of the last 2 of 3 consecutive measurements was used for analysis. Serum, plasma, and whole blood samples were drawn from an antecubital vein.18 Serum glucose was measured by a hexokinase method, and plasma total cholesterol was measured with an enzymatic method.19 High-density lipoprotein cholesterol (HDL-C) was measured after dextran-magnesium precipitation,20 and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation.21 Fibrinogen was measured by thrombin-time titration method, and factor VIII activity was measured by determining the clotting time of human factor VIII–deficient plasma obtained from George King Biomedical Inc.18 von Willebrand factor antigen was determined by ELISA kits from American Bioproducts Co.18 White blood cell (WBC) count was determined by automated particle counters within 24 hours after venipuncture in local hospital hematology laboratories. Test-retest reliability coefficients were 0.72 for fibrinogen, 0.86 for factor VIII, 0.68 for von Willebrand factor, and 0.96 for WBC.22,23

Carotid artery atherosclerosis was determined by high-resolution B-mode ultrasound. Trained technicians scanned the extracranial carotid arteries, both the right and left common carotid, carotid bifurcation, and internal carotid. In each segment, B-mode ultrasound assessed the far wall thickness of 1-cm portions with a maximum number of 11 measurements. All 6 carotid artery sites were measured, and the mean carotid artery intima-media wall thickness was estimated.

Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL, a nonfasting glucose level ≥200 mg/dL, use of hypoglycemic agents, or a history of physician-diagnosed diabetes mellitus. Ninety-six percent of participants with diabetes reported onset after 30 years of age,4 and therefore most are presumed to be type 2. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensives. A history of MI was defined as evidence of a prior MI by ECG or a self-reported history of physician-diagnosed heart attack. Cigarette smoking and medication use were assessed by standardized questionnaires. Smoking status was classified as never smoked, former smoker, or current smoker. Medication use was classified as aspirin use, β-blocker use (nonselective or cardioselective), ACE inhibitor use, or other antihypertensive medication use, using the medical therapeutic classification code. Physical activity in sports was assessed by an adaptation of the Baecke physical activity questionnaire, scored from 1 (low) to 5 (high), and was classified as low (<2), moderate (2 to <4), or high (≥4).24

Ascertainment of Incidence or Mortality
We followed all participants from the baseline examination to the date of incidence or death, loss to follow-up, or through December 31, 1997. All participants were annually contacted by telephone to identify all hospitalizations and deaths. We also searched lists of discharges from local hospitals. For patients hospitalized with potential MI, trained abstractors recorded the presenting signs and symptoms and photocopied up to 3 12-lead ECGs for Minnesota coding.26 For potential strokes, the abstractors recorded signs and symptoms and photocopied neuroimaging (CT or MRI) and other diagnostic reports. Deaths were identified from death certificates, and potential out-of-hospital fatal CHD events were investigated by an interview with 1 or more next of kin and a questionnaire completed by the patient’s physician. CHD events were validated by a committee of physicians using standardized criteria.27 Incident strokes were validated by a combination of computerized algorithm and physician review.28

We defined CHD events as a definite or probable hospitalized MI or definite fatal CHD. Unstable angina or coronary revascularization was not included because of concerns about ethnic differences in diagnosis and use of procedures. Stroke events were defined as a definite or probable hospitalized embolic, thrombotic, or hemorrhagic stroke. Transient ischemic attacks and a small number of undocumented fatal strokes were excluded. The broader CVD death category was based only on the death certificate and included any underlying cause of death codes of 390 through 459, as coded by state health departments according to the International Classification of Diseases, 9th Revision.

Statistical Analysis
We included 13790 men and women ages 45 to 64 years who participated in the ARIC baseline examination from 1987 to 1989. We excluded those with a history of a prior cardiovascular surgery, coronary angioplasty, stroke, or cancer at baseline and those missing baseline history of diabetes or MI or other covariate values. General linear models were used to test mean differences for carotid artery intima-media wall thickness and other CVD risk factors across diabetes and MI categories after controlling for baseline age, sex, race, and ARIC field center. We also used log linear models to test frequency differences in categorical data. Proportional hazards regression was used to examine the RRs of CHD and stroke events and mortality from CVD for participants with or without history of MI or diabetes.29 RRs and 95% CIs for incidence or mortality were estimated after adjustment for age, sex, race, and ARIC field center and after additional adjustment for baseline levels of cigarette smoking, physical activity, HDL-C and total cholesterol levels, systolic blood pressure, β-blocker use, ACE inhibitor use, and other antihypertensive medication use. Inspection of empirical cumulative hazards plots [logarithm (survival function) versus log(time) across diabetes and MI categories] indicated that the proportional hazards assumption was justified. We also estimated incidence and death rates per 1000 person-years across diabetes and MI categories. Kaplan-Meier survival curves were also constructed to compare probability of CHD events in patients with diabetes and patients with MI. All statistical procedures were performed by Statistical Analysis Systems software (SAS Institute) and STATA statistical software (Stata Corporation).

Results
As shown in Table 1, patients with diabetes who had greater mean carotid artery intima-media thickness than did patients without diabetes (P<0.001). Patients who had a history of MI also had greater carotid artery wall thickness compared with their counterparts without prior MI (P<0.001). Patients who had both diabetes and MI had the greatest carotid wall thickness, whereas persons who were free from both had the lowest carotid wall thickness. Table 1 also shows that diabetic patients without MI had a wall thickness similar to nondia-
TABLE 1. Baseline Characteristics of Diabetic and Nondiabetic Men and Women With or Without History of Myocardial Infarction (MI): The ARIC Study

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Diabetes (DM)</th>
<th>Nondiabetic (No-DM)</th>
<th>P Values for Contrasts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Prior MI</td>
<td>Prior MI</td>
<td>No Prior MI</td>
</tr>
<tr>
<td></td>
<td>(n=1460)</td>
<td>(n=98)</td>
<td></td>
</tr>
<tr>
<td>Mean levels*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid intima-media thickness, mm</td>
<td>0.78</td>
<td>0.83</td>
<td>0.73</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.7</td>
<td>32.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>219</td>
<td>217</td>
<td>214</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>44.4</td>
<td>41.6</td>
<td>53.0</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>139</td>
<td>136</td>
<td>137</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127</td>
<td>128</td>
<td>121</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>319</td>
<td>331</td>
<td>300</td>
</tr>
<tr>
<td>Factor VIII, %</td>
<td>153</td>
<td>156</td>
<td>128</td>
</tr>
<tr>
<td>Von Willebrand factor, %</td>
<td>135</td>
<td>136</td>
<td>115</td>
</tr>
<tr>
<td>White blood cell count, 10^9/μL</td>
<td>6.7</td>
<td>7.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Physical activity score</td>
<td>2.33</td>
<td>2.48</td>
<td>2.45</td>
</tr>
</tbody>
</table>

| Frequency, % |          |                     |                      |          |         |
| Hypertension | 58.2 | 70.4 | 30.1 | 46.6 | † | † | † |
| Current smoking | 22.7 | 22.5 | 26.0 | 35.0 | † | † | † |
| Aspirin use | 45.8 | 57.1 | 48.8 | 55.5 | † | † | † |
| ACE inhibitor use | 5.4 | 9.2 | 2.5 | 5.0 | † | † | † |
| β-Blocker use | 13.4 | 32.7 | 6.8 | 31.1 | † | † | † |
| Other antihypertensive use | 18.1 | 40.8 | 8.9 | 35.3 | † | † | † |

*Adjusted for age, sex, race, and field center.
† < 0.001.

There were no statistical differences in fibrinogen (P=0.94), von Willebrand factor (P=0.14), or WBC count values (P=0.95) between diabetic patients without MI and nondiabetic patients without MI, but systolic blood pressure (P<0.001) and Factor VIII activity (P<0.001) were higher and HDL cholesterol (P=0.02) and LDL cholesterol (P<0.001) were lower in diabetic patients without MI. The prevalence of current smoking (P<0.001), aspirin use (P<0.001), β-blocker use (P<0.001), and other antihypertensive medication use (P<0.001) was higher in nondiabetic patients with MI than in diabetic patients without MI, whereas the prevalence of hypertension (P<0.001) and ACE inhibitor use (P<0.001) was higher in diabetic patients without MI.

During an average of 9 years of follow-up (125,998 person-years), we identified 634 fatal CHD or nonfatal MI events, 312 fatal or nonfatal stroke events, and 358 deaths coded as CVD. Table 2 shows the RR of CHD and stroke events and mortality from CVD in persons with or without a history of MI or diabetes. After adjustment for age, sex, race, and ARIC field center, nondiabetic patients with MI had 1.8 times the risk of MI compared with diabetic patients without MI (95% CI, 1.28 to 2.38; P<0.001). After additional adjustments for multiple other baseline risk factors, nondiabetic patients with MI had 1.9 times the risk of fatal CHD or nonfatal MI events compared with diabetic patients without MI (95% CI, 1.35 to 2.56; P<0.001). The Kaplan-Meier survival curves also indicate that diabetic patients without MI had greater event-free time compared with nondiabetic patients with MI (Figure). Similar results were also observed when the data were stratified by sex and race groups.

Table 2 also shows that nondiabetic patients with MI had 1.6 times the risk of CVD mortality compared with diabetic patients without MI (95% CI, 1.06 to 2.31; P=0.02) after adjustment for age, sex, race, and ARIC field center. After adjustment for all covariates, nondiabetic patients with MI had 1.8 times the risk of CVD mortality of diabetic patients without MI (95% CI, 1.22 to 2.72; P=0.003). In contrast, nondiabetic patients with MI had a similar stroke risk as diabetic patients without MI after adjustment for age, sex, race, and ARIC field center (RR, 0.96; P=0.89) and after additional adjustment for multiple risk factors (RR, 1.05; P=0.87).

Three supplemental analyses were run. First, there were 134 participants who had self-reported physician-diagnosed diabetes but at the baseline examination did not have elevated serum glucose concentrations or report diabetic medication. Reanalysis with these participants excluded from diabetic patients yielded virtually identical results for Table 2. Second, there were 558 diabetic patients newly diagnosed at baseline on the sole basis of elevated serum glucose assay. Table 2 results were also unchanged after moving these newly diagnosed diabetic patients to the nondiabetic group. Third, we returned the participants excluded because of a prior cardiovascular surgery, coronary angioplasty, or stroke at baseline, and our results remained unchanged.
Discussion

Whether diabetic patients without history of MI have the same risk of CHD events as MI patients without diabetes remains controversial. Our major finding was that diabetic patients without MI had lower risk of CHD events and mortality from CVD over 11 years compared with nondiabetic patients with MI. This finding is consistent in direction with a Scottish population-based study in which nondiabetic patients with MI had 2.9 times the risk of CVD mortality of type 2 diabetic patients without MI.13 Our findings are also consistent with an Australian population-based study,14 the Nurses’ Health Study,30 the Physicians’ Health Study,31 and Health Professionals Follow-up Study,32 in which type 2 diabetic patients without MI had lower risk of CHD events compared with MI patients without diabetes. In contrast, our findings are inconsistent in direction with Haffner et al,11 in which Finnish type 2 diabetic patients without MI had similar or even higher rates of CHD and stroke events and mortality from CVD compared with nondiabetic patients with MI. We observed

Kaplan-Meier survival curves for a coronary heart disease event by baseline diabetes and MI status; the ARIC study, 1987 to 1997.
a similar stroke risk between diabetic patients without MI and nondiabetic patients with MI, also in contrast with Haffner et al, who showed a higher risk of stroke in diabetic patients without MI than in nondiabetic patients with MI.

Because the study by Haffner et al seemed to impact national prevention guidelines, a detailed comparison is warranted. Haffner et al included only previously diagnosed diabetic patients (excluding diet-treated diabetes), whereas we included patients with previously and newly diagnosed diabetes (including diet-treated diabetes). However, supplemental analyses restricted to known diabetic patients yielded similar results. Haffner et al validated MI history at baseline, whereas we included baseline MI subjects with self-reported physician diagnosed MI or MI by ECG. We, but not Haffner et al, excluded prior stroke, cancer, and coronary revascularization. However, coronary revascularization was probably more common in our study than in Finland in the early 1980s, when the Haffner et al study was done. The definitions of incident CHD and stroke in the 2 studies seem to be fairly similar, and both studies adjusted for major CVD risk factors. Finally, as Haffner et al pointed out, their estimate had a wide confidence interval and could be consistent with our finding that diabetic patients without MI are at lower CHD risk than nondiabetic patients with previous MI.

The Organization to Assess Strategies for Ischemic Syndromes (OASIS) study also reported similar event rates for MI, stroke, and mortality from CVD between diabetic patients without CVD and nondiabetic patients with CVD over a 2-year observation period. However, the OASIS study is incomparable with the present study and the Finnish study, because their participants were hospitalized individuals with unstable angina or non–Q-wave MI at baseline. When we reanalyzed ARIC data to include those patients with a prior cardiovascular surgery, coronary angioplasty, or stroke at baseline, our results remained unchanged.

We found in ARIC that carotid intima-media thickness was similar between diabetic patients without MI and nondiabetic patients with MI. The Insulin Resistance Atherosclerosis Study (IRAS) also showed no statistical differences in common and internal carotid artery wall thickness, or its progression, between diabetic patients without MI and nondiabetic patients with MI. The IRAS study showed that, compared with nondiabetic patients with MI, diabetic patients without MI had higher levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1), markers of hypercoagulability and hypofibrinolysis that are also associated with atherosclerosis and MI. Although ARIC did not measure PAI-1, we found that inflammatory marker (WBC count) and hemostatic factors (fibrinogen and von Willebrand factor) did not differ between diabetic patients without MI and nondiabetic patients with MI. More studies are needed to determine whether other atherosclerotic risk factors such as platelet activity or acute-phase protein levels are similar between diabetic patients without MI and nondiabetic patients with MI.

Diabetes is a strong and independent risk factor for CHD and stroke. Dyslipidemia, hypertension, hyperglycemia, impaired fibrinolysis, and increased coagulation contribute to the development and progression of atherosclerosis in persons with type 2 diabetes. In general, diabetes predisposes to incident MI, and CHD is the leading cause of death among diabetic patients. After MI, diabetic persons have a more rapid atherosclerotic process compared with nondiabetic patients with MI. However, diabetic patients without MI seemed in ARIC to have lower risk of CHD events compared with nondiabetic patients with MI.

A strength of this study is that our data represent population-based samples of United States middle-aged African-American and white men and women. Our study also adjusted for major CVD risk factors and medication use in its statistical models, unlike the Scottish population-based study. On the other hand, multivariate adjustment may not be critical, because the fully adjusted and minimally adjusted RRs in our study were not very different (Table 2). One limitation of our study is that we were not able to adjust for preventive agents introduced in the 1990s, including statins, which may have been applied differently in diabetic and nondiabetic patients. We unfortunately also had no information on time since MI for the diabetic and nondiabetic patients with MI at baseline; any differences in duration of disease between these groups might have led to undetected survival or lead-time biases.

The recent national cholesterol guidelines recommended to treat diabetic patients equivalent to CHD patients, based on absolute CHD risk findings from the Finnish study and other studies. The ARIC, Scottish, Australian, and United States nurses, male physicians, and male health professionals results differ from the Finnish population-based data. Because ARIC diabetic participants are from the general population, their rate of CVD is lower than that of high-risk populations. At the very least our data suggest that there may still be a role for CHD risk stratification of diabetic patients to determine treatment strategies.

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References

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