Prediction of Mortality by Ultrasound Screening of a General Population for Carotid Stenosis

The Tromsø Study

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Background and Purpose—The extensive use of ultrasound examination of carotid arteries has revealed stenosis in many asymptomatic subjects, and clinical studies have shown that carotid stenosis is a risk factor for cardiovascular disease and death. However, information on stenosis as detected in a general population and its relation to mortality is scarce. The purpose of this population-based study was to assess whether carotid stenosis is a predictor of death.

Methods—In 1994 to 1995, 248 subjects with suspected carotid stenosis were identified among 6727 men and women 25 to 84 years of age who were examined with ultrasound. These subjects and 496 age- and sex-matched control subjects were followed up for 4.2 years, and the number and causes of deaths were registered.

Results—The unadjusted relative risk for death was 2.72 (95% CI, 1.57 to 4.75) for subjects with stenosis compared with control subjects. Adjusting for cardiovascular risk factors increased the relative risk to 3.47 (95% CI, 1.47 to 8.19). The adjusted relative risk in persons with stenosis and no cardiovascular disease or diabetes was 5.66 (95% CI, 1.53 to 20.90), which was higher than in subjects with stenosis and self-reported disease (1.79; 95% CI, 0.75 to 4.27). There was a dose-response relationship between degree of stenosis and risk of death ($P=0.002$ for linear trend). Carotid stenosis was a stronger predictor of death than self-reported cardiovascular disease or diabetes.

Conclusions—Carotid stenosis is a strong and independent predictor of death. (Stroke. 2000;31:1871-1876.)

Key words: carotid stenosis • mortality • population-based studies • ultrasonography

The use of ultrasound examinations of carotid arteries in clinical practice, clinical trials, and population health surveys has identified many persons with asymptomatic carotid stenosis. In some studies in which patients are referred to ultrasound examinations on various clinical indications, carotid stenosis has been shown to be a significant predictor of death.1–3 Randomized clinical trials designed for comparison of surgery and medical treatment as the most appropriate treatment for carotid stenosis have found that both symptomatic4–5 and asymptomatic6 subjects with stenosis are at high risk of cerebral stroke and cardiovascular death.

In contrast, only 2 population-based studies7–8 have examined the relationship between carotid stenosis and mortality. Both studies included elderly (≥65 years) subjects only, and 1 included men only.8 The purpose of this population-based study of 6727 male and female subjects ranging from 25 to 84 years of age, revealing 248 cases of suspected carotid stenosis, was to assess whether carotid stenosis, as detected by ultrasound examination of a general population, is a predictor of death.

Subjects and Methods

Population

In 1994 to 1995, a population health survey was conducted in the municipality of Tromsø, Norway, by the University of Tromsø in cooperation with the National Health Screening Service. The study comprised 2 screening visits 4 to 12 weeks apart. All inhabitants in the municipality >24 years of age were invited to the first visit, and all subjects 55 to 74 years of age and 5% random samples in the other 5-year age groups were invited to both visits. In addition, 307 men 45 to 54 years of age were invited because they had participated in an intervention study in a previous survey of the Tromsø Study; therefore, the sample size for these age groups was higher than 5%.

The protocol for the first visit was similar to the previous surveys in this population and included standardized measurements of height, weight, blood pressure, nonfasting serum lipids, and fibrinogen. Blood pressure and nonfasting serum lipids were remeasured at the second visit, which also included ultrasonographic examination of the right carotid artery. A total of 3323 men and 3404 women, 79% of those eligible, attended both visits and were examined with ultrasound. The letter of invitation contained questions on previous myocardial infarction or stroke, prevalent angina pectoris or diabetes mellitus (yes/no), treated hypertension (never/previouly/currently), and cigarette smoking. The questionnaire was checked for logical inconsistencies at the examination. The study was approved by the
Regional Committee for Medical Research Ethics, and written consent was obtained from all participants.

**Cardiovascular Risk Factors**

Height and weight were measured in participants wearing light clothing without shoes; body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was recorded in a separate, quiet room by a specially trained nurse. An automatic device (Dinamap Vital Signs Monitor) was used. Serum cholesterol and triglycerides were analyzed by standard enzymatic methods, and fibrinogen was measured with the PT-Fibrinogen reagent (Instrumentation Laboratory). The serum analyses were performed at the Department of Clinical Chemistry, Tromsø University Hospital.

**Ultrasonography**

The ultrasound methods have been described in detail previously. Briefly, high-resolution B-mode ultrasonography was performed with an ultrasound scanner (Acuson Xp10 128, ART upgraded) equipped with a linear-array transducer. The common, internal, and external carotid arteries were identified by combining B-mode (7 MHz) and color-Doppler/pulsed-wave Doppler (5-MHz) ultrasound. We attempted to identify and record atherosclerotic plaques from 6 sites of the carotid artery: the near and far walls of the internal carotid artery, the bifurcation segment of the common carotid artery, i.e., the distal part of the common carotid artery, and the common carotid artery from the bifurcation and downstream to the supraclavicular region. A random sample of 784 subjects was examined on both right and left carotid arteries to provide information about bilateral carotid stenosis. A carotid artery was defined as being stenotic if 1 or both of the 2 criteria were met. For the hemodynamic criterion to be met, peak systolic velocity at the tightest, stenotic part (PSVs) had to be 

\[
0.2 \text{ m/s higher than peak systolic velocity at the point of reference (PSVr) or } 0.1 \text{ m/s higher if the stenosis was located at the carotid bifurcation or the bulb of the internal carotid artery. The distal part of the internal carotid artery was used as the point of reference. For the structural criterion to be met, plaque had to cause } \geq 35\% \text{ reduction in lumen diameter on a longitudinal B-mode scan. The degree of stenosis was calculated by the peak systolic velocity ratio method: } (1 - \text{PSVr/PSVs}) \times 100\%. \text{ Complete occlusion of the carotid artery was graded as } 100\% \text{ stenosis.}
\]

Three sonographers screened the subjects: one was a neurologist (O.J.) with 10 years’ experience in ultrasound examination of the carotid artery; the second was a physician (E.S.-B.); and the third was a specially trained technician. A 2-month training protocol was completed before the survey started. A reproducibility study on plaque occurrence found that between- and within-sonographer agreement was substantial, with \( \kappa \) values of 0.72 (95% CI, 0.60 to 0.84) and 0.76 (95% CI, 0.63 to 0.89), respectively.

**Cases With Carotid Stenosis and Control Subjects**

For each case with suspected stenosis, 2 control subjects were randomly drawn among subjects who did not have stenosis. The cases and control subjects were matched by age (±2 years), sex, date of examination, and living area within the municipality (rural or urban areas).

All persons with suspected stenosis and 1 of the 2 control subjects in each triplet were referred to the outpatient clinic at Department of Neurology, University Hospital, Tromso, for clinical examination and ultrasonographic reevaluation and reclassification. All examinations were performed by 2 experienced neurologists (O.J., E.B.M.).

A flow chart of the selection procedures is shown in Figure 1. The subjects were followed from the date at screening or at ultrasound reclassification to December 1, 1998, or to the date of death. Deceased subjects were identified by linkage to the National Population Register, and details of all deaths were documented whenever possible by hospital records and autopsy reports.

The reproducibility on the grading of stenosis at reclassification was satisfactory, with a mean absolute difference between sonographers of 10.8%. The \( \kappa \) values for agreement on categories of stenosis dichotomized at various cutoff points (50%, 60%, and 70% stenosis) were 0.57 (95% CI, 0.33 to 0.81), 0.66 (95% CI, 0.4 to 0.91), and 0.79 (95% CI, 0.54 to 1.00), respectively.
Statistical Analysis
Differences between cases and control subjects in mean values of baseline cardiovascular risk factors were tested for statistical significance by use of 2-way ANOVA with match number of triplets (1 to 248) and stenosis (yes/no) as factors. Differences in proportions were tested by χ² tests and Fisher's exact test (2 tail). The Kaplan-Meier method was used to calculate survival for the groups, and the log-rank test was used to test the difference in survival between the groups. Death rates were calculated as the number of deaths by person-years of observation (time to death or censoring). Unadjusted relative risks were estimated by calculation of ratios of mortality rates. Cox proportional-hazards regression model was used to estimate the influence of carotid stenosis on death adjusted for risk factors. Stratified analyses were used in analyzing the matched triplets (1 case and 2 control subjects) adjusted for smoking, BMI, systolic blood pressure, total and HDL cholesterol, triglycerides, and fibrinogen.

To test whether there was a dose-response relationship between degree of carotid stenosis and mortality, the subjects were categorized in 5 groups according to degree of stenosis on the basis of findings at the ultrasound reclassification at the outpatient clinic: (1) subjects without carotid stenosis (reference group), (2) those with <45% stenosis, (3) those with stenosis between 45% and 74%, (4) those with stenosis between 75% and 99%, and (5) those with 100% stenosis (ie, occlusion). The strength of the dose-response relationship was expressed by probability values for linear trend in the Cox regression model. When bilateral stenoses were present, the measures from the tightest stenosis of the 2 sides were used in the calculation of degree of stenosis.

Two-sided values of P<0.05 were considered statistically significant. The SAS software package version 6.12 was used.12

Results
A total of 248 subjects with suspected carotid stenosis at the screening and 496 matched control subjects were included in the analysis of screening results (analysis A, Figure 1). There was a male predominance (61.3%) (Table 1). Cases had higher levels of systolic blood pressure, total cholesterol, and triglycerides and were more likely to smoke, be treated for hypertension, and have a history of cardiovascular disease (CVD). There was no significant difference between cases and control subjects with regard to BMI, HDL cholesterol, diastolic blood pressure, and the prevalence of diabetes mellitus.

The follow-up time until death or the censoring date of December 1, 1998, lasted up to 4.2 years. The mean observation time was 3.6 years (median, 3.8 years) for cases and 3.8 years (median, 3.8 years) for control subjects. Table 2 shows that among the 248 cases, 30 persons (12.1%) died during the observation time compared with 23 deaths (4.6%) among the 496 control subjects. In cases, the death rate was 3.35 per 100 person-years in control subjects, giving a relative risk for death associated with stenosis, and categorized according to degree of stenosis. No additional information was achieved when the analyses were stratified by sex.

### Table 1. Screening Characteristics of Participants With Suspected Carotid Stenosis and Matched Control Subjects

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Cases</th>
<th>Control Subjects</th>
<th>P for Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>61.3</td>
<td>61.3</td>
<td>Matching variable</td>
</tr>
<tr>
<td>Age, y</td>
<td>67.6 (6.3)</td>
<td>67.4 (6.2)</td>
<td>Matching variable</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>39.5</td>
<td>22.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.3 (4.2)</td>
<td>26.2 (3.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>149.8 (22.5)</td>
<td>143.7 (20.5)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81.2 (12.4)</td>
<td>81.1 (10.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>7.09 (1.32)</td>
<td>6.74 (1.21)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.42 (0.42)</td>
<td>1.48 (0.44)</td>
<td>0.052</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.93 (1.05)</td>
<td>1.71 (0.96)</td>
<td>0.004</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.83 (0.95)</td>
<td>3.53 (0.88)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Treated hypertension, %</td>
<td>42.9</td>
<td>22.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD or diabetes, %</td>
<td>44.0</td>
<td>21.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16.7</td>
<td>7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>27.2</td>
<td>11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral stroke</td>
<td>9.3</td>
<td>3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.7</td>
<td>4.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Values are means (SD's) when appropriate. CVD indicates self-reported myocardial infarction, angina pectoris, or cerebral stroke.

diabetes (3.61 deaths per 100 person-years). The log-rank test showed significant statistical difference between the survival curves for those with and without carotid stenosis (P=0.0002) (Figure 2). The difference was significant both in men (P=0.007) and in women (P=0.005).

CVD was the main cause of death in both control subjects and cases (Table 3). However, death resulting from CVD was more common among subjects with stenosis than in control subjects. The absolute risk of death from ischemic cerebral stroke was small, even among subjects with stenosis.

Table 4 shows mortality for the subjects reexamined at the outpatient clinic (n=477), reclassified with regard to presence of stenosis, and categorized according to degree of stenosis (analysis B, Figure 1). The death rates and unadjusted and adjusted relative risks for death increased by increasing degree of stenosis (Table 4). Thus, unadjusted and adjusted relative risks for death increased to 7.47 (95% CI, 2.53 to 20.49) and 5.50 (95% CI, 1.63 to 18.52) among those with occlusion (P=0.002 for linear trend), indicating a significant dose-response of carotid atherosclerosis on mortality. Among the 237 subjects who had stenosis, the adjusted relative risk for death per 10% increment of degree of stenosis was 1.20 (95% CI, 1.03 to 1.41) (data not shown). Death was significantly (P=0.04) associated with CVD or diabetes regardless of status of stenosis. No additional information was achieved when the analyses were stratified by sex.
This study shows that carotid stenosis is a strong and independent predictor of death. Cases with stenosis who reported CVD or diabetes had only a slightly higher death rate than those with stenosis who did not report CVD or diabetes, which means that prevalent CVD or diabetes did not add much to the risk of death in subjects with carotid stenosis. The higher relative risk associated with stenosis in subjects without clinical disease (3.08) compared with cases with stenosis who reported prevalent CVD or diabetes (1.79) is due to the low death rate among stenosis-free control subjects without clinical disease. The multivariate adjusted relative risk for death associated with stenosis is particularly strong for subjects who reported no prevalent CVD or diabetes (5.66). At the screening, 214 subjects reported CVD or diabetes (22 deaths), and 530 subjects reported no such diseases (31 deaths).

There was a dose-response relationship between degree of stenosis and risk of death. The highest relative risk appeared among the 19 persons who had carotid occlusion (6 of them had no CVD or diabetes) with a death rate of 9.7 per 100 person-years. This implies that as many as 30% of these subjects died during follow-up compared with 4.5% of subjects without stenosis. Advanced carotid atherosclerosis therefore seems to be a strong predictor of death also in the absence of clinical disease. Only 55% of the 60 cases with >70% stenosis reported coronary disease, previous stroke, or diabetes mellitus. The death rate for the 33 cases with clinical disease and with >70% stenosis was 8.1 compared with 7.8 per 100 person-years in the 27 subjects without such diseases (data not shown).

CVD was the cause of death in 80% of cases with stenosis compared with 43.5% in those without stenosis. In the group with stenosis, 6.7% died of an ipsilateral ischemic stroke. Most died of coronary heart disease. Several other studies have found that carotid stenosis is a stronger predictor of cardiac death than death caused by cerebral stroke.1–3,13 This is also in line with ultrasound and autopsy studies showing that the presence and extent of carotid atherosclerosis correlate well with atherosclerosis elsewhere in the circulation, including the coronary arteries.14–16

Subjects with carotid stenosis were offered annual clinical and ultrasound follow-up, whereas control subjects were
examined only at study entry. Those cases who disclosed early symptoms or signs consistent with heart or cerebrovascular disease were given medical advice or therapy or were referred for further investigations and treatment. This may have resulted in a lower mortality rate among cases, thus causing an underrating of the relative risk for death in those with stenosis compared with stenosis-free control subjects.

To the best of our knowledge, only 2 studies have previously evaluated whether carotid stenosis, as detected by ultrasound screening of a general population, is a predictor of death. In the Cardiovascular Health Study (CHS),7 5114 men and women ≥65 years of age were examined by ultrasound and classified according to degree of stenosis. The unadjusted relative risk for death among subjects with stenosis compared with those without stenosis (ie, those without carotid atherosclerotic plaques) was slightly higher and the adjusted relative risk for death was lower compared with our findings. The mean age in our study was 6 years younger than in CHS, and the participation rate was higher in our study, 79% versus 57% in CHS. The higher age in CHS may have contributed to the lower adjusted relative risk estimates compared with the results of our study. Similar to our findings, the CHS investigators found that death rates were highest among subjects with carotid occlusion and that carotid stenosis was a better predictor of death than self-reported CVD.

In a smaller Swedish study on 10-year mortality among 68-year-old men,17 the annual death rate among subjects with carotid stenosis (n=117) was higher than in those without stenosis (relative risk, 1.45; P=0.03). However, the association disappeared after adjustment for other risk factors. In a later publication,8 those investigators found that this higher relative risk for death was present only among those men who did not suffer from ischemic heart disease at baseline. The lower relative risk for death in that study compared with our results may be due to higher cardiovascular morbidity (eg, 42.3% had prevalent ischemic heart disease compared with 24.0% of those who reported coronary disease in our population >67 years of age) and male sex.

An association between carotid stenosis and death has been found in clinical studies.1,3 However, different inclusion criteria in population-based and clinical studies make comparisons difficult. In general, patients referred to ultrasound laboratories on clinical indications supposedly have more active clinical disease and consequently higher risk of death.

In a population-based study from Framingham,15 the presence of neck bruit, a clinical finding that is highly correlated with carotid stenosis, was associated with a 1.7-fold-higher relative risk of death in men (P<0.05) and a 1.9-fold-higher risk in women (P<0.01). Wiebers et al,2 in another population-based study, found the relative risk of death by neck bruit to be 2.2.

Prompted by the recently reported beneficial effect of endarterectomy in patients with asymptomatic carotid stenosis,6 the value of screening for asymptomatic carotid stenosis has been discussed. It has been found that ultrasound screening for carotid stenosis is not cost-effective regarding carotid endarterectomy.18,19 Any benefit from regular screening, however, is not restricted to only a possible impact on stroke incidence caused by carotid endarterectomy. Most people with carotid stenosis die from coronary heart disease and not from stroke,1–3,7,13,17 as also shown in the present study. The main consequence of ultrasound screening of a general population is that subjects with high risk for coronary disease will be identified. Medical intervention as part of preventive strategies may therefore save as many from disease and death as carotid endarterectomy. Our results are not an argument for routine screening of general populations to detect carotid stenosis. That is hardly a cost-effective procedure. The main purpose of our study was to use ultrasonographic measurements as part of the study of CVD origin. However, many subjects will incidentally have asymptomatic carotid stenosis disclosed by ultrasound examinations performed as part of scientific studies or on clinical indications. We therefore believe that knowing the risk of death in such subjects must be of interest.

This study has shown that the presence of carotid stenosis as detected by ultrasound screening of a general population is a strong predictor of death, stronger than self-reported CVD or diabetes. The relative risk for death is particularly strong for subjects with stenosis who reported no prevalent CVD or diabetes. There is a dose-response relationship between degree of carotid stenosis and death. Subjects with carotid stenosis should be treated as high-risk subjects and offered clinical follow-up to lower cardiovascular risk factor levels.
and to recognize early clinical signs of CVD for further diagnostic and therapeutic interventions.

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References
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