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Operative Versus Nonoperative Management of Asymptomatic High-Grade Internal Carotid Artery Stenosis: Improved Results With Endarterectomy

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In a 4-year period, 129 asymptomatic high-grade (80–99%) internal carotid artery stenoses were identified in 115 patients. Because we previously demonstrated a strong relation between degree of carotid stenosis and subsequent development of ipsilateral related events (stroke, transient ischemic attack, and carotid occlusion), we changed our previous policy and began to offer carotid endarterectomy to good surgical risk patients referred to us with asymptomatic high-grade carotid stenosis. A total of 56 carotid endarterectomies were performed while 73 lesions were followed nonoperatively. Operated and nonoperated groups were similar with regard to age, prevalence of hypertension, cardiac disease, diabetes, and aspirin use. Life table analysis to 24 months revealed a higher rate of stroke (19 vs. 4%, $p = 0.08$), transient focal neurologic deficits (28 vs. 5%, $p = 0.008$), and carotid occlusion (29 vs. 0%, $p = 0.003$) in the nonoperated group. Eight of the 9 strokes in the nonoperated group occurred within 9 months of diagnosis of the high-grade lesion; none were preceded by a transient ischemic attack. There was 1 perioperative stroke (1.8%) but no in-hospital operative deaths and no difference in the late death rates of the two groups. This suggests that the preservation of neurologic status in patients with asymptomatic high-grade internal carotid artery stenosis can be improved by carotid endarterectomy. (*Stroke* 1987;18:1005–1010)

Recent developments in ultrasonic duplex scanning have improved the diagnosis of carotid artery disease, and it is now possible to accurately classify the degree of stenosis,^{1,2} permitting study of the relation between degree of arterial narrowing and occurrence of neurologic events. In a previous study, we followed, with serial duplex scans, 167 asymptomatic patients with carotid artery disease and cervical bruits. For the group as a whole, the annual incidence of symptoms, strokes or transient ischemic attacks (TIAs), was 4% per year. However, we found that 47% of the patients with an 80–99% diameter-reducing stenosis developed an ipsilateral stroke, TIA, or occlusion within 36 months.³ Two other studies have also recently confirmed that the finding of a high-grade carotid artery stenosis is an important predictor of a neurologic event.^{4,5}

As a result of our study, we began to recommend carotid endarterectomy to patients found to have an asymptomatic 80–99% internal carotid stenosis. Operation was recommended only if the patient was otherwise a good surgical candidate. The purpose of this

report is to summarize our results using this approach for the period January 1983 through December 1986.

Subjects and Methods

During the 4-year period approximately 6,000 carotid duplex ultrasound examinations were performed in the vascular laboratories of the University of Washington Hospital and the Seattle Veterans Administration Hospital. These studies were conducted both as screening examinations for university and private referring physicians and as part of our long-term research program assessing the natural history of carotid artery disease. Patients were classified as having either symptomatic or asymptomatic carotid lesions. A lesion was considered symptomatic if the patient had a lateralizing ischemic episode appropriate to the distribution of the high-grade lesion [completed stroke, retinal infarction, motor or sensory TIA, reversible ischemic neurologic deficit (RIND), or amaurosis fugax]. Those patients without neurologic symptoms and those with nonspecific visual complaints, dizziness, or syncope not associated with TIAs or strokes were classified as asymptomatic.

Previously published and angiographically validated duplex spectral criteria^{1,2} for classification of internal carotid stenosis were used to grade all internal carotid arteries into 1 of 6 categories: normal, 1–15% stenosis, 16–49% stenosis, 50–79% stenosis, 80–99% stenosis, or occlusion. This report focuses on the clinical course of those patients identified with high-grade

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(80–99%) lesions not producing symptoms. Only those patients with presumed atherosclerotic lesions were included. Patients with fibromuscular disease and stenosis after a previous carotid endarterectomy were excluded.

Those patients with asymptomatic 80–99% diameter-reducing carotid lesions whose private physicians believed carotid endarterectomy to be potentially indicated and who were referred to a vascular surgeon at any of the three participating University of Washington hospitals (University Hospital, Pacific Medical Center, and the Seattle Veterans Administration Hospital) were advised to undergo cerebral angiography and carotid endarterectomy if they were deemed an acceptable surgical risk. The final decision to recommend operation was made by the patient's attending surgeon and was based on assessment of the patient's medical status, especially with respect to known malignancies and their pulmonary and cardiac risk factors. Patients followed without operation therefore consisted of those whose physicians recommended against surgery, those who refused operation, and those rejected for operation by one of the attending surgeons.

Endpoints

On a schedule of every 3–6 months clinic visits and duplex scans, both operated and nonoperated patients were monitored for endpoints, defined as the occurrence of stroke, lateralizing transient ischemic episodes (TIA or RIND), or occlusion of the internal carotid artery as determined by duplex scanning. If multiple events occurred in the distribution of an identified ipsilateral high-grade lesion, only the initial event was counted as an endpoint.

Follow-up

Operated patients were evaluated for both operative neurologic complications and other complications that might have occurred as a result of the surgery. The operated and nonoperated patients were compared with respect to those risk factors thought to potentially influence both the progression of carotid disease and/or the occurrence of stroke. These included hypertension defined by clinical diagnosis or use of antihypertensive medications, a diagnosis of diabetes mellitus, known peripheral vascular atherosclerotic occlusive or aneurysmal disease (claudication or known aneurysm), the degree of stenosis of the contralateral carotid artery, and the presence of cardiac ischemic disease manifested by angina pectoris, a positive history, or electrocardiogram suggesting a previous myocardial infarction. The patients were also assessed for whether they were prescribed aspirin after the discovery of their high-grade lesion. Patients who failed to return for follow-up appointments were contacted by telephone to ascertain their current status.

Statistical Analysis

Data were coded and entered into a personal computer and then transferred to a mainframe computer for

statistical analysis using the Statistical Package for the Social Sciences (SPSS Update 7-9).⁶ Death and event rates were compared between the operated and nonoperated sides using the life table format described by Kaplan and Meier.⁷ Event rates for the operated sides were examined for the period following endarterectomy only. Survival for the operated and nonoperated groups was compared using the method of Lee and Desu.⁸ Ages of the operated and nonoperated patients were compared with the two-tailed Student's *t* test, whereas the prevalence of risk factors was compared using Fisher's exact test.

Results

During the 4 years of the study, 129 high-grade internal carotid artery stenoses not associated with symptoms were identified by duplex scanning in 115 patients; 14 patients had bilateral lesions. There were 87 men and 28 women, average age 66.6 (range 47–95) years. Fifty-six sides (43%) were treated with carotid endarterectomy at one of the University of Washington hospitals prior to the development of a transient ischemic episode, stroke, or internal carotid occlusion. Seventy-three sides (57%) were followed without operation.

The two groups were compared with respect to age, duplex status of the contralateral carotid artery, aspirin use, the presence of peripheral vascular disease, and the prevalence of hypertension, diabetes, ischemic heart disease, and neurologic symptoms occurring in the distribution of the contralateral carotid artery prior to the discovery of the asymptomatic high-grade carotid lesion. With the exception of a higher rate of previous neurologic symptoms (TIA, amaurosis fugax, or stroke) in the distribution of the opposite carotid artery among the operated patients, the operated and nonoperated patients were similar for each category (Table 1).

Operated Sides

Endarterectomy was generally performed early, with 81% of the operated patients treated within 3

Table 1. Comparison of Operated and Nonoperated Groups

	Operated (n = 56)	Nonoperated (n = 73)	p
Age (years)	63.7	68.7	NS
History of neurologic symptoms contralateral to asymptomatic 80–99% stenosis	18%	7%	0.05
Contralateral side >50% stenosis	64%	59%	NS
Diabetes	37%	25%	NS
Hypertension	84%	84%	NS
Peripheral vascular disease	58%	57%	NS
Ischemic heart disease	71%	58%	NS
Aspirin use	91%	79%	NS

NS, no significant difference ($p > 0.05$).

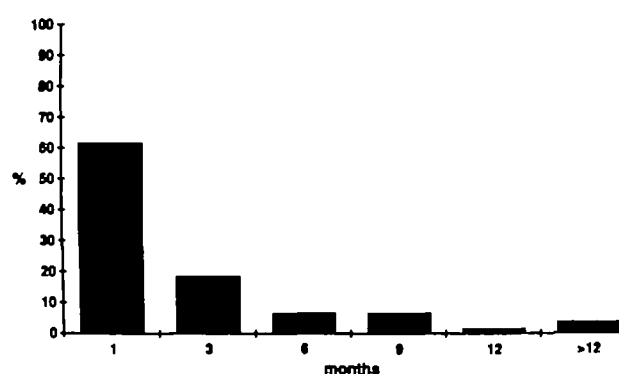


FIGURE 1. Time to operation after diagnosis of asymptomatic 80–99% internal carotid artery stenosis ($n = 56$).

months of the discovery of the high-grade lesion (Figure 1). The reasons for delayed treatment (i.e., endarterectomy >3 months after detection of the lesion) included the patient's initial cardiac status, temporary refusal by the patient, and changing of physicians.

All patients consenting to surgery underwent angiography without complication. There was 1 perioperative stroke with mild residual motor weakness in a patient with a 50–79% contralateral internal carotid artery stenosis (permanent neurologic deficit rate of 1.8% for operation). There was 1 transient perioperative neurologic deficit, which resolved completely within 3 days after operation. One patient died at home 2 weeks after operation from an unexpected myocardial infarction. There were 5 local complications that included 3 cervical hematomas and 2 temporary cranial nerve injuries.

Two neurologic events occurred during postoperative follow-up. One patient had a stroke 7 months after carotid endarterectomy, associated with a recurrent 80–99% lesion. This patient was treated with repeat carotid endarterectomy and had near-complete resolution of his neurologic deficit. One additional patient had a TIA 15 months after operation. Noninvasive testing revealed a <50% stenosis, and the patient was treated nonoperatively; no further neurologic events have occurred with 12 additional months of

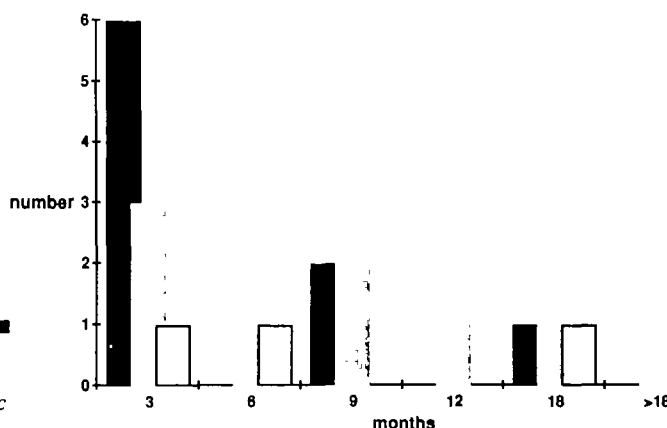


FIGURE 2. Time from diagnosis of asymptomatic 80–99% internal carotid artery stenosis to occurrence of an event in 26 unoperated carotid arteries. 62% of events occurred within 6 months of diagnosis, and 85% occurred within 1 year. Black, stroke; gray, transient ischemic episodes; white, asymptomatic carotid occlusion.

follow-up in this patient. There were no known postoperative carotid occlusions. Seven late deaths occurred in operated patients (Table 2).

Nonoperated Sides

Seventy-three sides were followed without operation; 10 were in patients considered for surgery but turned down because of advanced age or coexisting medical conditions. Twelve deaths occurred in the nonoperated group (Table 2).

There were 26 events in the distribution of the nonoperated high-grade internal carotid stenosis during follow-up (Figure 2). There were 9 strokes, none of which were preceded by a TIA (Table 3). All strokes occurred in patients who were otherwise good surgical candidates; surgery was not done due to either patient refusal or physician delay. Five of these strokes were associated with progression of the stenosis to an ipsilateral internal carotid occlusion. There were 14 transient ischemic episodes, 3 associated with internal carotid occlusion, leaving 11 patent carotid arteries after a transient ischemic episode. One patient died 1 year

Table 2. Comparison of Causes of Deaths in Operated and Nonoperated Groups

	Operated	Nonoperated
Cardiac	4	5
Cancer	2*	2
Pulmonary	0	2
Gastrointestinal bleeding	0	1
Bowel infarction	0	1
Multiple organ failure	0	1
Sepsis	1	0
Unknown	1	0
Total	8	12

*1 patient who died of lung cancer and is listed as a late postoperative death in the operated group had an unoperated contralateral high-grade carotid stenosis as well.

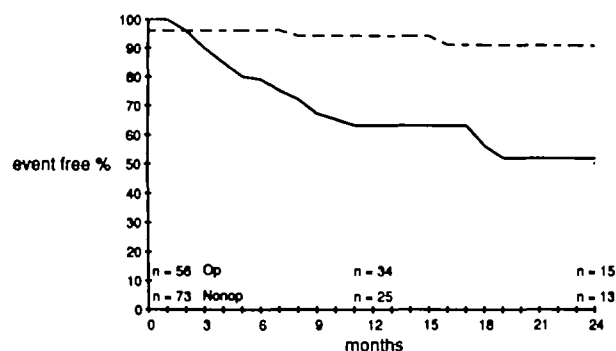


FIGURE 3. Life table analysis for all events (stroke, transient ischemic episodes, asymptomatic internal carotid artery occlusions) in nonoperated (—) vs. operated (---) sides following carotid endarterectomy (includes perioperative events) ($p = 0.0005$).

Table 3. Strokes in Operated and Nonoperated Patients

Pt.	Months from diagnosis	Status of contralateral side	Aspirin use	Ipsilateral carotid occlusion	Reason for nonoperative treatment	Neurologic result
<i>Perioperative</i>						
132	—	50–79% stenosis	Yes	No	—	Minimal residual weakness L arm
<i>Postoperative</i>						
349	7	1–15% stenosis	Yes	No	—	Stroke associated with high-grade restenosis of ipsilateral carotid; mild residual motor weakness
<i>Nonoperated</i>						
103	2	50–79% stenosis	Yes	Yes	Patient refusal	Severe, permanent hemiplegia
109	3	Occlusion	No	No	Physician delay	Retinal artery embolus with permanent blindness
111	17	1–15% stenosis	Yes	Yes	Patient refusal	Permanent hemiplegia; walks with assistance
114 (R)	1	80–99% stenosis	Yes	Yes	Physician delay	Moderate residual motor weakness
114 (L)	2	Occlusion	Yes	Yes	Physician delay	Mild residual motor weakness
146	3	50–79% stenosis	Yes	Yes	Patient refusal	Persistent speech, sensory deficit
324	2	?	No	No	Patient refusal	Level of permanent disability uncertain
343	9	80–99% stenosis	Yes	No	Patient refusal	Unable to use L hand; permanent deficit
350	7	1–15% stenosis	Yes	No	Patient refusal	Expressive aphasia; moderate motor weakness

Pt, patient; R, right; L, left.

later from lung cancer without further neurologic events. One did not have surgery because of poor cardiac status, but is alive after 6 months follow-up without any subsequent neurologic symptoms. One patient refused operation and is event-free after 6 months follow-up, while 1 patient's physician recommended against surgery. This patient is also well after 6 months follow-up. The remaining 7 patients all underwent uneventful carotid endarterectomy. Three additional internal carotid arteries occluded asymptotically. Thirty-eight percent of all events (stroke, transient ischemic episode, asymptomatic occlusion) occurred within 3 months, 62% within 6 months, and 85% within 1 year of diagnosis of the high-grade lesion (Figure 2).

Of the 11 carotid occlusions noted by follow-up duplex scanning, 5 also underwent angiography. The diagnosis of occlusion was confirmed in each case.

Operated vs. Nonoperated Sides

There was a significant increase in the total event rate (stroke, TIA or RIND, and occlusion) in the nonoperated versus operated sides (48 vs. 9% at 24 months, $p = 0.0005$) (Figure 3). Transient neurologic deficits (TIA or RIND) were more frequent in the distribution of the nonoperated carotid lesions (28 vs. 5%, $p = 0.008$). The occurrence of stroke and/or carot-

id occlusions, both irreversible events, was more frequent in the nonoperated versus operated group (36 vs. 4% at 24 months, $p = 0.007$) (Figure 4). The combination of stroke and death was more common in the nonoperated versus operated sides (41 vs. 22% at 24 months, $p = 0.06$) (Figure 5). Stroke also occurred at an increased rate in the nonoperated patients ($p = 0.08$) (Figure 6). The risk of stroke in the distribution of the nonoperated lesions was 15% at 1 year and 19% at 2

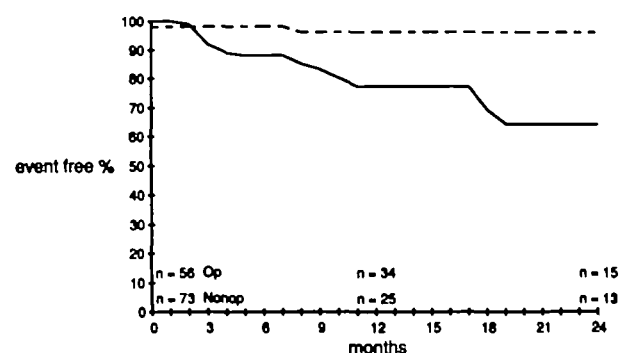


FIGURE 4. Life table analysis for occurrence of stroke and internal carotid artery occlusion in nonoperated (—) vs. operated (---) sides following carotid endarterectomy (includes perioperative events) ($p = 0.007$).

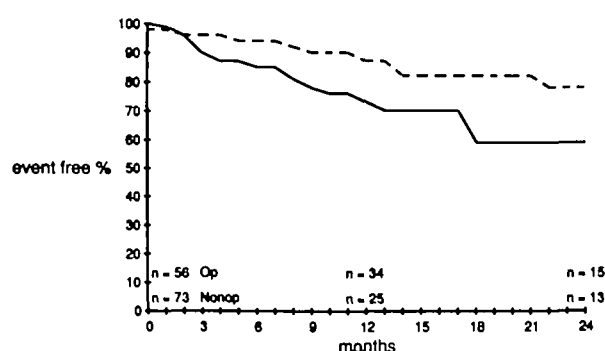


FIGURE 5. Life table analysis for occurrence of stroke and death in nonoperated (—) vs. operated (---) sides following carotid endarterectomy (includes perioperative events) ($p = 0.06$).

years following diagnosis of the high-grade lesion. In the operated group the corresponding figures were 4% at 1 year and 4% at 2 years following operation. There was no difference in the death rates of the two groups (Figure 7).

Discussion

The only goal of carotid endarterectomy is the preservation of neurologic function. While disagreement remains even for the symptomatic patient, the greatest concern has been expressed for the application of this operation to the patient with asymptomatic carotid disease.^{9,10} There is little doubt that for asymptomatic patients as a group, the annual rate of stroke is remarkably low, in the range of 2–4% annually.^{11,12} The major problem for the medical community has been trying to decide which patients with carotid disease are at an increased risk for stroke and deserve an aggressive surgical approach.

In our 1984 study we identified a subgroup of asymptomatic patients (those with 80–99% diameter-reducing lesions by duplex scanning) who had an extremely high event rate, with 47% developing a stroke, TIA, or ipsilateral internal carotid occlusion, usually within 6 months after the discovery of the lesion.³ The

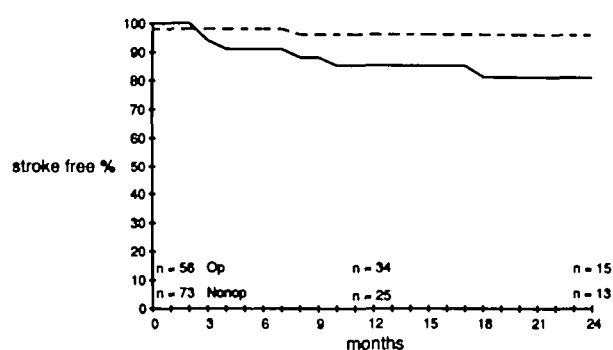


FIGURE 6. Life table analysis for occurrence of stroke in the distribution of nonoperated (—) vs. operated (---) sides following carotid endarterectomy (includes perioperative events) ($p = 0.08$).

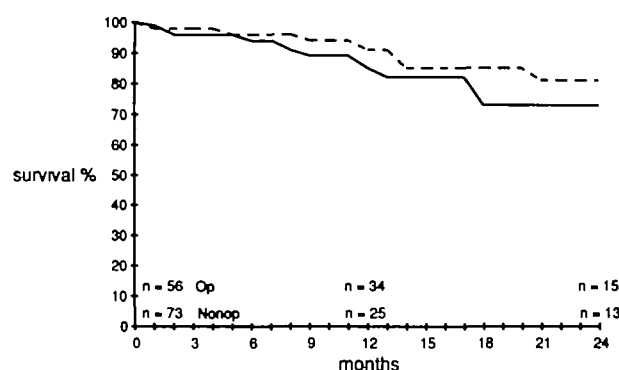


FIGURE 7. Life table analysis for death in nonoperated (—) vs. operated (---) patients following carotid endarterectomy ($p = 0.33$).

relation between ischemic events and the degree of carotid stenosis has also been confirmed by other, more recent studies.^{4,5}

It is important to remember, however, that asymptomatic 80–99% carotid lesions identified by duplex scanning are infrequent. In this study only 129 such lesions were identified in the course of performing approximately 6,000 carotid duplex examinations (2%). In our previous study of patients with asymptomatic bruits, only 7% of the patients were found to have an 80–99% stenosis of their carotid artery.³ This is in contrast to other recently published series concerning the natural history of high-grade carotid stenosis^{4,5} in which up to 22% of the patients with asymptomatic bruits were classified by continuous-wave Doppler examination as having high-grade carotid lesions.⁴ The relatively low stroke rate reported in these series compared with ours may reflect a greater sensitivity of duplex scanning in identifying the very-high-grade asymptomatic lesion that truly places the patient at risk for stroke.

It was the high rate of events associated with severe stenosis in our previous study that prompted our change in attitude favoring surgical management of these patients. While this change and the current study could be criticized for not being a randomized trial and therefore potentially subject to inadvertent bias, it is clear that the two groups in this report are reasonably well matched for potential contributing factors that might affect outcome. One may even argue that the higher incidence of previous neurologic symptoms contralateral to the asymptomatic high-grade lesion in the operated patients actually placed this group at greater neurologic risk than the nonoperated group. In fact, all the strokes that occurred in the nonoperated group developed in patients who were otherwise good candidates for surgery and had never had a previous neurologic symptom. The patients were not operated upon because of patient refusal or physician delay. In addition, the high event rate noted for patients with high-grade stenoses in our earlier study was confirmed during the present study. Another important consideration is that the strokes that occurred in the nonoperated patients were not preceded by a warning TIA.

In addition, while some may argue that a total occlusion that does not produce symptoms should not be considered an adverse event, we disagree. Several studies have documented an increased stroke rate in the distribution of a previously asymptomatic occluded internal carotid artery.^{13,14}

The results presented here show that in properly selected patients, carotid endarterectomy can be performed for high-grade asymptomatic lesions with an acceptable perioperative stroke rate (<2%). In addition, it is clear a successful procedure favorably alters the dangerous natural history of high-grade carotid lesions with regard to the occurrence of transient neurologic deficits, carotid occlusions, and the combination of carotid occlusion and stroke. There is also a strong suggestion of benefit when stroke alone is considered as an endpoint. This benefit may be underestimated as 50% of patients who had TIAs in the non-operated group underwent subsequent carotid endarterectomy. While it is clear that patients with carotid disease have a higher-than-normal mortality, we believe it is important that the period of survival be free of neurologic events and deficits.

Another finding of particular interest emerges from this study. It appears that if a patient with an asymptomatic high-grade stenosis does not have an event in the first 9–12 months after diagnosis, the risk of an event occurring sharply decreases. Perhaps this is due to the fact that the surface characteristics of the lesion, which predispose to the development of thrombosis with or without embolization, may be modified. This factor should be of considerable importance and interest in future studies.

Finally, what about patients with established carotid disease who have lesser degrees of stenosis? This group constitutes the overwhelming majority of patients with asymptomatic carotid disease. Because duplex scanning can be used to follow the disease and its stability, repeat studies should be done at least every 6 months to monitor the lesion. If the lesion shows evidence of progression, then the follow-up interval should be shortened and the patient should be offered carotid endarterectomy if the plaque narrows the artery to 80%, provided that the patient is an acceptable operative risk and that the hospital and surgeon can demonstrate a low morbidity and mortality for carotid endarterectomy. Because these high-grade lesions are relatively uncommon but obviously dangerous, we be-

lieve that this is not only the correct but most conservative approach to the care of patients with asymptomatic carotid disease.

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