

Original Contributions

Vascular Risks of Asymptomatic Carotid Stenosis

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Background and Purpose: We sought to determine the risks of stroke, myocardial ischemia, and vascular death in patients with asymptomatic carotid stenosis.

Methods: Six hundred ninety-six patients with asymptomatic carotid stenosis referred to the Doppler laboratory were followed prospectively for a mean time of 41 months. These patients were studied both clinically and by carotid Doppler ultrasound, including evaluation of the effect of stroke risk factors.

Results: Transient ischemic attacks occurred in 75 patients and stroke in 29, while 132 had ischemic cardiac events. Five patients died from stroke and 59 from cardiac causes.

Annual stroke rate was 1.3% in patients with carotid stenosis $\leq 75\%$ and 3.3% in those with stenosis $> 75\%$. Ipsilateral stroke rate was 2.5% in patients with $> 75\%$ carotid stenosis. Annual cardiac event rate was 8.3% and death rate 6.5% in patients with severe carotid stenosis.

Conclusions: With carotid stenosis $\leq 75\%$, the stroke rate is negligible (1.3% annually) whereas the combined risk of cardiac ischemia and vascular death is as high as 9.9%. With stenosis $> 75\%$, combined transient ischemic attack and stroke rate is 10.5% per year, with 75% of events ipsilateral to the stenosed artery. (*Stroke* 1991;22:1485-1490)

Evidence has accumulated in recent years that asymptomatic neck bruits are a risk factor for subsequent stroke, myocardial infarction, and death.¹⁻⁶ It is also clear that the stroke risk is low, and, although neck bruits occur in over 10% of the elderly, the concomitant risk of stroke and death is only slightly higher than that of an age-matched population.² However, because most neck bruits do not reflect significant carotid stenosis, or indeed any arterial pathology,^{1,3-5} evaluation of the outcome of asymptomatic carotid stenosis (with or without neck bruits) is more relevant.

We have prospectively followed since 1982 an accumulating cohort of patients with asymptomatic neck bruits by monitoring their clinical outcome and extracranial carotid Doppler ultrasound evaluation at regular intervals.⁴ The low frequency of outcome events previously restricted our statistical evaluations, but with longer follow-up and more patients, our data have become more appropriate for analysis.

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Subjects and Methods

We prospectively followed patients referred to our Doppler laboratory with asymptomatic carotid bruits with periodic clinical and carotid Doppler evaluations as previously described.⁴ These included completing standard protocols at each visit and recording risk factors, ischemic cerebral or cardiac events, and other relevant clinical details. A total of 696 patients were followed, 369 women and 327 men. Mean age was 64 ± 8 (range 45-90) years. Mean follow-up was 41 ± 31 (range 6-95) months.

We no longer auscultate the neck in these patients at follow-up, although, during enrollment to the study, the presence of neck bruits was established by at least two independent examiners.⁷ Stroke risk factors used for the analysis were age, sex, hypertension, ischemic heart disease, diabetes, peripheral vascular disease, serum cholesterol, smoking, obesity, and family history. Concomitant medications (aspirin and β -blockers) were also recorded. The definitions of risk factors were identical to our previous report.⁴ However, the reported high incidence of peripheral vascular disease noted previously was based on either the presence of intermittent claudication or femoral artery bruits or the absence of pedal pulses. This was revised to include only patients with unequivocal symptoms or signs of vascular insufficiency in the limbs.

The referral sources to the Doppler laboratory were estimated on a sample of 426 patients. Most

TABLE 1. Vascular Outcome in 696 Patients With Mild, Moderate, and Severe Asymptomatic Carotid Stenosis, Classified by Initial Doppler Values

Vascular outcome	Initial Doppler grade			Total (n=696)
	Mild, <50% (n=303)	Moderate, 50–75% (n=216)	Severe, >75% (n=177)	
Cerebral events				
TIA only	11	28	36	75
Stroke (survivors)	12	2	10	24
Cardiac events (survivors)	28	25	20	73
Deaths				
Vascular				
Cardiac	21	21	17	59
Stroke	1	3	1	5
Other	3	2	2	7
Nonvascular	11	10	3	24

<50% stenosis= \leq 6 kHz; 50–75% stenosis=6–11 kHz; >75% stenosis= \geq 12 kHz. TIA, transient ischemic attack.

(33%) were referred by family physicians, 24% by neurologists, 16% by cardiologists, 7% by neurosurgeons, and 20% by other physicians.

For carotid artery insonation, we used a Model 1060 Dopscan with B-mode scanning (Carolina Medical Electronics). We have evaluated the accuracy of this method since 1986 and have established a high degree of sensitivity and specificity compared with angiography.⁸ The limitations of this technique include the difficulty of distinguishing severe carotid stenosis from carotid occlusion and the difficulty of detecting arterial stenoses <50%. We therefore reclassified the degrees of carotid stenosis as mild (<50%, <6 kHz), moderate (50–75%, 6–11 kHz), and severe (>75%, 12–20 kHz). Carotid stenosis was diagnosed as relating only to the internal or common carotid artery. Carotid occlusion was diagnosed only when all criteria were met, including low velocities in the common carotid artery and no detectable Doppler signals distal to the occlusion.⁹ This is only possible using B-mode scanning, a modality we did not possess at the time of the previous study.

Noncompliant patients were telephoned concerning further clinical end points. Only two patients were lost to follow-up over the study period. We documented details of all deaths, whenever possible, by hospital records and autopsy reports; causes included sudden death and death from stroke, myocardial infarction, cardiac failure, or ruptured aorta. Deaths from secondary effects of vascular disease were also included in the analysis; for instance, a patient admitted for cardiac bypass surgery who died before surgery due to congestive cardiac failure initiated by preoperative infusion of normal saline was classified as a cardiac death.

Cerebral ischemic events comprised transient ischemic attacks (TIAs), amaurosis fugax, and ischemic or hemorrhagic stroke. When patients had both TIA and stroke, only stroke was counted as an end point.

Cardiac ischemic end points were new-onset angina and myocardial infarction; when patients had both, only the myocardial infarction was counted as

an end point. Sudden death was assumed in all cases to be cardiac. If patients had both ischemic cerebral and cardiac events, both were included in the separate analyses. Deaths were analyzed separately. Efforts were made to distinguish stroke death from cardiac death, but this was sometimes impossible, and, unless death followed closely upon stroke, it was assumed to be cardiac. This may have biased the data toward cardiac causes of death.

The Wilcoxon rank test modified for censoring was used to evaluate the association of outcome with covariant risk factors (age, sex, hypertension, serum cholesterol, smoking, previous cardiac disease and peripheral vascular disease, and aspirin ingestion). The Wilcoxon rank test was also used to test the divergence of event curves for TIAs and stroke, ischemic cardiac events, and vascular deaths; their annual rates were determined by the Kaplan-Meier method. The χ^2 goodness-of-fit test using χ^2 was applied to the observed cumulative death rate at 10-month intervals compared with age- and sex-matched estimates of the Ontario population for 1982–1986,¹⁰ which was the equivalent study period. The expected and observed rates were plotted at yearly (not 10-month) intervals. The Cox proportional hazard model was used to test the effect of putative risk factors (as above, but with the addition of the severity of carotid stenosis) on subsequent cerebral ischemic events. All probability values are two tailed.

Results

During follow-up, 29 patients had a stroke (two with cerebral hemorrhage). Five of the 29 patients died, and five others had TIAs prior to stroke. Of the 132 patients with cardiac events (mainly myocardial infarction), 59 died. The rate of cardiac death was therefore nearly 12-fold that of stroke (Table 1).

Seventy-five patients had TIAs only, and an additional five patients had TIAs followed by stroke. One of these five had a brain stem infarction and had only mild carotid stenosis; another had a coag-

TABLE 2. Annual Percentage Rate of Vascular Events Over Period of Follow-up

Degree of stenosis	TIA	Stroke	Cardiac	Vascular death
<50% (mild)	1.0	1.3	2.7	1.8
50-75% (moderate)	3.0	1.3	6.6	3.3
>75% (severe)	7.2	3.3	8.3	6.5

TIA, transient ischemic attack.

ulopathy complicated by TIAs but also had only a mild carotid stenosis. Of the remaining three, all had carotid stenosis of >75%, and one of these died acutely. Carotid surgery was performed on 43 patients, of whom 17 were asymptomatic. The 26 symptomatic patients all had carotid stenoses of ≥60%. Data on patients who remained asymptomatic at the time of carotid surgery were censored from further analysis.

Because the annual event rate of cerebral ischemic events (TIA and stroke) in patients with >75% carotid stenosis declined as the study progressed, cerebral events were less frequent with each year of follow-up (Table 2 and Figure 1). For instance, in the first year, the frequency of cerebral events in the severe stenosis group was 18%; over 4 years this was only 38%, that is, 9.5%/yr.

However, the annual cardiac event rate (approximately 8%) and the annual vascular death rate (approximately 6%) did not vary significantly each year in the severe stenosis group (Figures 2 and 3). The mortality rate in the study cohort was significantly increased ($\chi^2=100.3$, $p<0.0001$) compared with the age- and sex-matched group based on the Province of Ontario Registrar General data for 1982-1986 (Figure 4).

When the influence of the putative stroke risk factors on ischemic cerebral events was evaluated,

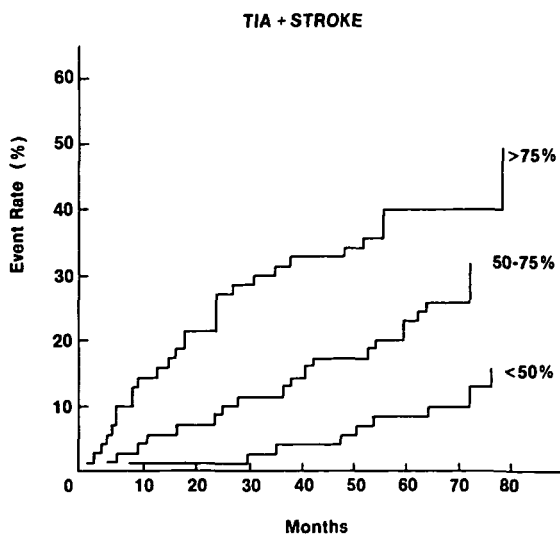


FIGURE 1. Cumulative event rates of transient ischemic attacks (TIAs) and strokes in patients with mild (<50%), moderate (50-75%), and severe (>75%) carotid stenosis.

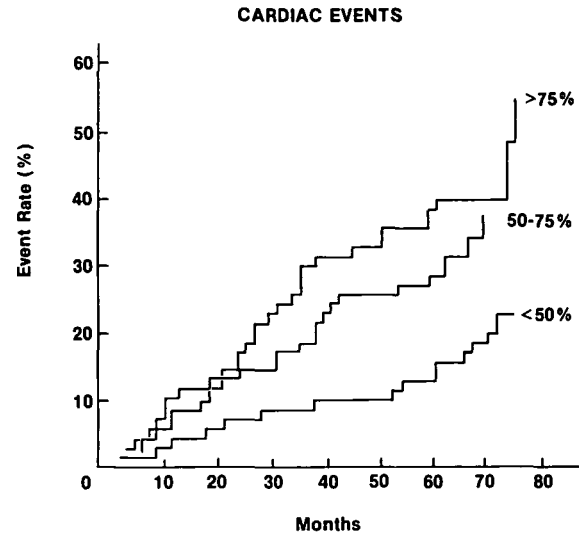


FIGURE 2. Cumulative event rates of cardiac ischemic events in patients with mild (<50%), moderate (50-75%), and severe (>75%) carotid stenosis.

both the presence of concomitant ischemic heart disease ($p<0.009$) and the severity of carotid stenosis ($p<0.01$) were significant (Wilcoxon test of univariate χ^2). The remaining risk factors were not significantly related, and no risk factors had any significant effect on ischemic cardiac events.

The influence of stroke risk factors on the three grades of severity of carotid stenosis (mild, moderate, and severe) was also evaluated. There were significantly more men ($p<0.0001$) in the moderate and severe stenosis groups, and they were significantly older ($p<0.0001$). Peripheral vascular disease ($p<0.001$) and hypertension ($p<0.001$) were significantly increased in the severe stenosis group, and more patients took aspirin ($p<0.0001$) and β -blockers ($p<0.001$) (Table 3). However, this figure has little significance because we do not know the compliance rate or duration of administration of these

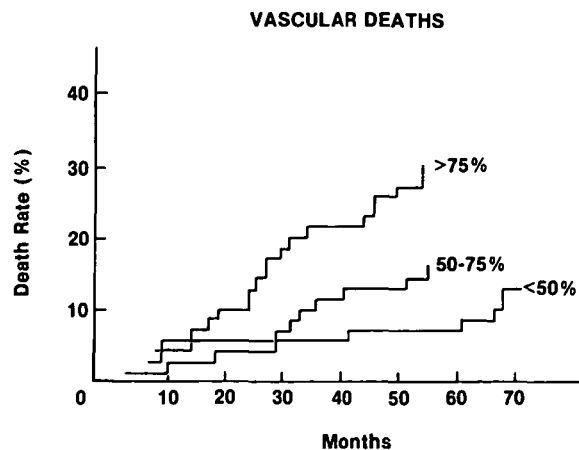


FIGURE 3. Cumulative event rates of vascular deaths in patients with mild (<50%), moderate (50-75%), and severe (>75%) carotid stenosis.

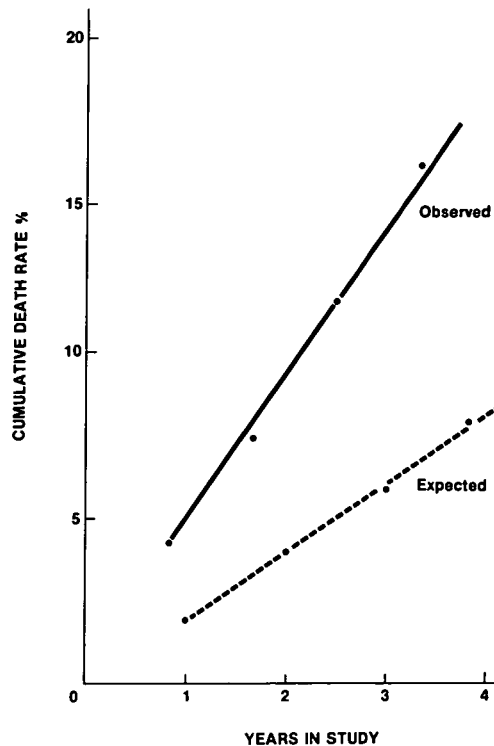


FIGURE 4. Cumulative death rates (observed and expected) in study cohort compared with age- and sex-matched population in the Province of Ontario.

drugs. In addition, physicians are more likely to give aspirin to patients with severe carotid stenosis, with or without symptoms. Serum cholesterol levels were also significantly higher in the severe stenosis group. Sample collection was less than the total numbers in each group because some patients often refused blood tests; thus, the figures are smaller but still significant ($p < 0.04$).

The distribution of carotid stenosis differed between the sexes, being more severe and more frequent in men ($\chi^2 = 21.1$, $p < 0.0001$; Table 3). The predominance of women in the cohort reflects the increased frequency of neck bruits in women referred to our laboratory.

Of the 102 patients with cerebral ischemic events, carotid Doppler examinations revealed no evidence of underlying arterial stenosis in 35. Of the remaining 67 patients, 14 had vertebrobasilar ischemic events and three had cerebral ischemic events contralateral to the carotid artery with the most severe stenosis. Therefore, events in 50 patients were ipsilateral to the carotid artery with the most severe stenosis. This difference (50 compared with 17) is significant at $p < 0.05$, giving an "ipsilaterality" of 75% (50 of 67).

Discussion

The stroke rate in our patients with asymptomatic carotid stenosis was only 3.3%/yr, even in those with carotid stenosis of $>75\%$. Also, in this highest-risk group, annual cardiac events were 8.3% and death (nearly always vascular) 6.5%. In addition, because the ipsilaterality of cerebral events to the carotid artery with the most severe stenosis was 75%, the annual stroke rate for those with ipsilateral carotid artery stenosis would be only 2.5%. In this group, therefore, it seems difficult to justify carotid surgery.

The remaining patients, with carotid stenoses of $\leq 75\%$, have an even lower stroke risk (Table 2). They constitute the majority of patients in all studies of asymptomatic carotid stenosis, which probably explains the low overall risk (1.1%) when they are compared with age- and sex-matched controls.² In patients with carotid stenosis of $<50\%$, vascular events were rare whereas in those with stenoses of 50–75%, cardiac events and vascular deaths still outnumber the low annual stroke rate (Table 2). In a

TABLE 3. Risk Factors in Patients With Mild, Moderate, and Severe Carotid Stenosis

Risk factors ⁴	Mild, $<50\%$ (n=303)	Moderate, 50–75% (n=216)	Severe, $>75\%$ (n=177)	p^*
Age (yr)	62.0 \pm 9.2	65.6 \pm 7.0	66.6 \pm 7.9	<0.0001
Sex (M/F)	113/190	109/107	105/72	<0.0001
Hypertension [†]	116	110	86	<0.001
Symptomatic peripheral vascular disease	51	46	53	<0.001
Aspirin use	80	113	98	<0.0001
β -blocker use	65	77	56	<0.001
Raised serum cholesterol	103	72	47	<0.04
Ischemic heart disease [‡]	89	79	67	NS
Diabetes [§]	32	29	29	NS
Congestive heart failure	18	10	12	NS
Obesity	37	23	27	NS
Family history	208	144	116	NS
Smoking (past or present)	211	147	132	NS

*Significance determined by Wilcoxon rank test.

[†]Defined as blood pressure sustained at $>160/90$ mm Hg.

[‡]History of angina or myocardial infarction.

[§]Treated previously with diet or drugs for hyperglycemia.

comparison of patients with asymptomatic neck bruits to a matched population without neck bruits, the bruit group had three times the stroke risk of the nonbruit group; however, this risk was still only 1.5%/yr.¹¹ Clearly, carotid surgery can be of no value in patients with stenosis of $\leq 75\%$.

We have failed to discover other factors that might identify a high-risk subgroup. Only the severity of carotid stenosis and the presence of ischemic heart disease affected vascular outcome. Age, male gender, peripheral vascular disease, and serum cholesterol levels related to the severity of carotid stenosis but not to outcome (Table 3).

There was a continuous decline of the cerebral ischemic event rate during the duration of follow-up, with most events apparently occurring during the first year. This may indicate a high degree of awareness by both patients and physicians that results in the reporting of minor symptoms during the early phase of the study. During subsequent years, the enthusiasm to report such events may diminish.

There may be a "harvesting" effect from carotid surgery, a removal of patients with severe stenoses who are most likely to have ischemic cerebral events. In addition, those with severe carotid stenosis are more likely to experience end points and so are more frequently censored from the study.

The preponderance of female patients in our asymptomatic cohort was the reverse of that seen in stroke registries or surveys, in which males invariably predominate in symptomatic populations.^{12,13} This was previously noted by Ford et al,¹⁴ who could not explain the predominance of women with asymptomatic neck bruits in their study cohort and who also noted that neck bruits were less likely to be associated with carotid stenosis in women than in men. However, this could not explain the low stroke risk in our patients because we related vascular outcomes solely to the severity of the carotid stenosis and not to the presence of neck bruits.

There has been considerable expression of concern for the prophylactic role of carotid endarterectomy in both symptomatic and asymptomatic patients.¹⁵⁻¹⁷ This concern is not just due to the low stroke rate, but also includes the problem of different stroke pathologies. One of the ipsilateral strokes in our series was a cerebral hemorrhage, a condition unlikely to benefit from carotid endarterectomy. We also did not document the number of lacunar infarctions, which may account for one in five strokes¹³; these presumably would be unaffected by carotid endarterectomy. This could bring the spontaneous ipsilateral annual stroke rate to below 2% in the highest risk group, making even the lowest perioperative risks unacceptably high. The Ad Hoc Committee on Carotid Surgery Standards of the Stroke Council, American Heart Association, recommends a total perioperative risk rate of $<3\%$.¹⁸

The combined end point of TIA and stroke was 10.5% in our study (Table 2). Because TIAs are harbingers of stroke, their prevention must imply

secondary prevention of future ischemic stroke. Recent reports of the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial support the importance of severity of carotid stenosis in producing symptoms (at least with stenosis $>70\%$) and the remarkable reduction of stroke risk by carotid surgery.^{19,20} The same should apply to asymptomatic carotid lesions.

These hypothetical perspectives are being put to the test by current, randomized, surgical trials in patients with asymptomatic carotid stenosis,²¹ which will in total evaluate over 2,000 patients and may clarify this continuing controversy once and for all.

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