Identifying Patients With Symptomatic Carotid Artery Disease at High and Low Risk of Severe Myocardial Infarction and Cardiac Death

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Background and Purpose—The extent of cardiac investigation required in patients with coexistent symptomatic carotid and cardiac disease is unsettled. This study compared the outlook for patients symptomatic from carotid stenosis with and without a history of symptomatic ischemic heart disease (IHD).

Methods—The risk of combined outcome of severe myocardial infarction and cardiac death was evaluated in patients from the North American Symptomatic Carotid Endarterectomy Trial.

Results—A total of 1124 patients had a history of symptomatic IHD and 1691 did not. The median age was 66 years; 70% were male. With history of IHD at entry, the 5-year risk of combined outcome of severe myocardial infarction and cardiac death was 16.5% (95% CI, 13.9 to 19.0). Without history at entry, risk was 6.7% (95% CI, 5.1 to 8.3). Risk of unheralded severe MI and cardiac death was only 3.3%.

Conclusions—Most patients with symptomatic carotid stenosis without symptomatic IHD had a low risk of severe myocardial infarction and cardiac death. With many risk factors, these patients had a risk high enough to warrant cardiac investigations.

Key Words: carotid artery diseases ■ heart disease ■ ischemia ■ prognosis
athy, recent congestive heart failure, and valvular disease likely to cause cardioembolism, were excluded from the trial. Patients with valvular heart disease unlikely to be associated with embolism or a remote history of either atrial fibrillation or congestive heart failure were eligible for entry into the trial. During follow-up, patients with hypertension, diabetes mellitus, or hyperlipidemia received best contemporary treatment, which was monitored by the central office. Cigarette smoking was discouraged. Enteric-coated aspirin was recommended for all patients throughout the trial. In the event of recurrent cerebral ischemic events despite aspirin, other platelet inhibitors or anticoagulants were permitted at the discretion of the treating physician.

Initial assessment consisted of a standardized history, examination, and investigations, details of which have been described previously.\textsuperscript{12,13} It included assessment of prior cardiac disease, in particular angina, MI, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, congestive cardiac failure, atrial fibrillation, and valvular heart disease. A 12-lead ECG and chest x-ray were performed at baseline and reviewed centrally. The ECGs were coded for left ventricular hypertrophy (on the basis of voltage criteria) and previous MI (presence of Q waves deeper than one third the height of the R wave). If the initial ECG suggested a previous asymptomatic MI, these patients were classified as not having a history of symptomatic IHD. The cardiothoracic ratio was measured on the chest x-ray.

Participating neurologists at the centers performed medical and neurological assessments on all patients at entry: 1, 3, 6, 9, and 12 months; and every 4 months thereafter. At each follow-up visit, any new occurrences of angina, MI, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or other cardiac disease were recorded. The diagnosis of angina was accepted when recorded on the follow-up form and did not require confirmation by a cardiologist. The diagnosis of MI required ECG or cardiac enzyme changes.

All deaths in NASCET were adjudicated internally and externally. The results of autopsy (when available), investigations, and detailed descriptions of the event were used to assign the cause of death. Sudden death was designated as cardiac in origin if the patient died within 24 hours and no autopsy or clinical information was available to accurately pinpoint an alternative cause of death.

Methods Pertaining Particularly to the Present Study

The severity of all MI was assessed (P.C.G.) from information obtained from follow-up data forms, inpatient notes, hospital discharge letters, and other correspondence. Cardiac failure complicating MI was defined as the presence of clinical or radiological evidence of left ventricular failure. The MI was coded as either fatal or nonfatal and, if nonfatal, as either mild or severe with the Killip classification.\textsuperscript{19} If the MI was uncomplicated, it was designated mild (the equivalent of Killip I severity). If it was associated with pulmonary venous congestion, pulmonary edema, or hypotension, it was designated severe (Killip II to IV). If a nonfatal cardiac arrest occurred, it was also designated severe. The Killip classification was chosen because it is a standardized and validated method for classifying the severity of MI. A cardiologist (R.W.G.) independently reviewed 40 randomly selected records and assigned the severity of MI using the same criteria. The interobserver \( \kappa \) was 0.73 (95\% CI, 0.51 to 0.95).

The medical condition of the patient either at the time of or at the previous follow-up visit before severe MI or cardiac death was also reviewed (P.W.G.) to ascertain the level of disability resulting from cardiac disease, stroke, dementia, and other disabling illnesses. Patients were deemed disabled if they were not capable of independent living. The presence of untreatable cardiac disease (inoperable coronary artery disease or cardiac failure refractory to medical therapy) or disseminated malignancy was also noted because these patients would not be candidates for cardiac intervention.

The primary analysis in the present study consisted of comparing 2 groups of patients: those with and those without a history of symptomatic IHD defined as a history of angina or symptomatic MI at entry into NASCET. The risks of combined outcome of MI and cardiac death were derived from Kaplan-Meier event-free survival curves and tested for statistical significance with a log-rank test. Cox proportional-hazards regression modeling was performed to identify baseline patient characteristics that increased the risk of combined outcome of severe MI and cardiac death. Associations were expressed in terms of hazard ratios, which may be interpreted as relative risks.

Results

Of the 2885 NASCET patients, 70 (2.4\%) did not have a history of IHD but had a remote history of other cardiac disorders. These patients were excluded from the present study because the focus was on IHD. The remaining 2815 patients were included in the present study. Of the 2815 patients, 1124 (39.9\%) had a history of symptomatic IHD at entry into the trial: 105 of 1124 (9.3\%) had concomitant cardiac disorders (congestive heart failure, atrial fibrillation, or valvular heart disease), and 379 of 1124 (33.7\%) had undergone either coronary artery bypass grafting or percutaneous transluminal coronary angioplasty before entry. The remaining 1691 of the 2815 patients (58.6\%) did not have a history of symptomatic IHD or other cardiac disorders, although 142 of 1691 (8.4\%) had asymptomatic MI on ECG. Baseline characteristics are shown in the 2 left columns of the Table for patients with and without a history of symptomatic IHD at entry.

During the course of the trial, with an average follow-up of 5 years, the predominant initial cardiac symptom was angina, which occurred in 306 patients (27.2\%) with a history of symptomatic IHD and in 215 (12.7\%) of those without IHD. During follow-up, a total of 284 patients had 289 cardiac procedures: 188 coronary artery bypass grafts, 62 percutaneous transluminal coronary angioplasties, 29 pacemaker insertions, 8 valve replacements, and 2 defibrillator insertions. Approximately twice as many patients with a history of symptomatic IHD had cardiac procedures during follow-up compared with patients without a history (13.7\% versus 7.7\%).

Among the 1124 patients with a history of symptomatic IHD, a total of 129 (94 mild, 35 severe) nonfatal MIs occurred in 111 patients, and 184 patients died of cardiac causes. Among the 1691 patients with no history of symptomatic IHD, 141 (101 mild, 40 severe) nonfatal MIs occurred in 127 patients, and 111 patients died of cardiac causes. The 5-year risk of combined outcome of any MI (mild or severe) and cardiac death was 22.1\% for patients with a history of symptomatic IHD compared with 10.9\% for patients without a history of symptomatic IHD (\( P < 0.001 \)).

The 5-year risk of combined outcome of severe MI and cardiac death for patients with a history of symptomatic IHD at entry was 16.5\% (95\% CI, 13.9 to 19.0) compared with 6.7\% (95\% CI, 5.1 to 8.3) in patients without a history of symptomatic IHD; for the subgroup of 142 patients who had asymptomatic MI on ECG, the 5-year risk was 11.2\% (95\% CI, 4.9 to 17.4). The Kaplan-Meier event-free survival curves show that the occurrence of these outcomes was approximately constant across time (Figure 1). In each of the 2 comparison groups, 26.0\% and 31.0\%, respectively, of the outcome events (ie, severe MI and cardiac death) were preceded by symptoms of angina or mild MI, 14.4\% and
16.1% by congestive heart failure, and 6.2% and 8.1% by atrial fibrillation. The mean time between any preceding cardiac symptom and outcome event was 1.8 years (range, 2 days to 4.6 years) and 1.3 years (range, 9 days to 4.1 years), respectively. For patients without a history of symptomatic IHD at entry, the 5-year risk of unheralded severe MI or cardiac death was only 3.3%. Before the occurrence of a severe MI or cardiac death, 24.0% were already medically disabled: 6.4% with stroke, 14.2% with other disorders (eg, dementia, peripheral vascular disease, arthritis, chronic obstructive airways disease, and disseminated malignancy), and 3.4% with untreatable cardiac disease. The causes and distribution of medical conditions were similar between the 2 groups.

The 2 right columns in the Table show the multivariate adjusted hazard ratios and corresponding 95% CIs for the association between each factor and the risk of combined outcome of severe MI and cardiac death in 2815 (1691/1124) patients. Because the test for interaction between all the risk factors and history or no history of symptomatic IHD was not statistically significant ($P = 0.69$, df = 10), a single hazard ratio is reported for each factor. The following 7 hazard ratios were statistically significant, with 5 having a ratio >1.5: age ≥75 years, history of hypertension, history of diabetes mellitus, smoking within the past year, creatinine >115 μmol/L, left ventricular hypertrophy on ECG, and MI on ECG.

The 5-year risk of combined outcome of severe MI and cardiac death increased with the number of risk factors that patients had at entry for those with and without a history of symptomatic IHD ($P<0.001$ for both groups, Figure 2). A combination of ≥4 of the 7 statistically significant risk factors was identified in 194 patients: 123 of 1124 (10.9%) with and 71 of 1691 (4.2%) without a history of symptomatic IHD. In the presence of ≥4 risk factors, the 5-year risk of combined outcome of severe MI and cardiac death increased to 33.9% for patients with a history of symptomatic IHD and to 23.5% for those without such a history. In contrast, in the absence of risk factors in patients both with and without a history of symptomatic IHD, the 5-year risk of combined

### Table: Baseline Characteristics of Patients With and Without a History of Symptomatic IHD at Entry and Adjusted Hazard Ratios for Severe MI or Cardiac Death

<table>
<thead>
<tr>
<th></th>
<th>History of Symptomatic IHD (n=1124), %</th>
<th>No History of Symptomatic IHD (n=1691), %</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 y</td>
<td>14.0</td>
<td>14.0</td>
<td>1.9</td>
<td>1.4–2.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>74.3</td>
<td>66.8</td>
<td>1.1</td>
<td>0.8–1.6</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>66.9</td>
<td>56.6</td>
<td>1.4</td>
<td>1.1–1.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25.1</td>
<td>19.0</td>
<td>2.7</td>
<td>2.0–3.5</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>37.1</td>
<td>32.6</td>
<td>0.7</td>
<td>0.6–1.1</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>19.8</td>
<td>11.8</td>
<td>1.1</td>
<td>0.8–1.5</td>
</tr>
<tr>
<td>Smoking in the past year</td>
<td>35.8</td>
<td>47.0</td>
<td>1.3</td>
<td>1.1–1.8</td>
</tr>
<tr>
<td>Creatinine ≥115 μmol/L</td>
<td>26.1</td>
<td>16.7</td>
<td>2.0</td>
<td>1.5–2.6</td>
</tr>
<tr>
<td>LVH on ECG</td>
<td>12.4</td>
<td>7.2</td>
<td>1.9</td>
<td>1.4–2.7</td>
</tr>
<tr>
<td>MI on ECG</td>
<td>33.6</td>
<td>8.4</td>
<td>1.7</td>
<td>1.3–2.3</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy.

Figure 1. Kaplan-Meier event-free survival curves for the combined outcome of severe MI and cardiac death according to history of symptomatic IHD at entry into NASCET. The 5-year risk of combined outcome of severe MI and cardiac death was 16.5% for patients with a history of symptomatic IHD (Yes) and 6.7% for patients without such a history (No). Comparing the 2 curves yielded $P<0.001$ by use of a log-rank test.

Figure 2. Five-year risk of combined outcome of severe MI and cardiac death according to the presence of 0 to ≥4 of the following 7 risk factors: age ≥75 years, history of hypertension, history of diabetes mellitus, smoking in the past year, creatinine ≥115 μmol/L, left ventricular hypertrophy on ECG, or MI on ECG. For patients with history of symptomatic IHD, a combination of 3 risk factors substantially increased the 5-year risk, whereas ≥4 risk factors were required to substantially increase the 5-year risk to approximately the same level for patients without a history of symptomatic IHD.
outcome of severe MI and cardiac death was low at 6.1% and 3.1%, respectively.

Discussion

The results of the present study show that the 5-year risk of combined outcome of severe MI and cardiac death in patients without a history of symptomatic IHD and symptomatic carotid disease was only 6.7%. Warning symptoms of angina or evidence of mild MI preceded approximately one third of the severe MI and cardiac deaths on average 1.5 years in advance. These observations suggest that patients being evaluated for symptomatic carotid artery disease may need cardiac investigation only after developing minor symptoms (angina or mild MI) or if they have many of the identified vascular risk factors. The argument for investigating patients is further diminished by the fact that at the time of the severe MI or cardiac death, 24% of the patients were medically disabled. Finally, although treatment has been proved efficacious for some subgroups of patients with symptomatic IHD, the evidence of benefit is lacking for patients without a history of symptomatic IHD.

A small (71 of 2885 NASCET patients) subgroup of patients with symptomatic carotid disease, no history of symptomatic IHD disease, and ≥4 identified risk factors had a very poor 5-year prognosis (ie, a 23.5% risk of severe MI or death). Because there is no evidence that treating asymptomatic coronary artery disease is efficacious, it is difficult to make firm recommendations regarding management. Ideally, these patients should be entered into randomized trials evaluating medical therapy, coronary angioplasty, or coronary bypass surgery. Alternatively, it is reasonable to suggest that these patients be considered for cardiac investigations by expert cardiologists. Patients with coexistent symptomatic coronary artery disease should be referred to cardiology experts to be managed according to current guidelines.

NASCET excluded patients with a potential for cardioembolism. Nevertheless, there is an association between the severity of carotid artery disease and the extent of coronary artery disease. Therefore, NASCET patients were prone to develop cardiac dysfunction during long-term follow-up. Accordingly, the NASCET database was used to determine which patients presenting with cerebral ischemia should have extensive cardiac investigation. The average annual rate of any MI or cardiac death of 3.1% in 2815 NASCET patients was similar to that of other large trials of cerebral ischemia that had average annual rates of any MI or vascular death ranging from 2.0% to 3.9%. The rate was lower than the 7.2% in the asymptomatic Veterans Affair trial of men, which had a higher prevalence of smoking and peripheral vascular disease.

In conclusion, the present study reports the first deliberate attempt to determine which patients with symptomatic carotid artery disease should be submitted to extensive and expensive cardiac investigations. The results are generalizable to patients with symptomatic carotid artery disease who are without evidence of overt cardiac dysfunction predisposing to embolism. They are applicable to a substantial number of individuals because approximately half a million strokes occur annually in the United States. It appears appropriate for the majority of patients without symptomatic cardiac disease at the time of presentation with symptomatic carotid disease to manage their risk factors, monitor patients frequently for the presence of minor symptoms of coronary artery disease, and refer patients for more intensive cardiac studies only when ischemic cardiac symptoms exist or develop.

Acknowledgments

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References

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