Cardiac Prognosis of Patients With Carotid Stenosis and No History of Coronary Artery Disease

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Background and Purpose Patients with carotid stenosis have a high frequency of asymptomatic coronary artery disease (CAD). The purpose of this study of patients with asymptomatic carotid stenosis was to test the hypothesis that patients without a history of CAD have the same cardiac prognosis as patients with a history of CAD.

Methods Men enrolled in the Department of Veterans Affairs study on the efficacy of carotid endarterectomy for asymptomatic carotid stenosis underwent a baseline cardiac evaluation (history, physical examination, and electrocardiogram) to document previous angina or myocardial infarction. Patients were randomized to medical therapy alone or medical therapy and carotid endarterectomy. Medical therapy consisted of aspirin 650 mg twice daily and treatment of risk factors. All episodes of angina, myocardial infarction, or sudden death during follow-up (average of 47.9 months) were recorded.

Results Of 444 men enrolled in the study, 200 (45%) had a history of CAD. During the study 86 (43%) of 200 patients with CAD and 81 (33%) of 244 patients without a history of CAD had cardiac ischemic events (P=.03). In patients without a history of CAD, the first cardiac event was myocardial infarction or sudden death in 45 patients (36%). Factors that were independently associated with cardiac events in patients without a history of CAD were diabetes (odds ratio [OR], 2.14; 95% confidence interval [CI], 1.15 to 3.97), intracranial occlusive disease (OR, 2.13; 95% CI, 1.13 to 4.02), and peripheral vascular disease (OR, 2.04; 95% CI, 1.14 to 3.66). Forty-two percent of patients with two of these factors and 69% of patients with all three factors had cardiac events.

Conclusions Men with carotid stenosis and no history of CAD have a lower rate of cardiac events than men with carotid stenosis who have a history of CAD. However, a subgroup of patients with carotid stenosis and no history of CAD who have coexistent intracranial occlusive disease, diabetes, or peripheral vascular disease have a risk of cardiac events similar to that of patients with a history of CAD. (Stroke. 1994;25:759-765.)

Key Words • aspirin • carotid endarterectomy • death • myocardial infarction

Virtually every population study and stroke therapy trial has shown that coronary artery disease (CAD) is the major cause of death in patients with cerebrovascular disease.1-7 There are limited data, however, on whether the high risk of cardiac death in patients with cerebrovascular disease is restricted largely to patients with a history of CAD. One population study of patients with transient ischemic attacks showed that cardiac mortality was independent of cardiac history; however, this finding has not been confirmed or refuted in a large prospective study.

Previous studies have shown that 25% to 70% of patients with cerebrovascular disease and no history of CAD have abnormal exercise electrocardiography or thallium myocardial perfusion imaging.8-13 Moreover, Hertzer et al14 showed that 40% of patients with carotid stenosis and no history of CAD have greater than 70% stenosis of at least one coronary artery. These findings suggest that patients with cerebrovascular disease and no history of CAD may be at a risk of cardiac events similar to that of patients with a history of CAD. Demonstration that patients with cerebrovascular disease and no history of CAD have a high frequency of cardiac events would justify development of effective strategies for detecting and treating asymptomatic CAD in these patients, particularly if the majority of cardiac events were sudden death or myocardial infarction (MI) without preceding angina.

The Department of Veterans Affairs (VA) study on the efficacy of carotid endarterectomy for asymptomatic carotid stenosis offered a unique opportunity to evaluate both neurological and cardiac outcomes prospectively in a large number of patients with carotid stenosis. The neurological outcome of patients in this study has recently been published.15 We also evaluated the cardiac outcome of these patients, focusing specifically on the hypothesis that patients with carotid stenosis and no history of CAD have the same cardiac prognosis as patients with carotid stenosis who have a history of CAD.

Subjects and Methods

The overall design of the VA multicenter study of the efficacy of carotid endarterectomy for asymptomatic carotid stenosis has
been described previously.15,16 The methods described below refer specifically to the cardiac aspects of this study.

Patient Selection

Potential candidates for the study were male veterans with ≥50% stenosis of at least one extracranial internal carotid artery documented by cerebral angiography. Exclusion criteria included previous cerebral infarction or transient ischemic attack ipsilateral to carotid stenosis, ipsilateral carotid siphon or middle cerebral artery stenosis exceeding the severity of the extracranial internal carotid artery stenosis, severe intellectual impairment or psychiatric disease, life expectancy less than 5 years, long-term anticoagulant therapy, aspirin intolerance, and medical conditions that, in the opinion of the local investigator, constituted an unacceptably high risk for surgical therapy (eg, severe hypertension, severe cardiopulmonary disease, myocardial infarction during the previous 3 months, or unstable angina requiring concomitant coronary artery bypass graft [CABG]).

Baseline Cardiac Evaluation

The baseline cardiac evaluation consisted of a history, physical examination, and an electrocardiogram (ECG). The history and physical examination were performed by, or under the direction of, the surgeon or neurologist participating in the trial. All ECGs were interpreted by cardiologists at the participating centers. Patients were considered to have no history of CAD if they did not have a history of CABG, angina, symptomatic MI, or evidence of an asymptomatic MI by ECG. Patients with any of these features were considered to have a history of CAD.

The original protocol did not include a mandatory cardiology consultation for each patient before randomization; however, this requirement was added to the protocol 18 months into the study after a number of perioperative cardiac complications occurred. Patients randomized before this addition to the protocol did not subsequently undergo a mandatory cardiology consultation. The rates of perioperative MI and MI or sudden death during follow-up in these two groups of patients (ie, those who had a mandatory cardiology consultation and those who did not) were compared.

Baseline Evaluation of Vascular Risk Factors

Detailed information on the following clinical and angiographic features was obtained on all patients: age, race, hypertension, diabetes, cigarette smoking, peripheral vascular disease (history of claudication or peripheral arterial reconstructive surgery), hematocrit, bilateral extracranial internal carotid artery stenosis ≥50%, and intracranial occlusive disease documented by bilateral carotid angiography. Intracranial occlusive disease was defined as ≥50% stenosis of the carotid siphon or middle cerebral artery on either side (note that carotid siphon or middle cerebral artery stenosis exceeding the severity of the ipsilateral extracranial carotid artery stenosis was one of the exclusion criteria for the study). Baseline measures of cholesterol and triglycerides were not required as part of the study protocol.

Treatment, Follow-up, and Cardiac End Points

All patients were treated with aspirin at an initial dose of 650 mg twice daily. The dose was reduced to 325 mg daily for patients who could not tolerate larger doses. Patients with hypertension and diabetes were treated with appropriate medical or dietary therapy or both, and smoking was strongly discouraged. Approximately half the patients in the trial were randomly selected to undergo carotid endarterectomy.

Patient recruitment began in April 1983 and ended in September 1987. Patients were followed until March 1991. Routine follow-up of each patient was scheduled at 13-week intervals in the first year after randomization and at 26-week intervals in subsequent years. At each follow-up visit, patients were questioned about the occurrence of chest pain. All suspected episodes of angina were documented. Patients suspected of having a myocardial infarction since the previous outpatient visit, for which they were not hospitalized (a rare occurrence), were referred to a cardiologist for further evaluation. Patients who were hospitalized during the trial were evaluated to determine the reason for hospitalization. All episodes of angina or symptomatic MI that led to hospitalization or occurred during hospitalization were recorded. When patients died in the hospital, the cause of death was determined by review of the medical records or by the findings at autopsy, if performed. When patients died at home, a definite cause of death could only be established if an autopsy was performed; otherwise, a probable cause of death was assigned based on the reports of emergency technicians or the history obtained from the patient’s family. Sudden death outside the hospital was presumed to be caused by ventricular dysrhythmias associated with cardiac ischemia.

All deaths were reviewed by the End Points Committee; those considered cardiac in origin were reviewed by a cardiologist (M.R.S.) to determine if they were caused by cardiac ischemia or nonischemic cardiac causes (eg, valvular disease or nonischemic congestive heart failure). Each patient’s cardiac status at study entry was blinded to the reviewers.

Statistical Analysis

Vascular risk factors and cardiac event rates during follow-up were compared in patients with CAD at study entry versus patients without CAD. χ² tests were used to compare rates and proportions of categorical variables; t tests were used to compare the means of continuous variables. Cumulative event-free rates for the time to MI (fatal or nonfatal) or sudden death were estimated by the Kaplan-Meier product limit method, and the two groups (ie, patients with a history of CAD and patients without a history of CAD) were compared by the log-rank statistic. After verifying the proportional hazards assumption, the relative risks for the MI or sudden death analysis and 95% confidence intervals were determined using the Cox model, which incorporates the duration of follow-up. All statistical comparisons were two-tailed.

Univariate and multivariate analyses were subsequently performed to identify factors that were associated with an increased risk of cardiac events during follow-up. Univariate analyses were performed using χ² tests to compare the rates of cardiac events in patients with versus patients without each risk factor. Multivariate analysis was performed using stepwise logistic regression (the proportional hazards assumption of the Cox model did not apply to all risk factors). All the statistical analyses were performed with the STATISTICAL ANALYSIS SYSTEM or BMDP statistical software.

Results

Screening and Cardiac Status at Study Entry

Eleven VA medical centers screened 1935 adult men for the trial, of which 444 patients were enrolled in the study. The reasons for exclusion and the numbers of patients excluded for each reason have been published previously.15 Of the 444 patients enrolled in the study, 244 (55%) had no history of CAD at study entry. The remaining 200 patients (45%) had a history of CAD: 118 had a symptomatic MI, 64 had angina alone, 15 had evidence of an asymptomatic MI by ECG, and 3 had undergone CABG but denied angina or MI. Fifty-nine (29.5%) of 200 patients with CAD at study entry had undergone CABG.

Risk Factor Analysis in Patients With Versus Patients Without a History of Coronary Artery Disease

Vascular risk factors of the 200 patients with CAD and the 244 patients without a history of CAD at study
entry are shown in Table 1. Hypertension (P<.001), bilateral carotid stenosis (P=.06), and diabetes (P=.07) were more common in patients with CAD. The percentage of patients who had ever smoked was similar in both groups, but patients without CAD were significantly more likely to be current smokers.

Cardiac Events During Follow-up in Patients With Versus Patients Without a History of Coronary Artery Disease

The average length of follow-up in the study was 47.9 months. During the study, 86 (43%) of 200 patients with CAD and 81 (33%) of 244 patients without a history of CAD had at least one cardiac ischemic event (P=.03). The first cardiac event in the 86 patients with a history of CAD was angina in 27 patients (31%), nonfatal MI in 19 patients (22%), and fatal MI or sudden death in 40 patients (47%). In the 81 patients without a history of CAD who had at least one cardiac event, the first event was angina in 36 patients (44%), nonfatal MI in 17 patients (21%), and fatal MI or sudden death in 28 patients (35%). Excluding angina as an end point, 60 (25%) of 244 patients without a history of CAD had nonfatal MI (22 patients) or fatal MI/sudden death (38 patients) during follow-up, whereas 67 (33%) of 200 patients with CAD had nonfatal MI (20 patients) or fatal MI/sudden death (47 patients) (P=.04). Autopsies in 9 of 85 patients whose deaths were attributed to cardiac ischemia confirmed acute MI in 7 patients, ischemic cardiomyopathy with congestive heart failure in 1 patient, and an old MI with diffuse patchy fibrosis of the left ventricle in the other patient.

The temporal distributions of MI or sudden death in patients with and patients without a history of CAD are illustrated in the Figure. Comparisons by the log-rank test show a significantly lower percentage of patients free of MI or sudden death in patients with a history of CAD (P=.01). The relative risk of MI or sudden death in patients with a history of CAD was 1.54, with a 95% confidence interval (CI) of 1.08 to 2.20. The temporal distribution of stroke ipsilateral to carotid stenosis (including perioperative stroke) is also presented in the Figure. Inspection of the Kaplan-Meier curves for cardiac and neurological end points demonstrates that the rate of MI or sudden death far exceeded the rate of ipsilateral stroke, regardless of cardiac history.

Risk Factors Associated With Cardiac Ischemic Events

In the 200 patients with CAD at study entry, none of the vascular risk factors evaluated were associated with an increased risk of new cardiac events during follow-up. In the 244 patients without a history of CAD, univariate
TABLE 2. Predictors of Cardiac Events During Follow-up in 244 Patients Without a History of Coronary Artery Disease at Study Entry

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cardiac Event Rate In Patients With Risk Factor</th>
<th>Cardiac Event Rate In Patients Without Risk Factor</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71/210 (34)</td>
<td>10/34 (29)</td>
<td>.63</td>
</tr>
<tr>
<td>Black</td>
<td>7/20 (35)</td>
<td>74/224 (33)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3/14 (21)</td>
<td>78/230 (34)</td>
<td></td>
</tr>
<tr>
<td>Ever smoked</td>
<td>75/227 (33)</td>
<td>6/17 (35)</td>
<td>.85</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>48/135 (36)</td>
<td>33/109 (30)</td>
<td>.38</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29/80 (48)</td>
<td>52/184 (28)</td>
<td>.004</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44/135 (33)</td>
<td>37/109 (34)</td>
<td>.82</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>56/112 (39)</td>
<td>25/102 (25)</td>
<td>.02</td>
</tr>
<tr>
<td>Hematocrit &gt;50%</td>
<td>6/10 (60)</td>
<td>75/234 (32)</td>
<td>.07</td>
</tr>
<tr>
<td>Intracranial occlusive disease*</td>
<td>27/58 (47)</td>
<td>54/186 (29)</td>
<td>.014</td>
</tr>
<tr>
<td>Bilateral carotid stenosis ≥50%</td>
<td>45/118 (38)</td>
<td>36/126 (29)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. The mean±SD age of patients with cardiac events was 65.1±6.9 years; the mean±SD age of patients without cardiac events was 65.0±6.6 years (P=.83).

*When a carotid siphon or middle cerebral artery was inadequately visualized, the artery was classified as normal (by convention). Excluding patients with an inadequately visualized intracranial vessel yielded a similar probability value (P=.008).

Stepwise logistic regression analysis showed that diabetes (P=.004), intracranial occlusive disease (P=.014), and peripheral vascular disease (P=.02) were associated with an increased risk of cardiac events during follow-up (Table 2).

Impact of Mandatory Cardiology Consultation on Cardiac Morbidity and Mortality

Two hundred ten patients were enrolled before a mandatory cardiology consultation was required (118 had no history of CAD, and 92 had a history of CAD). Of these 210 patients, 93 underwent carotid endarterectomy. Within 30 days of endarterectomy, 5 of 93 patients (5.4%) had MI (two fatal, three nonfatal). Both fatal MIs and two of the nonfatal MIs occurred in patients without a history of CAD. During follow-up, 23 of 118 (19%) patients without a history of CAD and 29 of 92 (32%) patients with a history of CAD had MI or sudden death.

After a mandatory cardiology consultation was added to the protocol, 234 patients were enrolled (126 had no history of CAD and 108 had a history of CAD). Of these 234 patients, 110 underwent carotid endarterectomy. Within 30 days of endarterectomy, 4 of 110 patients (3.6%) had MI (two fatal, two nonfatal). One

TABLE 3. Risk of Developing Cardiac Events by Number of Risk Factors Present (Diabetes, Intracranial Occlusive Disease, Peripheral Vascular Disease) in Patients With No History of Coronary Artery Disease

<table>
<thead>
<tr>
<th>No. of Risk Factors</th>
<th>No. of Patients With Cardiac Events</th>
<th>Odds Ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>8 (13)</td>
<td>...</td>
</tr>
<tr>
<td>1</td>
<td>121</td>
<td>43 (36)</td>
<td>3.58</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>21 (42)</td>
<td>4.71</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>9 (69)</td>
<td>14.63</td>
</tr>
</tbody>
</table>

CI indicates confidence interval. Values in parentheses are percentages.

*All significant at P<.001.

analysis showed that diabetes (P=.004), intracranial occlusive disease (P=.014), and peripheral vascular disease (P=.02) were associated with an increased risk of cardiac events during follow-up (Table 2).

Stepwise logistic regression analysis showed that intracranial occlusive disease, diabetes, and peripheral vascular disease were associated with an increased risk of cardiac events when adjusted for all the other risk factors. The odds ratio (OR) associated with diabetes was 2.14 (95% CI, 1.15 to 3.97), the OR associated with intracranial occlusive disease was 2.13 (95% CI, 1.13 to 4.02), and the OR associated with peripheral vascular disease was 2.04 (95% CI, 1.14 to 3.66). Patients with combinations of these three risk factors had the highest risk of cardiac events: whereas only 13% of patients with none of these factors had cardiac events, 36% of patients with one factor, 42% of patients with two factors, and 69% of patients with all three factors had cardiac events (Table 3).
of the fatal MIs and one of the nonfatal MIs occurred in patients who had no history of CAD. During follow-up, 31 of 126 (25%) patients without a history of CAD and 35 of 108 (32%) patients with a history of CAD had MI or sudden death. The rates of perioperative MI and MI or sudden death during follow-up were not significantly different in patients enrolled before compared with patients enrolled after a mandatory cardiology consultation was required.

Discussion

Previous studies have shown that 25% to 70% of patients with cerebrovascular disease and no history of CAD have evidence of asymptomatic CAD; however, only one of these studies evaluated long-term cardiac outcome in these patients. In that study, 106 patients with carotid stenosis and no history of CAD were followed for an average of 5.4 years after carotid endarterectomy. Eight of 27 patients (29.6%) with abnormal thallium-201 myocardial perfusion imaging studies had an MI or unstable angina during follow-up compared with only 1 of 79 patients (1.3%) with normal myocardial perfusion imaging studies (P < 0.01).

The results of the present study provide more definitive evidence that men with carotid stenosis and no history of CAD have an extremely high rate of angina, MI, or sudden death during follow-up (33% over an average of 4 years) despite treatment with aspirin and careful management of vascular risk factors. Although men with carotid stenosis and a history of CAD have a significantly higher rate of cardiac events (43% over an average of 4 years), a subgroup of patients with no history of CAD who have coexistent intracranial occlusive disease, diabetes, or peripheral vascular disease have a risk of cardiac events similar to that of patients with a history of CAD (Tables 2 and 3). Moreover, patients without a history of CAD consist of a subgroup without CAD and a subgroup with asymptomatic CAD (± 25% to 70% of the entire group based on previous studies of patients with carotid stenosis). Because virtually all cardiac ischemic events in the patients without a history of CAD would have occurred in the subgroup with asymptomatic CAD, the results of this study in patients with carotid stenosis and asymptomatic CAD have a cardiac prognosis similar to that of patients with carotid stenosis who have stable CAD (patients with unstable CAD were excluded from the study).

Patients in this study were identified by the presence of asymptomatic carotid stenosis, yet the rate of MI or sudden death far exceeded the rate of stroke, regardless of cardiac history (Figure). Although patients who underwent carotid endarterectomy had a lower rate of ipsilateral stroke (4.7%) than patients treated medically (9.4%), this difference did not achieve statistical significance, possibly because the high rate of cardiac death during follow-up substantially reduced the power of the study to detect such a difference. A corollary of these findings is that any benefit of carotid endarterectomy in patients with asymptomatic carotid stenosis will be manifested only during follow-up substantially reduced the power of the study to detect such a difference. A corollary of these findings is that any benefit of carotid endarterectomy in patients with asymptomatic carotid stenosis will be manifested only during follow-up.

Although strategies have evolved for evaluating and treating symptomatic CAD in patients with carotid stenosis, this is not true of asymptomatic CAD. If the first cardiac event in the majority of patients with carotid stenosis and no history of CAD was angina, it would be prudent to follow patients clinically until they manifested angina. However, because the majority of asymptomatic patients with carotid stenosis and no history of CAD have evidence of asymptomatic CAD and no history of CAD were MI or sudden death. This finding suggests the need for a more aggressive diagnostic and therapeutic approach to asymptomatic CAD in patients with carotid stenosis. One approach to consider would be a mandatory cardiology consultation for all patients with carotid stenosis. However, the results of this study suggest that a clinical evaluation by a cardiologist without routine use of noninvasive myocardial perfusion imaging appears to be ineffective in reducing the perioperative MI rate and the long-term risk of MI or sudden death in patients with carotid stenosis.

An alternative strategy to consider based on the results of this study would be to perform noninvasive myocardial perfusion imaging in the subgroup of patients with carotid stenosis and no history of CAD who have diabetes, peripheral vascular disease, or coexistent intracranial disease. Noninvasive screening for asymptomatic CAD in high-risk patients has not become standard medical practice because of the high cost of these procedures and a perception that asymptomatic CAD is relatively benign and the lack of a consensus on therapy for asymptomatic CAD. Previous studies of patients without carotid stenosis indicate that the annual mortality rate in asymptomatic patients with silent myocardial ischemia and asymptomatic CAD is 3% to 6%, which suggests that asymptomatic CAD may be justifiable based on current knowledge. Patients with coexistent diabetes, intracranial occlusive disease, or peripheral vascular disease should undergo noninvasive myocardial perfusion imaging studies to identify patients with underlying asymptomatic CAD. Since severe and extensive myocardial hypoperfusion is associated with a high risk of future cardiac events, patients with this finding should undergo coronary angiography, which can be performed safely with carotid angiography. Patients with severe multivessel or left main disease should be considered for CABG, whereas patients with less extensive disease should be treated with β-blockers or calcium channel blockers or angiolast. The results of ongoing studies comparing medical therapies for silent myocardial ischemia should be incorporated into this protocol as they become available. Recommendations regarding the cardiac evaluation of patients with carotid stenosis and no history of CAD who have a lower burden of risk factors than the patients in this trial.
must await prospective studies on the cardiac prognosis of these patients.

Appendix


Acknowledgment

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