Surgical *Versus* Nonoperative Treatment of Symptomatic Carotid Stenosis

211 Patients Documented by Intravenous Angiography

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From 1980 through 1982, intravenous extracranial digital subtraction angiography (DSA) was performed in 6684 patients at the Cleveland Clinic. Of these, 211 previously unoperated patients had prior transient ischemic attacks (TIA) or strokes in conjunction with >50% carotid stenosis on unequivocal DSA studies. Nonoperative management was employed in 126 patients, including 120 (84%) who received antiplatelet therapy or formal anticoagulation. The remaining 85 patients underwent carotid endarterectomy. During a mean follow-up interval of 36 months, there was no overall difference in survival, late TIA, or stroke between the nonoperated and surgical cohorts. However, parity was maintained in these groups only because of the prevalence of intermediate (50-69%) stenotic lesions and stable internal carotid occlusions in the nonoperated group. Carotid endarterectomy provided superior stroke prevention for patients with >70% unilateral stenosis (p = 0.04), for those with >50% bilateral stenosis (p = 0.004), and for those with internal carotid occlusions associated with >50% contralateral stenosis (p = 0.03). The special risk of such discrete subsets should be recognized in order to plan appropriate treatment at the present time, as well as to conduct safe clinical trials in the future.

AROTID ENDARTERECTOMY was first performed over 3 decades ago, but there still seems to be no universal consensus whether patients with transient ischemic attacks (TIA) or mild, completed strokes caused by appropriate atherosclerotic lesions in the carotid bifurcation should receive either surgical or medical treatment. For a number of reasons, it is difficult to reconcile this controversy using much of the information that already is available in the literature. First, most reports describing the results of surgical or nonoperative management have not provided control groups of symptomatic patients who were treated otherwise. With an occasional exception, the severity of carotid disease under medical therapy has rarely been documented by angiography.¹ In From the Department of Vascular Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio

addition, life table calculations have not been employed with sufficient consistency to allow an objective comparison of the late stroke incidence in surgical and medical series. Finally, studies attempting to meet at least some of these requirements have cited excessive or curiously outdated postoperative complication rates as a pivotal liability to surgical treatment.^{2,3}

Despite speculation concerning its effectiveness, however, carotid endarterectomy has become one of the most common peripheral vascular operations in the United States. Although precise figures are difficult to obtain. Dyken and Pokras⁴ estimated that the annual number of extracranial arterial procedures in this country increased from 15,000 in 1971 to 85,000 in 1982. Employing a different data base, Rutkow and Ernst^{5,6} found that carotid endarterectomy was the most frequent major vascular operation performed from 1979 through 1983 and that its use escalated by 76% during the same period, a rate of change that was exceeded only by aortic aneurysm resection. Neurologists in particular have expressed serious reservations concerning the indications and safety of carotid endarterectomy on the scale on which it presently is practiced, and influential members of this specialty in North America and the United Kingdom have suggested that the merit of surgical treatment can only be established on the basis of prospectively randomized, multicentered trials.^{7,8} In a similar study sponsored by the National Institutes of Health, medical treatment recently was found to be equivalent to intracranial bypass for the prevention of further cerebral ischemia among patients with carotid siphon disease.^{9,10} These results were published in a prestigious medical journal and were widely reported throughout the lay press within 2 months of their disclosure to the participating centers. Such data may substan-

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tially influence public policy during an era of cost containment in health care, and intracranial revascularization probably will not continue to be a realistic option even for selected patients at most hospitals.

Considering the uncertain natural history of symptomatic extracranial disease, the volume of cervical carotid operations currently performed, and the publicized conclusions of the intracranial bypass study, a large multicentered trial of carotid endarterectomy and antiplatelet management for bifurcation lesions is inevitable. While this approach may eventually benefit the general public and its health care resources, any proposed study should follow at least three fundamental guidelines: (1) the extent and severity of all extracranial carotid lesions must be adequately documented on entry; (2) late results must not be prejudiced by an unacceptable incidence of perioperative complications; and (3) subsets of patients at special risk for late stroke must be recognized so that their outcome is not obscured within the overall results. The importance of these principles is underscored by the following report of 211 neurologically symptomatic patients who received either carotid endarterectomy or contemporary medical therapy after carotid stenosis exceeding 50% of lumen diameter had been documented by intravenous digital subtraction angiography (DSA) of unassailable quality. The information comprising this report was independently collected and evaluated well before the results of the multicentered trial of intracranial bypass were released. Nevertheless, the conclusions supported by our data now seem even more timely.

Patient Information

From 1980 to 1982, the Cleveland Clinic maintained the first, if not the only, DSA unit in northeastern Ohio. During this interval, 6684 patients underwent intravenous extracranial DSA examinations, and many then returned to their referring physicians for subsequent management. For the purpose of this report, all of these DSA studies were personally reviewed in order to determine the incidence of subsequent TIA and stroke associated with either surgical or medical treatment. Complete follow-up data were obtained from patients, their surviving family members, or physicians for all candidates who had experienced previous neurologic symptoms and met the following requirements:

(1) The extracranial DSA was unequivocally diagnostic and demonstrated >50% stenosis of one or both common carotid or internal carotid arteries.

(2) There was no history of prior cerebrovascular operations.

(3) Any carotid endarterectomy following the DSA examination was performed by one of the authors. Patients who required simultaneous carotid reconstruction and coronary bypass were excluded.

(4) Complete late information was available (none lost to follow-up).

No DSA was accepted unless it demonstrated both extracranial carotid systems clearly enough to be comparable to standard angiography (Fig. 1).¹¹ Under these strict criteria, a total of 211 patients qualified for the study, including 126 who received nonoperative management following their DSA examinations and 85 others who underwent carotid endarterectomy. While this investigation is neither prospective nor randomized in the traditional sense, late information was obtained for all patients who satisfied the entrance requirements, and their treatment was as random as the advice of the many family practitioners, internists, neurologists, and surgeons who were responsible for it.

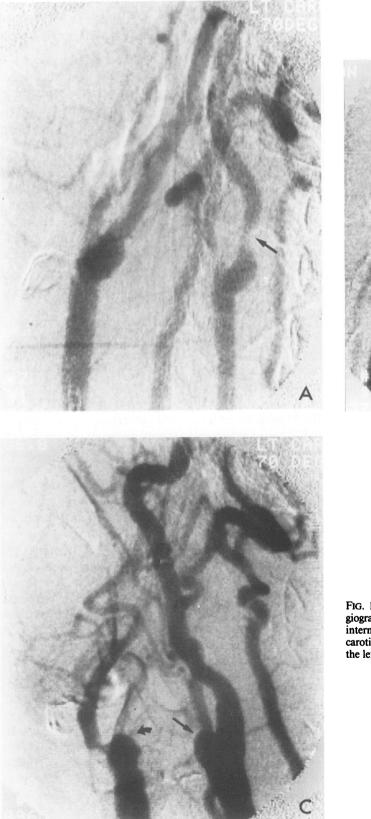
Clinical Features

A summary of several clinical features is presented in Table 1. The two cohorts comprised a total of 134 men (64%) and 77 women (36%), ranging from 18 to 86 years of age (mean: 64 years). Previous neurologic symptoms included focal TIA in 94 patients (45%), prior strokes in 107 (51%), and vertebrobasilar syndrome in ten (4%). Of the 94 patients with transient, lateralizing symptoms, 61 (65%) had experienced hemispheric motor or sensory deficits, while the remaining 33 (35%) described amaurosis fugax alone. Hypertension requiring medical management was present in 149 patients (71%), and 37 patients (18%) were insulin-dependent diabetics. The follow-up interval for all 211 patients presently is 2–55 months (mean: 36 months).

Two differences in the composition of the treatment groups could be identified by statistical analysis. A greater majority (72%) of the surgical cohort were men (p = 0.028, Fisher exact test), and prior strokes were more prevalent (65%) among patients who received nonoperative treatment ($p = 3.8 \times 10^{-7}$).

Angiographic Carotid Disease

The severity of extracranial carotid disease demonstrated by DSA is described in Table 2. Irrespective of the source of previous neurologic symptoms, the maximum degree of angiographic stenosis was 50-69% of lumen diameter in 59 (28%) of all 211 patients and exceeded 70% of the diameter in 73 others (35%). Complete occlusion of the common carotid or internal carotid artery was demonstrated in a total of 79 patients (37%). Conceding the fact that intimal erosion often may escape detection by intravenous DSA, unilateral atheromatous ulceration was identified in 58 patients (27%), and bilateral changes were discovered in another seven (3%).



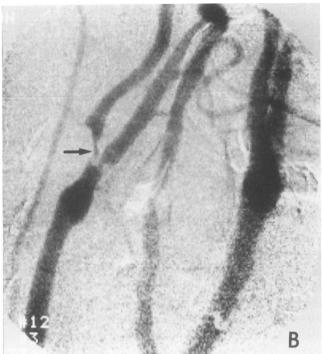


FIG. 1. Examples of the quality of intravenous digital subtraction angiography required for this study: (A) 50-60% stenosis (arrow) of the left internal carotid artery; (B) 90% stenosis (arrow) of the right internal carotid; (C) occlusions of the right internal carotid (curved arrow) and the left external carotid (straight arrow).

Two distinctions may be noted between the angiographic findings in the nonoperated and surgical groups. More patients receiving nonoperative therapy (49%) had internal carotid occlusions ($p = 1.1 \times 10^{-5}$), whereas highgrade stenotic lesions were more common (53%) among those who underwent carotid endarterectomy ($p = 7.5 \times 10^{-6}$).

Management

In the nonoperated group, previous neurologic symptoms were associated with patent vessels and appropriate extracranial carotid stenosis or ulceration in 67 patients (53%) and with documented internal carotid occlusions in 53 (42%). The remaining six patients (5%) had no obvious angiographic lesions. One hundred (79%) of the 126 patients were prescribed and complied with antiplatelet therapy (aspirin and/or dipyridamole), and six others (5%) received formal anticoagulation with Coumadin[®]. A subset of 20 patients (16%) had no specific medical treatment during the follow-up interval after their DSA studies.

In the surgical group, previous symptoms could be attributed directly to patent but diseased extracranial carotid arteries in 76 patients (89%), while another nine (11%) were found to have internal carotid occlusions corresponding to the side of prior TIA or strokes. Including nine contralateral procedures in the subset with internal carotid occlusions, a total of 97 carotid endarterectomies (12 bilateral) were performed in the 85 patients who underwent surgical treatment. In addition, empiric medical management was continued throughout the follow-up period with the use of antiplatelet agents in 74 patients (87%) and with Coumadin anticoagulation in three (4%).

Results

Surgical Complications

There were no early deaths in the surgical group, but one (1.2%) of the 85 patients experienced an operative stroke, which is included in all life table results of surgical treatment in this report. In comparison, nine iatrogenic strokes (2.2%) occurred following a total of 406 carotid endarterectomies that the authors performed in patients with previous neurologic symptoms during the complete study period of 1980–1982 (unpublished data).

Late Survival

Twenty-two (18%) of the patients in the nonoperated group and 20 (24%) of the surgical patients have died within a mean follow-up interval of 36 months. Late mortality was attributed to cardiac events in 26 patients (62%), to cancer in five (12%), and to all other causes in 11 (26%). Only one patient (1%) in each treatment group sustained a fatal stroke. Life table data were calculated

 TABLE 1. Comparison of Clinical Features between the Nonoperated and Surgical Groups

	No operation		Carotid Endarterectomy	
Clinical Features	No.	%	No.	%
Patients	126	100	86	100
Men Women	73 53	58 42	61 24	72 28
Age				
Range Mean	18-86 63		50-86 66	
Previous symptoms				
Focal TIA Prior stroke Vertebrobasilar	36 82 8	29 65 6	58 25 2	68 29 3
Risk factors				
Hypertension Diabetes mellitus	92 25	73 20	57 12	67 14
Follow-up interval (mos.)				
Range Mean	2-55 36		2-54 36	

TIA = transient ischemic attacks.

according to Cutler and Ederer¹² and were analyzed for statistical significance using the method described by Lee and Desu.¹³ Figure 2 depicts actuarial survival for the entire series, as well as for subsets of patients who had either previous TIA or prior strokes. There was no significant difference in survival between the nonoperated and surgical groups throughout the 4–5 years comprising the study period ($p \ge 0.38$).

Clinical indications of associated coronary artery disease (CAD) appeared to influence late survival to a greater extent than did the neurologic status. Of the 211 patients

TABLE 2. Maximum Degree of Extracranial Carotid Disease Demonstrated by Intravenous Digital Subtraction Angiography in the Nonoperated and Surgical Groups

Angiographic Carotid Disease	No Operation $(N = 126)$		Carotid Endarterectomy (N = 85)	
	No.	%	No.	%
Stenosis				
50-69%	36	29	23	27
>70%	28	22	45	53
Occlusion	62	49	17	20
Intimal ulceration				
None	88	70	58	68
Unilateral	33	26	25	29
Bilateral	5	4	2	3

A 952 (126)100 888 0 838 (120)815 .815 . (111) 906 (60) (12)- 8: .824 (85) 80 .824 (70)(77)% • .667 (3) .667 60 (54)ALL PATIENTS (N= 211) NO OPERATION CAROTID ENDARTECTOMY 40 B .952 (42) 100 .88I (40) 881 (37) .820 .820 **و** (21) (7) 917 867 .867 80 (60) (55) (52) % .693 (42) .693 (3) 60 PREVIOUS TIA (N=102) • NO OPERATION • CAROTID ENDARTERECTOMY 40 С 952 100 (84)892 (80).817 . (74) 748 .748 880 a 80 (25) (40)(5) 0 % 720 .7ŽO (22) (18)60 • .609 PRIOR STROKE (N=109) (12)NO OPERATION CAROTID ENDARTERECTOMY 40 2 3 4 5 L YEARS

FIG. 2. Life table survival for all patients and for symptomatic subsets. (Numbers in parentheses indicate patients who are still eligible for consideration.)

in this investigation, 70 had no evidence of CAD either by history or by electrocardiographic findings. Another 85 patients were suspected to have CAD by these criteria, and 56 others have at some time required myocardial revascularization. Cumulative 5-year survival for these three subsets was 90%, 69%, and 88% among the the 126 patients who received nonoperative management of their extracranial lesions, compared to cumulative figures of 78%, 50%, and 92% for the 85 patients who underwent carotid endarterectomy. In the surgical group, 5-year survival for patients who had incidental coronary bypass (92%) was significantly better (p = 0.002) than for those with suspected but uncorrected CAD (50%).

Neurologic Events

Crude incidence. During identical periods of observation, late neurologic events thus far have occurred in 15% of the 126 patients in the nonoperated group (9 TIA, 10 strokes) and in 14% of the 85 patients who underwent carotid endarterectomy (6 TIA, 6 strokes). All events were associated with hemispheric motor and/or sensory deficits or with monocular retinal ischemia. As indicated in Table 3, the overall incidence of late stroke was comparable in the two treatment groups. While the surgical cohort contained too few women and diabetics for adequate comparisons, none of the slight differences achieved statistical significance ($p \ge 0.22$). In the nonoperated group, 9% of patients for whom antiplatelet agents were prescribed have had subsequent TIA, and another 10% have sustained late strokes. No neurologic events have occurred in smaller subsets of patients receiving either Coumadin anticoagulation or no treatment at all.

Cumulative data. Figure 3 illustrates cumulative freedom from all subsequent neurologic events (TIA and strokes) and the total incidence of late stroke in the non-operated and surgical groups. Irrespective of previous symptoms, there were only minor differences in overall complication rates, and none of these approached statistical significance. At least two observations may be made from these data. First, any perceived benefit of carotid endarterectomy would have been seriously compromised if more than one (1.2%) of the 85 surgical patients had sustained operative strokes. Secondly, parity in the outcome of nonoperative and surgical treatment (Fig. 3) reflects the clinical presentation rather than an objective documentation of the distribution and severity of extra-

 TABLE 3. Comparison of the Crude Incidence of Late Stroke Occurring in the Nonoperated and Surgical Groups

Late Stroke	No Operation (N = 126)		Carotid Endarterectomy (N = 85)	
	No.	%	No.	%
Total	10	8	6	7
Men Women	6 4	8 8	2 4	3 17
Age				
Range Mean	53-80 64		58-81 70	
Previous symptoms				
Focal TIA Prior stroke Vertebrobasilar	2 7 1	6 9 12	5 1 0	9 4
Risk Factors				
Hypertension Diabetes mellitus	9 4	10 16	5 0	9
Follow-up interval (mos.)				
Range Mean	1-42 23		0–29 13	

TIA = transient ischemic attacks.

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cranial carotid disease. Since a DSA examination was necessary for inclusion in this particular study, however, subsets of patients at special risk for neurologic complications could be classified according to specific angiographic criteria.

Carotid stenosis. High-grade stenotic lesions were more common in surgical patients, but they also were present in sufficient numbers for analysis within the nonoperated group. As indicated in Figure 4, carotid endarterectomy thus far has had no measurable advantage over nonoperative treatment in the prevention of neurologic complications among patients with stenosis representing 50-69% of lumen diameter. Nevertheless, results of surgical management were clearly superior in patients having carotid stenosis of greater severity. In subsets with >70%stenosis, surgical treatment was associated with an 18% reduction in the incidence of all neurologic events. Moreover, late strokes occurred in 31% of patients in the nonoperated group in comparison to only 7% of those who underwent carotid endarterectomy. This difference was statistically significant (p = 0.04).

The graphic illustrations in this report depict the total incidence of all late TIA and/or strokes, but permanent complications caused by surgically correctable but un-

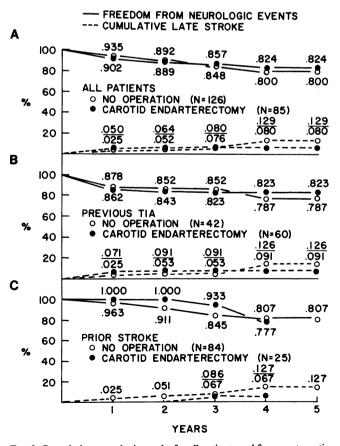


FIG. 3. Cumulative neurologic results for all patients and for symptomatic subsets.

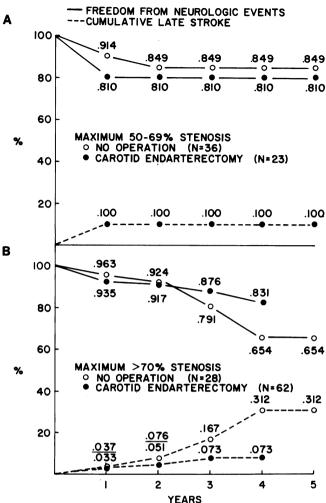


FIG. 4. Cumulative neurologic results according to the maximum severity of carotid stenosis by digital angiography.

operated carotid disease on the same side as previous hemispheric symptoms warrant particular interest. In the nonoperated group of 126 patients, 67 had prior neurologic symptoms directly referrable to patent common and internal carotid arteries. Sixteen of these 67 patients were found to have <50% stenosis on the appropriate side, and none in this subset experienced late strokes. Of the remaining 51 patients, 29 had 50–69% stenosis on the appropriate side, and 22 had >70% stenosis. The cumulative incidence of subsequent strokes caused specifically by these uncorrected lesions was 3.7% and 27%, respectively (p = 0.07).

Internal carotid occlusion. Seventeen of the 85 patients in the surgical group required carotid endarterectomy on the side opposite to documented internal carotid occlusions. As shown in Figure 5, 94% of the patients in this subset have remained free of neurologic events, and none has sustained late strokes. In the nonoperated group, occluded internal carotid arteries represented the maximum degree of extracranial disease in a total of 62 patients.

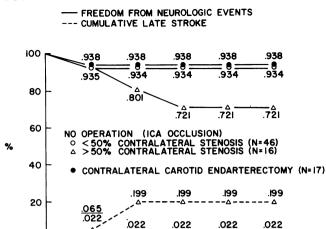


FIG. 5. Cumulative neurologic results according to the status of the contralateral carotid bifurcation on the side opposite to an internal carotid occlusion.

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Sixteen of these had >50% stenosis of the contralateral carotid bifurcation, while the remaining 46 patients had <50% stenosis on the opposite side. Late results in the subset of nonoperated patients with trivial contralateral disease were nearly identical to those of carotid endarterectomy. In comparison, only 72% of the small subset of patients with >50% contralateral stenosis remained free of subsequent neurologic events, and 20% of this subset have sustained late strokes (p = 0.03).

Bilateral carotid stenosis. The composite risk of bilateral carotid stenosis is illustrated in Figure 6. There were no statistically significant differences in the incidence of either TIA or late stroke between patients with unilateral carotid involvement in the nonoperated and surgical groups. Another 27 patients receiving nonoperative treatment and 40 others who underwent carotid endarterectomy had bilateral carotid disease representing some combination of lesions exceeding 50% stenosis and/or internal carotid occlusions. Subsequent neurologic symptoms occurred in 28% of the nonoperated subset, and 23% of these patients have sustained permanent deficits. In comparison, 97% of those with bilateral involvement in the surgical group have remained free of symptoms, and none of the patients in this subset have had late strokes (p = 0.004).

Ignored surgical lesions. For several years, three angiographic criteria generally have been employed to select symptomatic patients for carotid reconstruction at the Cleveland Clinic: (1) any degree of bifurcation stenosis or atheromatous ulceration consistent with a microembolic source for previous focal neurologic events; (2) >70% stenosis of the common or internal carotid artery on either side, irrespective of the distribution of prior symptoms; and (3) > 50% carotid stenosis in conjunction with contralateral internal carotid occlusion. Under these terms, 56 of the 126 patients comprising the nonoperated group in this report did not have a surgical lesion at the time of their initial DSA examinations. Instead, they were found to have either normal extracranial vessels or stable internal carotid occlusions on the same side as previous hemispheric symptoms and no serious stenosis involving the contralateral carotid bifurcation. Using these same criteria, however, the remaining 70 nonoperated patients had traditionally surgical disease for which carotid endarterectomy was not performed.

Figure 7 illustrates the cumulative results for these two subsets, as well as for the 85 patients in this investigation who received surgical management. Although all 211 patients in this series had similar neurologic symptoms, their 5-year outcome may best be stratified according to objective angiographic features. In the surgical group, 18% of patients have experienced subsequent neurologic

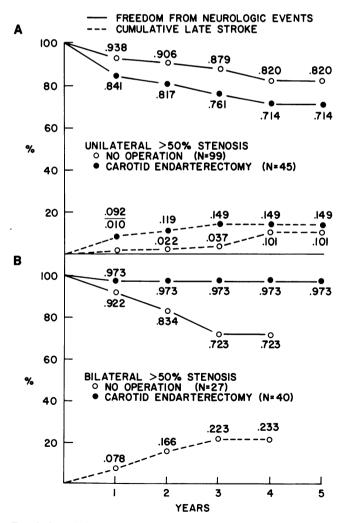


FIG. 6. Cumulative neurologic results according to the distribution of extracranial carotid stenosis.

symptoms, and 8% have had completed strokes. In the nonoperated group, 92% of the subset without surgical lesions have remained free of symptoms, and only 1.8% have had late strokes. In comparison, further symptoms have occurred in 25% of the 70 patients with uncorrected surgical lesions, and 21% of this subset have sustained permanent strokes (p = 0.03).

Discussion

Controversy concerning the appropriate treatment of symptomatic extracranial carotid disease is based on a single quintessential dilemma: many patients who presently undergo carotid endarterectomy would never experience permanent strokes even if no operations were performed. The selection of candidates for surgical management obviously is a critical issue, but independent attempts to determine which patients otherwise face the greatest risk for disabling complications often have provided conflicting data.

Although Whisnant et al.¹⁴ found that the 5-year cumulative incidence of subsequent stroke was 42% in untreated patients with TIA, other similar surveys of symptomatic patients have described inconsistent annual stroke rates ranging from less than 1% to over 15%.¹⁵ Bardin and Bernstein et al.^{16,17} have suggested that high operative risk and poor late results may discourage the use of carotid endarterectomy in patients who already have had prior strokes caused by carotid bifurcation lesions, but Mc-Cullough et al.¹⁸ encountered recurrent deficits in 42% of such patients that might have been prevented by early surgical intervention. The Canadian Cooperative Stroke Study Group¹⁹ originally indicated that, at least in men, antiplatelet therapy might be effective in the prevention of late stroke in symptomatic patients. Nevertheless, Carson et al.²⁰ have demonstrated that aspirin does not confer immunity from neurologic complications and may only suppress transient symptoms until carotid bifurcation disease has progressed to the point of subtotal stenosis or occlusion.

Confronted by these and countless other contradictory opinions, many cerebrovascular surgeons and neurologists not surprisingly appear to take adversarial positions concerning the merit of angiographic investigation and carotid endarterectomy. An adequate randomized trial of medical and surgical treatment eventually may address this polarized issue, but, until it does, a number of thoughtful reports already have presented convincing evidence that some symptomatic carotid lesions simply are more dangerous than others.

In a study of untreated TIA in which 93 of 144 patients underwent documentary cerebral angiography, Ziegler and Hassanein¹ discovered that nearly half of their subset with >70% carotid stenosis developed strokes within the first 3 years of observation. Imparato et al.,²¹ Lusby et

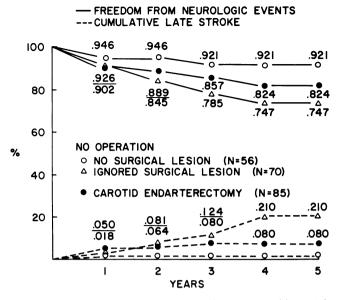


FIG. 7. Cumulative neurologic results according to the traditional definition of a surgical carotid lesion at the Cleveland Clinic (see text).

al.,²² and O'Donnell et al.²³ have demonstrated that highgrade stenosis often is associated with subintimal carotid hemorrhage. This complication produces a structurally unstable plaque with a propensity for cerebral microembolization that even may be aggravated by antiplatelet therapy or formal anticoagulation. Conversely, several investigations have shown that patients with unilateral internal carotid occlusions have a low risk for subsequent stroke, provided that serious contralateral stenosis is surgically corrected.^{24–26} While neurologic symptoms may be caused by shallow intimal ulcers, intermediate carotid stenosis, subtotal lesions, or internal carotid occlusions, their prognosis for future strokes is hardly comparable.

In our experience with the 211 symptomatic patients in this report, there was no overall difference in the incidence of late stroke between nonoperative and surgical treatment in the presence of >50% carotid stenosis confirmed by digital angiography. However, parity in outcome was maintained in these groups only because of the prevalence of intermediate (50-69%) stenosis and stable internal carotid occlusions in the nonoperated cohort. During a mean follow-up interval of 36 months, carotid endarterectomy provided statistically superior stroke prevention under the following specific circumstances: (1) >70% unilateral stenosis; (2) >50% bilateral stenosis; (3) internal carotid occlusion in conjunction with 50% contralateral stenosis. Five-year stroke prevention in the surgical group was consistent with the long-term benefit of carotid endarterectomy reported earlier from this center.²⁷ The conclusions that may be drawn from these results appear to strike a logical balance between the prevailing attitudes of both neurologists and surgeons. Provided they

experience no further neurologic events under medical treatment and serious progression of recognized disease is excluded by periodic reassessment, many symptomatic patients with intermediate degrees of extracranial carotid stenosis may be managed successfully with antiplatelet therapy alone. Nevertheless, our data also confirm that high-grade stenosis or severe bilateral involvement is associated with substantial stroke risk unless carotid endarterectomy is performed.

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