Prospective Evaluation of Carotid Bruit as a Predictor of First Stroke in Type 2 Diabetes

The Fremantle Diabetes Study

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Background and Purpose—We sought to examine prospectively the relationship between asymptomatic carotid bruit and stroke in type 2 diabetes.

Methods—We studied 1181 (91.3%) of a community-based sample of 1294 patients with type 2 diabetes. These patients had no history of cerebrovascular disease at recruitment during 1993–1996 and were followed until the end of January 2002. Hospital morbidity and death register data relating to cerebrovascular events were also available. Cox proportional hazards models were used to determine whether carotid bruit status was an independent predictor of stroke and to identify other significant cerebrovascular risk factors.

Results—One hundred thirty-four patients (11.3%) suffered a first stroke during 6.5 years of follow-up. In the first 2 years after study entry, first stroke (n=45/1181; 3.8%) was strongly predicted by the presence of carotid bruit(s) after adjustment for known cardiovascular risk factors and other potentially confounding variables (hazard ratio, 6.7; 95% CI, 3.0 to 14.9; P<0.001). Between 2 years and census, first stroke (n=89/1083; 8.2%) was not associated with carotid bruit(s) (P=0.97). Age and diastolic blood pressure were other determinants of stroke in the first 2 years, while age, atrial fibrillation/flutter, and microalbuminuria were independent predictors of subsequent stroke.

Conclusions—Type 2 diabetic patients found to have incidental carotid bruits have 6 times the risk of first stroke in the first 2 years than patients without a bruit and should receive intensified management of vascular risk factors. Carotid imaging with a view to surgical intervention in these patients remains controversial. (Stroke. 2003;34:2145-2151.)

Key Words: carotid artery diseases ■ diabetes mellitus, non-insulin-dependent ■ stroke
Clinical and Laboratory Methods
All patients had an initial comprehensive assessment and were requested to attend annual reviews for at least 5 years. At each visit, demographic and clinical information, including details of diabetes management and cardiovascular risk factors, was documented. A full clinical examination was performed, including physician assessment of the presence of carotid bruits. Any focal bruit found during auscultation over the carotid arteries that was not considered to represent either a venous hum or a murmur transmitted from heart valves or great vessels was recorded. Biochemical tests were performed on fasting blood and urine samples by standard automated methods. Microalbuminuria was defined as an albumin-to-creatinine ratio ≥3.0 mg/mmol in an early morning urine sample. A resting 12-lead ECG was recorded.

Patients were followed until first stroke, death, or the end of January 2002, whichever came first. All strokes and transient ischemic attacks experienced by each patient were ascertained from self-report and/or neurological examination at study entry and each follow-up visit. In addition, details of any hospital admission for stroke or death from stroke for any patient between April 1993 and January 2002 were obtained from the Western Australia Research Linked Database. This database includes the Western Australia death register and details of all hospital separations in Western Australia. Hospitalizations for stroke were defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 430 to 434 and 436 or International Statistical Classification of Diseases and Related Health Problems, Australian Modification (ICD-10-AM) codes 160 to 166 as either principal or secondary diagnosis codes. Two authors (T.M.E.D. and D.G.B.) independently scrutinized causes of death to identify which were due to stroke without knowledge of clinical details, including carotid bruit status. The 2 classifications were compared, and, when discrepancies occurred, patient notes were consulted and a consensus coding was obtained. The Western Australia Research Linked Database was also used to identify all FDS patients who underwent carotid endarterectomy during follow-up.

Statistical Analysis
Statistical analysis was performed with the computer package SPSS for Windows (version 10.0; SPSS Inc.). Data are presented as proportions or mean±SD, geometric mean (SD range), or, in the case of variables that did not conform to a normal or log-normal distribution, median (interquartile range). The Student t test was used for comparison of 2 means, the Fisher exact test for 2 proportions, and the χ2 test for multiple proportions. Two-group nonparametric comparisons were performed with the Mann-Whitney U test. A significance level of P<0.01 was used for univariate tests to reduce the likelihood of type 1 error.

Survival curves defined by carotid bruit status were constructed with the use of Kaplan-Meier estimates and compared with the log-rank test. Cox proportional hazards modeling was first used to determine whether carotid bruit was an independent predictor of stroke after adjustment for potential confounding variables. In a second analysis, Cox proportional hazards modeling (forward conditional variable entry and removal with P<0.05) was used to identify independent predictors of stroke among clinically plausible variables that included carotid bruit status. The validity of the proportional hazards assumption was assessed from log(-log[survival]) curves and examination of time-dependent covariates.

Results
Baseline Patient Characteristics
Of the 1294 FDS patients with type 2 diabetes, 109 (8.4%) had a history of stroke or transient ischemic attack before recruitment, and 4 subjects were not assessed for carotid bruits. The baseline characteristics of the remaining 1181 patients are summarized by carotid bruit status in Table 1. Carotid bruits were detected in approximately 1 in 20 patients. Patients with bruit(s) were older and had longer diabetes duration than those without. They had a significantly higher mean systolic blood pressure, were more likely to be taking blood pressure treatment, and were leaner. One quarter of patients with bruit(s) took regular aspirin compared with less than one fifth of those without bruits, while the majority of patients with atrial fibrillation/flutter were not taking warfarin therapy.

Carotid Bruit as a Predictor of First Stroke
The cumulative survival curves for patients remaining free of stroke in the 2 groups are shown in the Figure. There was a significant difference between the curves (P<0.0001, log-rank test). In a time-dependent Cox proportional hazards model including log(time) and carotid bruit status, the interaction between these variables was significant (P=0.036). This indicated that the proportional hazards assumption was invalid. Inspection of the survival curves revealed that the effect of carotid bruit status was strongest in the first 2 years (Figure). We therefore divided follow-up into from baseline to 2.0 years and from 2.0 years to census. The proportional hazards assumption held for both time periods (P=0.40).

In the initial Cox proportional hazards modeling, age, sex, body mass index, waist circumference, diabetes duration, glycemic control, blood pressure, blood pressure treatment, serum lipid measures, lipid-lowering therapy, aspirin use, microalbuminuria, presence of atrial fibrillation/flutter, smoking status, alcohol use, and exercise status were entered into 2 separate models defined by period of follow-up, and carotid bruit status was then added in each case. In the period between baseline and 2.0 years, 45 patients (3.8%) suffered a first stroke, of which 6 (13.3%) were fatal. After adjustment for potential confounders, first stroke was independently predicted by the presence of carotid bruit (P<0.001; Table 2). There was a >6-fold increased risk of first stroke in those with a bruit. For the period between 2.0 years and census, the surviving 1083 stroke-free patients were followed for an additional 4.9±1.6 years. Eighty-nine of these (8.2%) suffered a first stroke, of which 21.3% were fatal. The presence of carotid bruit(s) at study entry did not predict stroke during this period (P=0.97; Table 2).

Other Predictors and Features of First Stroke
Separate Cox proportional hazards forward conditional models were then applied to data from each period of follow-up to determine other independent predictors of first stroke. The results of these analyses are summarized in Table 3. For baseline to 2.0 years, age, diastolic blood pressure, and carotid bruit(s) remained in the model, the latter variable being the strongest predictor. For 2.0 years to census, age, diabetes duration, microalbuminuria, and atrial fibrillation were significant determinants of first stroke. There was an inverse association between total serum cholesterol level and risk of first stroke, while patients taking aspirin therapy were more likely to suffer stroke during this period.
Eighteen strokes occurred in patients with carotid bruit(s) during follow-up. We had complete clinical data for 10 of these and, in 9 (90%), the stroke was either on the same side as the bruit or, in 1 case, occurred in the presence of bilateral bruits. During follow-up, 25 FDS patients, or 1.9% of the 1294 with type 2 diabetes, underwent carotid endarterectomy. From available data, only 3 of these patients (12%) were free of symptoms of cerebrovascular disease at the time of surgery.

**Discussion**

The present results are from the largest reported community-based cohort of diabetic patients in which carotid auscultation formed part of vascular assessment. We found that, after adjustment for known cardiovascular risk factors and other relevant variables, the presence of an asymptomatic carotid bruit was independently associated with a >6-fold increased risk of stroke in patients with type 2 diabetes during the first 2 years after the bruit was detected. The presence of a carotid bruit had no impact on the incidence of stroke beyond this time.

Few studies have examined the temporal relationship between detection of an asymptomatic carotid bruit and outcome. In 1 study involving 149 patients with peripheral arterial disease, the presence of asymptomatic bruit did not influence the cumulative incidence of stroke during a follow-up period of >5 years, but mortality rates were understandably high (>30%). In another study of 500 referred outpatients with asymptomatic carotid bruit, 13% of whom had diabetes, those with high-grade (>75%) stenosis...
by Doppler ultrasonography had a steeply rising cumulative rate of ischemic cerebral events in the first 24 months compared with lesser degrees of occlusion, followed by a plateau at between 20% and 25% thereafter. Since these data are very similar in pattern and magnitude to those of our subjects with asymptomatic carotid bruit (Figure), it can be inferred that either the majority of our patients with bruits had relatively advanced carotid artery disease at study entry or the presence of diabetes in this group has the risk equivalence for stroke of high-grade stenosis in the nondiabetic population.

Although auscultation for carotid bruits has been shown to be a reliable indicator of underlying arterial stenosis in symptomatic patients in the general population, the effectiveness of carotid auscultation in screening for under-

### Table 2. Cox Proportional Hazards Model of Carotid Bruit as a Predictor of Time to First Stroke After Adjustment for Known Risk Factors and Potential Confounders at Study Entry

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Baseline to 2 Years</th>
<th>2 Years to Census</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, 10-year increase</td>
<td>1.5 [1.0, 2.3]</td>
<td>0.052</td>
</tr>
<tr>
<td>Male</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Diabetes duration, 5-year increase</td>
<td>1.1 [0.8, 1.3]</td>
</tr>
<tr>
<td></td>
<td>BMI, 1-kg/m² increase</td>
<td>1.0 [0.9, 1.1]</td>
</tr>
<tr>
<td></td>
<td>Waist circumference, 10-cm increase</td>
<td>0.9 [0.5, 1.7]</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure, 10-mm Hg increase</td>
<td>1.0 [0.8, 1.2]</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure, 10-mm Hg increase</td>
<td>1.3 [0.9, 1.8]</td>
</tr>
<tr>
<td>Blood pressure medication</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fasting plasma glucose, 1-mmol/L increase</td>
<td>0.9 [0.8, 1.1]</td>
</tr>
<tr>
<td></td>
<td>Glycated hemoglobin, 1.0% increase</td>
<td>1.2 [0.9, 1.6]</td>
</tr>
<tr>
<td></td>
<td>Total serum cholesterol, 1-mmol/L increase</td>
<td>1.3 [0.9, 1.9]</td>
</tr>
<tr>
<td></td>
<td>Serum HDL cholesterol, 0.1-mmol/L increase</td>
<td>1.0 [0.8, 1.1]</td>
</tr>
<tr>
<td></td>
<td>Ln(serum triglycerides)</td>
<td>0.7 [0.3, 1.7]</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Microalbuminuria</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Aspirin therapy</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Smoking status</td>
<td>Never</td>
</tr>
<tr>
<td></td>
<td>Ex-smoker</td>
<td>1.2 [0.8, 1.5]</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>2.1 [0.8, 5.4]</td>
</tr>
<tr>
<td></td>
<td>Exercise during the past 2 weeks</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Daily alcohol use, (1 standard drink increase)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Carotid bruit(s)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.0 [0.4, 2.6]</td>
</tr>
</tbody>
</table>
lying arterial disease has been questioned, especially in asymptomatic patients. Nevertheless, the present 2-year data and the relatively high incidence of diabetes-related ischemic stroke in other studies suggest that type 2 diabetes represents a special situation. This raises the issue of heightened risk factor management and perhaps also of further investigations such as carotid Doppler studies in asymptomatic patients with type 2 diabetes who have detectable carotid bruits.

Of relevance to cardiovascular risk factor management, our patients with carotid bruits had a higher mean systolic blood pressure than those without. This could result from less intensive monitoring and treatment because of their older age and leaner body mass index. In addition, their systolic hypertension and wider pulse pressure may have been a reflection of relatively advanced atherosclerosis. Nevertheless, the association between diastolic blood pressure and early stroke in the present study and the results of others have confirmed hypertension as a strong independent risk factor for cerebrovascular disease in diabetes, and intensive blood pressure-lowering has been shown to reduce stroke incidence.

In addition, United Kingdom Prospective Diabetes Study (UKPDS) epidemiological data suggest that there is no blood pressure threshold for benefit in prevention of stroke in type 2 diabetes. Thus, patients with carotid bruit in our cohort were already disadvantaged by a greater prevalence of hypertension even though more were taking antihypertensive therapy. In parallel with blood pressure data, UKPDS epidemiological analyses show a continuous positive relationship between glycohemoglobin and risk of stroke. Although glycemic control was not an independent risk factor for stroke in our patients, those with bruits tended to have higher glycohemoglobin levels than those without.

For serum lipids, use of lipid-lowering therapy, prevalence of microalbuminuria, smoking habit, prevalence of atrial fibrillation/flutter, and use of anticoagulant/antiplatelet therapy, there were no significant differences when our cohort was grouped according to carotid bruit status. Nevertheless, the results of the Heart Protection Study support a role for statin therapy in patients at increased risk of stroke such as those with type 2 diabetes, regardless of the serum total cholesterol concentration, and the minority of our patients were taking this form of therapy. Despite a strong independent association between atrial fibrillation/flutter and first stroke between 2.0 years and census, a finding consistent with UKPDS data, few of our patients with atrial fibrillation/flutter were anticoagulated at study entry. In addition, less than a third of our patients were taking regular aspirin regardless of carotid bruit status. One in 7 of our patients were current smokers. There are therefore a number of targets for interventions that, although appropriate for all patients with type 2 diabetes, could be more aggressively pursued in those with asymptomatic carotid bruits.

There is still controversy regarding surgery for asymptomatic carotid artery stenosis. Two recent reviews concluded that carotid endarterectomy in this situation is associated with marginal benefit and questionable safety, and large numbers of individuals must be treated to prevent a single stroke. Aggressive cardiovascular risk factor management has been recommended for these patients. Although there may be subgroups who clearly benefit from endarterectomy, their characteristics cannot be determined from existing evidence. It is possible that diabetic patients may constitute such a subgroup, but there are some concerns regarding a high rate of postoperative cardiac complications.
able evidence, it does not appear that further evaluation of asymptomatic type 2 patients with carotid bruits using Doppler is warranted.

In the cohort as a whole, the apparently paradoxical inverse relationship between total serum cholesterol level and late stroke might reflect a survivor effect. The average age of our patients was 64 years, and it is possible that those patients with type 2 diabetes and high serum cholesterol levels in the Fremantle community had died from coronary artery disease before they could be recruited. The aspirin-treated patients in our cohort were those at greatest vascular risk, which might help to explain the positive relationship between aspirin use and late stroke. An increase in hemorrhagic stroke might also have contributed, but, as the results of CT were not always available, an examination of this hypothesis was beyond the scope of the present study. An association between albuminuria and cerebrovascular disease has been reported in studies of patients with established diabetes, and our data were consistent with this finding. In the UKPDS, microalbuminuria was not a significant determinant of stroke. It is of interest that UKPDS patients were newly diagnosed. It may be that microalbuminuria becomes a more important marker of cerebrovascular disease with time, reflecting increasing diabetes-associated endothelial dysfunction.

The present study has limitations. First, a carotid bruit may not represent internal artery stenosis. Transmitted cervical, subclavian, or external carotid artery bruits can be difficult to distinguish from those arising from internal carotid arterial disease. Nevertheless, the strength of the relationship between detectable bruits and subsequent ipsilateral stroke argues against this as an important confounding influence. Second, ascertainment of cerebrovascular disease status before study entry relied principally on self-report, and there may have been misclassification of patients who did not report symptoms. In patients who underwent carotid endarterectomy during follow-up, the majority gave a history of cerebrovascular disease both at study entry and preoperatively. The 3 cases that were asymptomatic at time of surgery also reported no symptoms at study entry. These data provide some evidence that misclassification was not an important confounder and also confirm that carotid endarterectomy had minimal bearing on the incidence of stroke in our asymptomatic patients during follow-up.

Our data, from a community-based patient cohort, demonstrate that the detection of a carotid bruit confers a 6-fold increased risk of an early stroke in type 2 diabetic patients without a history of cerebrovascular disease. Although further investigation with a view to surgery does not appear justifiable on current evidence, the present data highlight the need for careful cervical auscultation as part of regular routine physical examinations and intensification of vascular risk factor management, especially hypertension, in patients with detectable bruits.

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References


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