Noninvasive Assessment of Stroke Risk in Asymptomatic and Nonhemispheric Patients with Suspected Carotid Disease

Five-year Follow-up of 294 Unoperated and 81 Operated Patients

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Based on the assumption that ≥50% stenosis of the internal carotid artery increases stroke risk, noninvasive tests are being used to screen patients for prophylactic carotid endarterectomy. To assess the validity of this concept, 104 asymptomatic and 190 nonhemispheric patients referred for cerebrovascular tests were reviewed after 5 years. Carotid stenosis ≥ 50% predicted a 15% stroke incidence at 2 years compared to a 3% incidence with 1–49% stenosis ($p < 0.05$). Five-year cumulative stroke incidence was 21% with ≥50% stenosis, 14% with 1–49% stenosis (NS), and 9% with 0% stenosis ($p < 0.05$). Stenosis ≥ 50% predicted increased cardiac mortality ($p < 0.025$). Hypertensive patients, >70 years, with ≥50% stenosis had a 37% incidence of stroke; normotensive patients, <70 years, with or without stenosis, had few strokes. In patients with ≥50% disease, surgery reduced the 5-year stroke rate from 21 to 8% ($p < 0.05$), mitigated the effects of age and hypertension, and improved survival. Noninvasive test results must be considered in conjunction with age and hypertension in predicting stroke risk.

THE RATIONALE FOR SURGERY in patients with asymptomatic carotid arterial disease rests on three assumptions: (1) the degree of internal carotid artery stenosis is proportional to the risk of stroke; (2) the risk of perioperative stroke or death is small; and (3) surgical removal of the plaque confers long-term protection from neurologic deficit. Since carotid endarterectomy is now the third most common operation in the United States[1,2] and as many as 50% of these procedures may be performed for asymptomatic disease,[3] it is appropriate that the efficacy of such therapy should be clearly established.[4,5]

The evidence that carotid stenosis is a prime risk factor for stroke rests largely on retrospective studies with varying lengths of follow-up.[5–10] Results of the few prospective studies of asymptomatic disease that have been reported suggest that the risk of stroke associated with carotid stenosis may not be very great.[11,12] On the other hand, the morbidity and mortality of carotid endarterectomy is low when the operation is performed by experienced surgeons in well-equipped centers.[6,13,14] That carotid endarterectomy benefits patients who have transient ischemic attacks (TIA's) is generally acknowledged; however, to date, there have been no reports of prospective randomized trials comparing carotid endarterectomy with nonsurgical management in asymptomatic patients. Such studies are in progress.

This retrospective study attempts to define the natural history of asymptomatic carotid artery disease, investigate the influence of carotid stenosis, age, hypertension, and other risk factors on prognosis, and evaluate the relative benefits of surgical and nonsurgical therapy. A major purpose was to test the validity of the concept that hemodynamically significant disease, detected noninvasively, identifies a subset of patients with a high risk of stroke.

Materials and Methods

During a 2-year period from January 1, 1978, to December 31, 1979, 112 asymptomatic patients and 215 patients with ill-defined (nonhemispheric) symptoms were referred to the noninvasive vascular laboratory for cerebrovascular evaluation. Asymptomatic patients were most frequently examined because of cervical bruits (69%) or as part of a work-up for associated vascular disease. Symptoms in the nonhemispheric group were vague and nonspecific. The majority had ill-defined dizzy spells (60%), but only 3% had vertigo or other symptoms typical

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TABLE 1. *Distribution of Age, Sex, and Risk Factors in Nonsurgical Patients*

	Asymptomatic (N = 104)		Nonhemispheric (N = 190)		Total (N = 294)	
	N	(%)	N	(%)	N	(%)
Males	52	(50)	79	(42)*	131	(45)
Females	52	(50)	111	(58)	163	(55)
Diabetes	19	(18)	28	(15)†	47	(16)
Hypertension	59	(57)	105	(55)	164	(56)
Previous MI	18	(17)	25	(13)	43	(15)
Carotid bruit	71	(68)	96	(51)	167	(57)
Age $\bar{X} \pm SD$	63 ± 12		66 ± 12‡		65 ± 11	

* $\chi^2 = 1.60$, df = 1, $0.20 < p < 0.30$.
† $\chi^2 = 1.60$, df = 3, $0.60 < p < 0.70$.
‡ $t = 2.05$, df = 292, $p < 0.05$.

of vertebro-basilar ischemia. A little over one-third (36%) were referred because of confusion, visual abnormalities, or memory disturbance. Twenty per cent complained of headaches, generalized weakness, or tingling in the extremities. No patient in this series had ever experienced lateralizing symptoms or signs, either at presentation or in the past.

Following the noninvasive assessment, five patients underwent a carotid endarterectomy and were excluded from this series; the remaining 322 were followed in the clinic or by letter questionnaire, chart review, telephone consultation, or autopsy and mortality records after a 5-year interval. Twenty-eight patients (8.7%) could not be traced after their initial noninvasive laboratory test. The remaining 294 patients (104 asymptomatic and 190 nonhemispheric) were the subject of this review. Nine patients, four asymptomatic and five nonhemispheric, underwent carotid endarterectomy at a time remote from their initial evaluation (between 19 and 52 months). Five patients had TIA's before their surgery. Follow-up was terminated after endarterectomy. Follow-up information was complete at 5 years for 264 patients (90%); these included 131 males and 163 females with a mean age of 64.8 years (range: 16 to 90 years).

All of the patients had both internal carotid arteries examined using a Hokanson pulsed Doppler ultrasonic arteriograph (D. E. Hokanson, Inc., Issaquah, Washington). Per cent reduction of the internal carotid artery was estimated to the nearest 20% between zero and 100%. To facilitate analysis of the data, patients were grouped into those with no evident disease (0%), those with less than 50% diameter reduction on one or both sides, and those with one or both internal carotid arteries reduced by 50% or more. During the period of this study, the sensitivity and specificity of this method for determining hemodynamically significant disease was 89% and 86%, respectively.[15] Sensitivity for detecting disease of any magnitude was 71% and specificity was 74%. Thirty-four patients (12%) had simultaneous x-ray evaluation, but the ultrasound diagnosis has been used in all the analyses.

For comparison, patients undergoing carotid endarterectomy for asymptomatic disease and nonhemispheric symptoms were also studied. Sufficient numbers of consecutive surgical patients with this presentation were obtained by extending the period of review from July 1, 1976, to June 30, 1982. Of the 101 subjects, six underwent combined carotid endarterectomy and aortocoronary bypass, and one had bilateral endarterectomies performed simultaneously. These patients have been excluded. Of the remaining 94 patients, six were lost to review following their discharge from the hospital, leaving 88 subjects (38 asymptomatic and 50 nonhemispheric) who underwent a total of 108 carotid endarterectomies. There were 50 males and 38 females with a mean age of 65.6 years (range: 35 to 84 years). Follow-up information extended to 101 months and was complete in 77 patients (90%) for at least 2.5 years (the minimum review time in the study).

Demographic details and known risk factors for stroke were recorded for each patient. Patients with a systolic blood pressure greater than 140 mmHg or a diastolic pressure greater than 90 mmHg, or both, were labeled hypertensive. Hypertensive patients controlled by medication were included in the hypertensive category. Electrocardiographic evidence of previous myocardial infarction, history of diabetes, age, sex, race, and degree of carotid disease were recorded for each patient in both surgically and nonsurgically managed patients. Information about regular antiplatelet medication was not always available in this retrospective study. Almost all the patients were or had been cigarette smokers; consequently this data was not subjected to analysis.

Data Analysis

Cumulative life table analysis was performed using the standard life table method.[16] The events considered were stroke and death from all causes. Patients lost to follow-up and those undergoing carotid endarterectomy were excluded after the appropriate interval. Age, sex, and race-matched comparative data were calculated from the Vital Statistics of the United States, 1980.[17] Mean data were compared using the Student's t test; proportions were compared using the Chi square test statistic with Yates correction for 2 × 2 tables. Significance of cumulative proportions were evaluated using the "Z" statistic. All significance values refer to a 2-tailed test.

Results

The sex ratio, mean age, and distribution of risk factors are shown in Table 1 for nonsurgical patients grouped by

TABLE 2. *Distribution of Age and Carotid Stenosis in Nonsurgical Patients*

Degree of Stenosis	Asymptomatic							Nonhemispheric						
	Male		Female		Total		Age	Male		Female		Total		
	N	(%)	N	(%)	N	(%)	$\bar{x} \pm SD$	N	(%)	N	(%)	N	(%)	$\bar{x} \pm SD$
0%	20	(38	31	(60)	51	(49)	59 ± 13	28	(35)	57	(51)	85	(45)	63 ± 13
1–49%	15	(29)	13	(25)	28	(27)	65 ± 10	19	(24)	27	(24)	46	(24)	64 ± 12
≥50%	17	(33)	8	(15)	25	(24)	69 ± 9	32	(41)	27	(24)	59	(31)	69 ± 10

presentation. The mean age of the nonhemispheric patients was slightly greater than that of the asymptomatic group ($p < 0.05$). The prevalence of diabetes, hypertension, previous myocardial infarction, and carotid bruit was similar in both groups. There were more females than males in the nonhemispheric patients, but again the two groups did not differ statistically.

There was no statistical difference in the distribution of carotid disease in asymptomatic and nonhemispheric patients, as shown in Table 2. More than half the subjects had some stenosis and half of these had lesions ≥ 50%. There were proportionately more females than males among patients with no detectable disease and more males than females in the ≥50% category. This difference was statistically significant ($p < 0.005$) in the combined groups and in the nonhemispheric patients ($p < 0.05$), but failed to reach significance in the asymptomatic subjects ($0.05 < p < 0.10$). Mean ages of asymptomatic patients differed from those of the nonhemispheric patients only in the category of no detectable disease. Asymptomatic patients with 1–49% and ≥50% stenoses were significantly older than those with no detectable disease ($p < 0.05$ and $p < 0.001$, respectively). In the nonhemispheric subjects, the mean age of those with no disease did not differ significantly from that of the patients with 1–49% disease; but both were significantly younger than patients with ≥50% disease ($p < 0.005$ and $p < 0.025$, respectively).

There was a positive association between hemodynamically significant disease and the presence of hypertension (Table 3), but there was no clear relationship between hypertension and age ($0.60 < p < 0.70$).

TABLE 3. *Relationship Between Blood Pressure, Degree of Stenosis, and Age*

	Degree of Stenosis*				Age (Years)†			
	<50%		≥50%		<70		≥70	
	N	(%)	N	(%)	N	(%)	N	(%)
Normotensive	102	(49)	28	(33)	86	(47)	44	(39)
Hypertensive	108	(51)	56	(67)	96	(53)	68	(61)

* $\chi^2 = 5.05$; df = 3; $p < 0.025$.
† $\chi^2 = 1.48$; df = 3; $0.60 < p < 0.70$.

During the 5-year period encompassed by this study, 13 (13%) of the 104 asymptomatic patients and 23 (12%) of the 190 nonhemispheric patients suffered a stroke. Neurologic deficits, either stroke, TIA or both, occurred in 16% of both groups (Table 4). Only one of the 36 strokes (3%) was known to have been preceded by a TIA, and this occurred in a nonhemispheric patient. There was no significant difference between the incidence of stroke or total neurologic deficits in males and females. In the asymptomatic group, the mean age of the females who suffered a stroke (74 ± 11 years) was higher than that of the males (68 ± 6 years), but this difference was not significant ($0.20 < p < 0.30$). The incidence of neurologic deficits paralleled the degree of stenosis; however, absence of detectable carotid disease did not predict a stroke-free survival (Tables 4 and 5). As shown in Table 5, at least 22% of the strokes developed on the side with the lesser degree of stenosis.

TABLE 4. *Distribution of Neurologic Events within a 5-year Follow-up Period*

Stroke Incidence

Degree of Stenosis	Asymptomatic						Nonhemispheric					
	Males		Females		Total		Males		Females		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
0%	2	(10)	3	(10)	5	(10)	3	(11)	4	(7)	7	(8)
1–49%	2	(13)	2	(15)	4	(14)	1	(5)	4	(19)	5	(11)
≥50%	3	(18)	1	(13)	4	(16)	3	(9)	8	(30)	11	(19)
Total	7	(13)	6	(12)	13	(13)	7	(9)	16	(14)	23	(12)
Age $\bar{x} \pm SD$	68 ± 6		74 ± 11		71 ± 9		72 ± 8		73 ± 12		73 ± 11	

Total Neurologic Deficits (Stroke and/or TIA)

Degree of Stenosis	Asymptomatic						Nonhemispheric					
	Males		Females		Total		Males		Females		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
0%	2	(10)	5	(16)	7	(14)	4	(11)	4	(7)	8	(9)
1–49%	2	(13)	2	(15)	4	(14)	3	(16)	5	(19)	8	(17)
≥50%	4	(24)	2	(25)	6	(24)	5	(16)	10	(37)	15	(25)
Total	8	(15)	9	(17)	17	(16)	12	(15)	19	(17)	31	(16)
Age $\bar{x} \pm SD$	68 ± 6		74 ± 10		71 ± 9		71 ± 6		72 ± 12		72 ± 10	

TABLE 5. *Distribution of Hemispheric Strokes According to Degree of Internal Carotid Stenosis in Nonsurgical Patients*

Presentation	Stroke on Side with Greater Stenosis N	(%)	Stroke on Side with Lesser Stenosis N	(%)	Stroke in Patient with No Detectable Disease N	(%)	Brainstem* or Uncertain N	(%)	Total N	(%)
Asymptomatic	5	(38)	1	(8)	5	(38)	2	(15)	13	(100)
Nonhemispheric	6	(26)	7	(30)	7	(30)	3	(13)	23	(100)
Total	11	(31)	8	(22)	12	(33)	5	(14)	36	(100)

* Two brainstem.

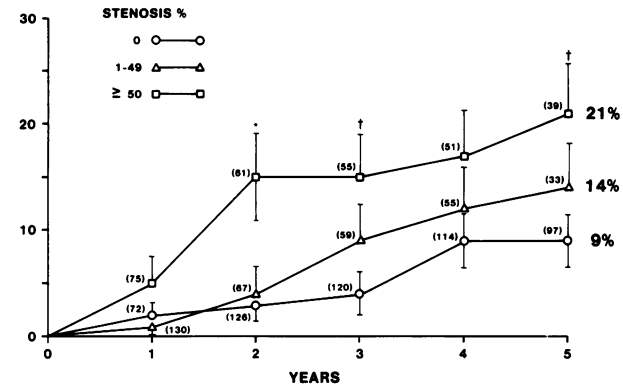

FIG. 1. Relationship of the degree of internal carotid arterial stenosis (as determined by noninvasive testing) to the cumulative stroke rate in unoperated asymptomatic and nonhemispheric patients. Vertical bars indicate ± one standard error of the estimate. Numbers in parenthesis indicate the number of patients remaining at the end of each interval. *≥50% *vs.* 1–49 and 0, ($p < 0.05$); †≥50% *vs.* 0, ($p < 0.05$).

Table 6 lists the cumulative proportions of asymptomatic and nonhemispheric, nonsurgical patients surviving stroke-free at yearly intervals and shows the effects of age, blood pressure, and carotid stenosis. With the exception of age, at the first interval, there were no statistically significant differences between the stroke-free survival rates for asymptomatic or nonhemispheric patients for any of these risk factors at any stage during the 5-year follow-up. Because these data were so similar, the two groups were considered together in all subsequent analyses.

Figure 1 illustrates the cumulative stroke rate among nonsurgically managed patients according to the degree of stenosis detected at the initial examination. Patients with hemodynamically significant disease (≥50%) had a higher stroke rate (15%) than all patients with <50% disease at the second year ($p < 0.05$). After that period patients with ≥50% lesions had a higher stroke rate than patients with no disease at 3 and 5 years ($p < 0.05$). There was no statistical difference after the second year in the cumulative stroke rates of patients with ≥50% disease and 1–49% disease. At 5 years, the stroke rates were 21% in the ≥50% group, 14% in the 1–49% group, and 9% in the group with no detectable disease.

TABLE 6. *Cumulative Stroke-free Survival of Asymptomatic and Nonhemispheric Nonoperated Patients**

Interval (Years)	<70 Years		≥70 Years	
	Asymptomatic	Nonhemispheric	Asymptomatic	Nonhemispheric
1	0.97 ± 0.02	1.00 ± 0.00	1.00 ± 0.00	0.92 ± 0.03†
2	0.96 ± 0.03	0.98 ± 0.01	0.91 ± 0.05	0.85 ± 0.04
3	0.96 ± 0.03	0.96 ± 0.02	0.81 ± 0.07	0.82 ± 0.05
4	0.92 ± 0.03	0.95 ± 0.02	0.78 ± 0.08	0.78 ± 0.05
5	0.92 ± 0.03	0.95 ± 0.02	0.74 ± 0.08	0.74 ± 0.05
	Normotensive		Hypertensive	
	Asymptomatic	Nonhemispheric	Asymptomatic	Nonhemispheric
1	1.00 ± 0.00	1.00 ± 0.00	0.97 ± 0.02	0.94 ± 0.02
2	0.98 ± 0.02	0.99 ± 0.01	0.91 ± 0.04	0.88 ± 0.03
3	0.98 ± 0.02	0.99 ± 0.01	0.86 ± 0.05	0.84 ± 0.04
4	0.98 ± 0.02	0.96 ± 0.02	0.80 ± 0.05	0.82 ± 0.04
5	0.95 ± 0.04	0.95 ± 0.03	0.80 ± 0.05	0.80 ± 0.04
	<50% Stenosis		≥50% Stenosis	
	Asymptomatic	Nonhemispheric	Asymptomatic	Nonhemispheric
1	0.99 ± 0.01	0.98 ± 0.01	0.96 ± 0.04	0.95 ± 0.03
2	0.96 ± 0.02	0.97 ± 0.02	0.86 ± 0.07	0.84 ± 0.05
3	0.92 ± 0.03	0.94 ± 0.02	0.86 ± 0.07	0.84 ± 0.05
4	0.90 ± 0.04	0.90 ± 0.03	0.79 ± 0.10	0.84 ± 0.05
5	0.88 ± 0.04	0.90 ± 0.03	0.79 ± 0.10	0.79 ± 0.06

Proportion ± standard error.

† $p < 0.05$.

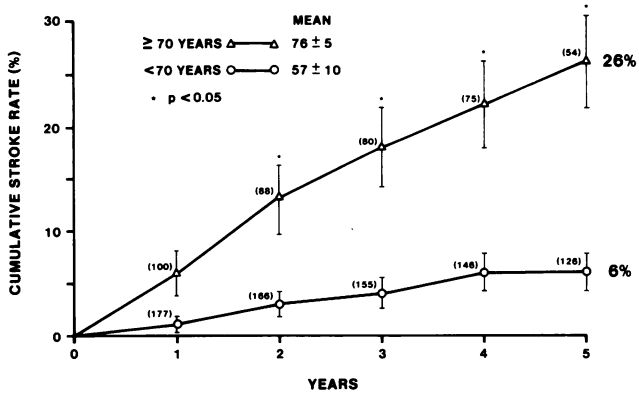

FIG. 2. Relationship of age to the cumulative stroke rate of unoperated asymptomatic and nonhemispheric patients with suspected carotid arterial disease.

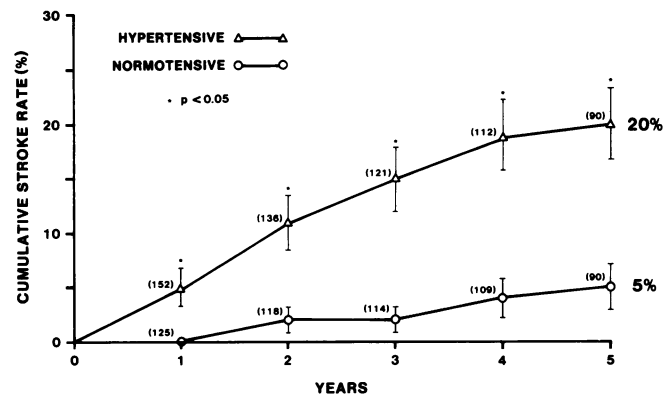

FIG. 3. Relationship of hypertension to the cumulative stroke rate of unoperated asymptomatic and nonhemispheric patients with suspected carotid arterial disease.

The influence of age and hypertension are shown in Figures 2 and 3. A significantly higher risk of stroke was observed in patients over the age of 70 after 2 years of follow-up, compared with younger individuals ($p < 0.05$). At 5 years, the stroke rate was 26% in the older patients and 6% in patients under 70 years. Hypertensive patients had a significantly worse stroke rate than nonhypertensive patients at all stages of follow-up ($p < 0.05$), with a 5-year cumulative stroke rate of 20% compared with 5% in normotensive subjects.

Cumulative death rates, including deaths from stroke, cardiac disease, and other causes, are plotted in Figure 4 according to the degree of stenosis. Until the final year of follow-up, the risk of dying associated with hemodynamically significant stenosis was significantly greater than that associated with 1–49% disease ($p < 0.05$). After the first year, survival was also worse in the ≥50% group than it was in patients with no detectable disease ($p < 0.05$). Cumulative death rates were 35% at 5 years for patients with ≥50% stenosis, 22% for patients with 1–49% stenosis, and 14% for those with no detectable stenosis.

In Table 7, the 5-year incidence of strokes, TIA's, and deaths are analyzed according to age, hypertension, and degree of carotid stenosis. There were 62 deaths in the series, of which 13 were attributed to stroke (21%). Twenty-nine were due to cardiac disease (47%); 20 (31%) were related to nonvascular illness, including cancer, pulmonary disease, and metabolic disorders. The fatal stroke rate in patients with ≥50% disease was 8%, compared with 3% in patients with less disease ($0.05 < p < 0.10$). In addition, patients with ≥50% stenosis had a greater risk of dying from cardiac disease (17%) than patients with <50% stenosis (7%) ($p < 0.025$). All cardiovascular complications, including stroke, TIA, and fatal myocardial infarction, were significantly more frequent in patients with ≥50% disease ($p < 0.0005$).

Advanced age established a population with a high incidence of stroke (23%) and total cardiovascular complications (42%). In younger subjects, the incidence of stroke and all vascular complications was markedly less, 5% and 13% respectively ($p < 0.0005$). Presence of hypertension was associated with a significantly increased incidence of stroke (18%) compared with that in normotensive patients (5%) ($p < 0.001$) but did not signify a greater risk of cardiac death ($0.60 < p < 0.70$). The combination of age ≥ 70 years, hypertension, and ≥50% stenosis isolated a group of patients with a 44% incidence of neurologic deficit and a 63% incidence of having developed some vascular related complication or of dying in 5 years. Conversely, young patients with little stenosis and no hypertension had a low 5-year incidence of vascular illness.

Carotid bruits were present in 167 patients (57%) but were not a good indicator of future stroke. Twenty patients with a bruit developed strokes (12%), while 16 patients with no bruit had strokes (13%). There were 26 patients

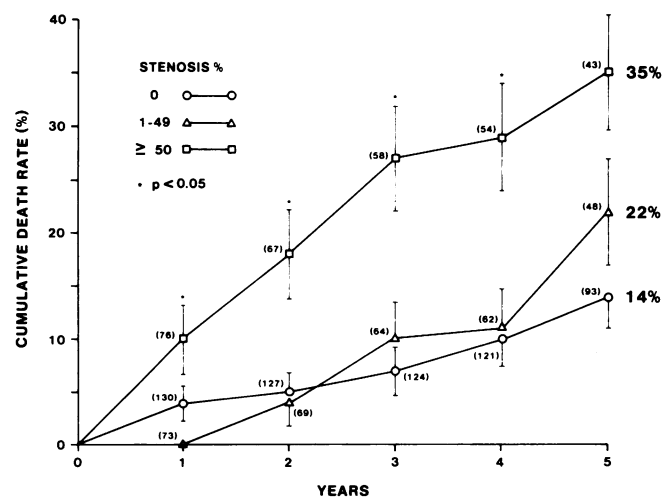

FIG. 4. Relationship of the degree of noninvasively determined internal carotid arterial stenosis to the cumulative death rates of unoperated asymptomatic and nonhemispheric patients with suspected carotid arterial disease. Deaths from all causes are included.

TABLE 7. *Distribution of Neurological and Fatal Events in a 5-Year Period, Interaction of Risk Factors*

	<70 Years								≥70 Years								
	No Hypertension				Hypertension				No Hypertension				Hypertension				
Stenosis %	<50		≥50		<50		≥50		<50		≥50		<50		≥50		Total
N	74		12		67		29		28		16		41		27		294
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Nonfatal events																	
Stroke	1	(1)	0	(0)	6	(9)	1	(3)	1	(4)	2	(13)	9	(22)	7	(26)	27	(9)
TIA	0	(0)	2	(17)	2	(3)	3	(10)	1	(4)	0	(0)	3	(7)	2	(7)	13	(4)
Fatal events																	
Stroke	0	(0)	0	(0)	0	(0)	2	(7)†	2	(7)	0	(0)	4	(10)**	5	(19)**	13	(4)
Myocardial infarction	2	(3)	1	(8)	5	(7)*†	2	(7)	4	(14)†	5	(31)*	4	(10)†	6	(22)*	29	(10)
Other	2	(3)	3	(25)	3	(4)*	0	(0)	4	(14)	1	(6)*	5	(12)**	2	(7)*	20	(7)
Total patients																	
Strokes	1	(1)	0	(0)	6	(9)	3	(10)	3	(11)	2	(13)	11	(27)	10	(37)	36	(12)
Neurological events	1	(1)	2	(17)	8	(12)	5	(17)	4	(14)	2	(13)	14	(34)	12	(44)	48	(16)
All vascular events	3	(4)	3	(25)	11	(16)	7	(24)	7	(25)	6	(38)	17	(41)	17	(63)	71	(24)

* Patient with prior stroke event, also included as nonfatal stroke.

† Patient with prior TIA event, also included as TIA.

who had ≥70% carotid stenoses. Four patients in this group had strokes during follow-up (15%), compared to 11 strokes (19%) among 58 patients with ≥50% but <70% stenosis. Thirteen patients had documented internal carotid artery occlusion; only one of these patients had a stroke during the 5 years (8%). Bilateral hemodynamically significant stenoses were present in 42 patients, and 42 had unilateral ≥50% diseases. Eight strokes (19%) occurred in the bilateral disease group, of which six proved to be fatal (14%); while seven strokes were recorded in the unilateral disease group (17%), only one was fatal (2%), ($0.05 < p < 0.10$). Diabetes was not an important risk factor; there were seven strokes in the 47 diabetics in the series (15%), compared with 31 strokes in the nondiabetic patients (13%).

Thirty-five (12%) of the 294 patients were known to be taking antiplatelet agents and 10 (3%) were on warfarin. In this group, the 5-year incidence of stroke was 16% and that of TIA was 13%. In the other patients, the incidence of stroke was 12% and the incidence of TIA was 2%. Total neurologic complications were statistically more frequent ($p < 0.025$) in the treatment group (29%) than in the other patients (14%). Although the two groups did not differ significantly in terms of age or presence of hypertension; 42% of those on antiplatelet agents or warfarin had ≥50% stenosis, while only 26% of the other patients had disease of that severity ($p < 0.05$).

TABLE 8. *Distribution of Age, Sex, and Risk Factors in Surgical and Nonsurgical Patients with ≥50% Carotid Stenosis*

	Nonsurgical (N = 84)		Surgical (N = 81)	
	N	(%)	N	(%)
Males	49	(58)	47	(58)
Females	35	(42)	34	(42)
Diabetes	16	(19)	18	(22)
Hypertension	53	(63)	52	(64)
Previous myocardial infarction	20	(24)	12	(15)
Age ≥ 70 (years)	43	(51)	25	(31)
Age $\bar{x} \pm$ SD	69 ± 10		66 ± 9*	
Range	(37–83)		(35–84)	

* $t = 2.19$, $df = 163$, $p < 0.05$.

Surgical Group

Of the 88 patients who underwent carotid endarterectomy, all but seven had internal carotid artery stenoses exceeding 50% diameter reduction. The ages, sex distribution, and risk factors in the remaining 81 patients are shown in Table 8 and are compared with the same data from 84 patients with ≥50% stenosis managed without surgery. The mean age of the nonsurgical group (69 ± 10 years) was slightly greater than that of the surgical group (66 ± 9 years), and this was statistically significant ($p < 0.05$). However, all the other risk factors were similarly distributed among the two groups ($0.20 < p < 0.30$).

Figure 5 compares the cumulative stroke rate in surgical and nonsurgical patients. One year after surgery, the operated patients showed no benefit in terms of stroke, but by 2 years, the surgical group had a 4% stroke rate, compared to a 15% stroke rate in the nonsurgical patients ($p < 0.05$). This benefit persisted; at 5 years, the surgical patients had a cumulative stroke rate of only 8%, but the stroke rate in the nonsurgical patients had risen to 21% ($p < 0.05$).

Table 9 shows the location of strokes in the postoperative period and during late follow-up in the surgical patients. Although the patient stroke rate was 2.5% in the perioperative period, the operative stroke rate was lower

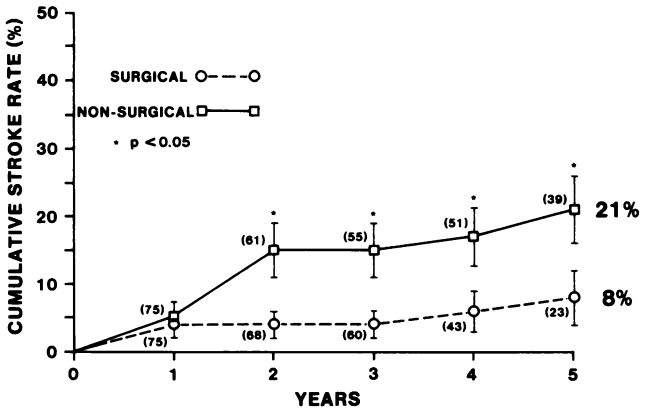

FIG. 5. Comparison of the cumulative stroke rates of surgically treated and nonsurgically managed asymptomatic and nonhemispheric patients with ≥50% stenosis of the internal carotid artery. Data at one year in the surgically treated patients include perioperative events.

(2.1%). Late strokes (4%) occurred on both the operated and nonoperated sides.

Figures 6 and 7 illustrate the effects of known risk factors, age and hypertension, upon the cumulative stroke rate in surgical and nonsurgical patients. Similar to the data in Figure 2, the stroke rate after 1 year in nonsurgical patients with ≥50% stenoses was higher in those patients who were 70 years of age or older than it was in younger subjects ($p < 0.05$). Surgical patients over 70 years fared significantly better than nonsurgical patients over 70, with a 5-year cumulative stroke rate of 8%, compared with 33% for the nonsurgical group. Nonsurgical patients under 70 had the same stroke rate as surgical patients both under and over 70 years (8%). Hypertensive patients in the surgical group also appeared to benefit in terms of stroke rate compared to the unoperated patients. The risk of hypertensive patients having a stroke following surgery was not statistically different from that of normotensive patients without surgery, but was significantly better than the nonsurgical hypertensive patients after the first year of follow-up ($p < 0.05$). Surgical therapy did not appear to confer significant benefits in either the young patients or in those without hypertension.

TABLE 9. *Distribution of Hemispheric Deficits in Surgical Patients*

	Asymptomatic (N = 37)		Nonhemispheric (N = 44)		Total (N = 81)	
	N	(%)	N	(%)	N	(%)
Postoperative stroke						
Operated hemisphere	1	(2.7)	1	(2.3)	2	(2.5)
Late stroke						
Operated hemisphere	2	(5.4)	0	(0.0)	2	(2.5)
Nonoperated hemisphere	0	(0.0)	1	(2.3)	1	(1.2)
Total	3	(8.1)	2	(4.5)	5	(6.2)

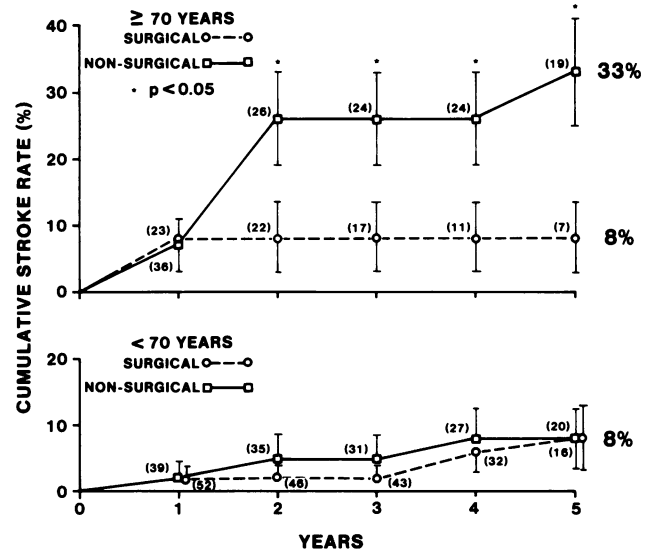

FIG. 6. Effect of age on the cumulative stroke rates of surgically treated and nonsurgically managed asymptomatic and nonhemispheric patients with ≥50% stenosis of the internal carotid artery.

There were no operative deaths. During follow-up, 18 of the surgical patients died (22%), compared to 27 of the nonsurgical patients (32%). The nonsurgical group, however, was slightly older and was followed for a longer period than the surgical group. Of the late surgical deaths, only one (6%) was stroke related; eight (44%) were due to a myocardial infarction; and the remaining nine (50%) were attributed to other causes. As shown in Table 7, seven (26%) of the nonsurgical deaths were due to stroke, 14 (52%) to myocardial infarction, and six (22%) to other causes. These differences approach statistical significance ($0.05 < p < 0.10$).

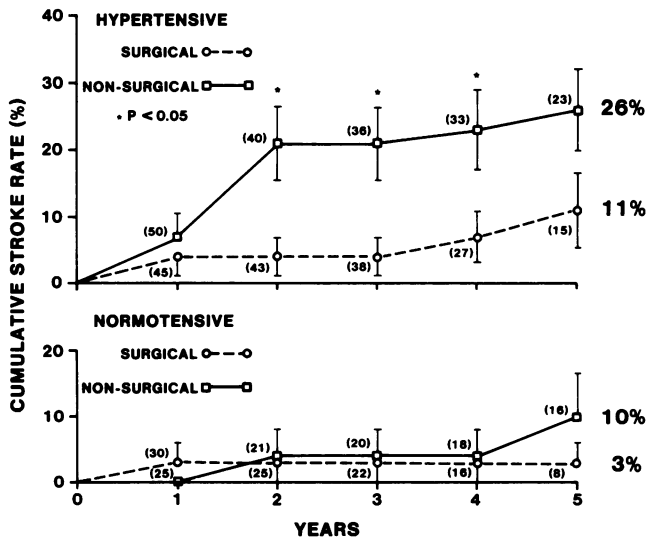

FIG. 7. Effect of hypertension on the cumulative stroke rates of surgically treated and nonsurgically managed asymptomatic and nonhemispheric patients with ≥50% stenosis of the internal carotid artery.

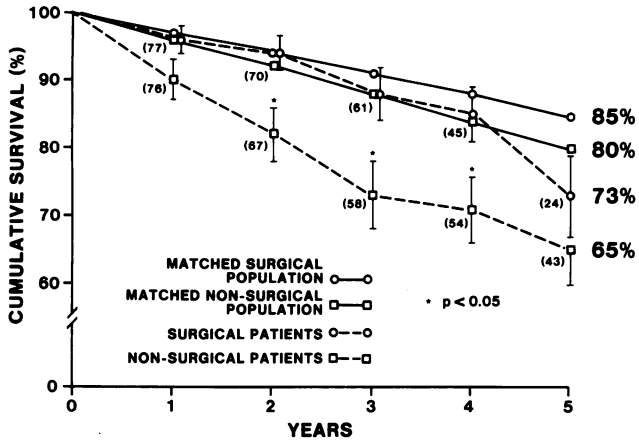

FIG. 8. Cumulative survival rates of surgically treated and nonsurgically managed asymptomatic and nonhemispheric patients with ≥50% stenosis of the internal carotid artery compared with ages, sex, and race matched U.S. population.

Late postsurgical deaths were proportionately slightly more frequent in the nonhemispheric group: one stroke death (2%), five fatal myocardial infarctions (11%), and six from other causes (14%). In the asymptomatic group, there were no stroke deaths. Three died of myocardial infarctions (8%) and three of other causes (8%).

Comparison of cumulative survival rates of the surgical and nonsurgical patients, all with ≥50% stenosis, are shown in Figure 8. These two groups are also compared with age, race, and sex adjusted life expectancy rates from the general population of the United States (1980).[17] The survival rates for nonsurgical patients, compared to surgical patients, were significantly worse through the fourth year ($p \leq 0.05$). At 5 years, the difference was not significant. Survival of the nonsurgical patients was also significantly worse than that expected for the general population throughout the follow-up period ($p < 0.05$). With the exception of the fifth year, survival of the surgical patients was only slightly inferior to that of their matched general population; the two curves did not differ significantly at any of the time periods.

Discussion

The present study was undertaken to clarify the individual and collective influences of internal carotid stenosis, hypertension, and age on long-term stroke rates in asymptomatic patients with suspected cerebrovascular disease. Patients with ill-defined "nonhemispheric" symptoms—almost certainly unrelated to extracranial carotid or vertebral arterial disease—were also included because they had similar risk factors and were found to have a virtually identical prognosis. The study was retrospective; yet because entry into the review group was defined by referral of patients to the vascular laboratory with no exclusions apart from those undergoing immediate carotid endarterectomy and because follow-up has been 90% complete over a 5-year period, its structure, in many respects, was comparable to a prospective trial.

The factors that coexist before the onset of a hemispheric stroke in an asymptomatic patient are many and have complex, poorly understood interactions. Advancing age and hypertension have been incriminated as major factors that alone or in combination increase risk of stroke;[18-21] our results were consistent with these observations. In fact, as isolated parameters, both age and hypertension were more powerful determinants of stroke than was the degree of stenosis. Patients > 70 had 4.2 times the risk of stroke than those < 70; hypertension increased the risk by a factor of 4.0; and stenosis ≥ 50% by 1.8 (Table 7). The 5-year incidence of stroke in our series (12%) was, however, considerably higher than that reported in general population surveys, even when the results are matched for age and hypertension.[18,19,22] Thus, the referral process, which was based on the presence of a bruit, peripheral vascular disease, coronary disease, and, in the case of the nonhemispheric patients, ill-defined cerebrovascular symptoms, preselected a high-risk group. Moreover, most of the patients were or had been cigarette smokers, 16% were diabetic, and 15% had had a previous myocardial infarction. All of these factors have been reported to be associated with an increased incidence of stroke, carotid arterial disease, or both.[11,20,21,23-27] Since there is no reason to suspect that the referral practice in our institution is unique, it is reasonable to assume that the results of our study are generally applicable to other vascular laboratory populations.

Thompson and associates reported a 17.4% incidence of stroke in 138 patients with asymptomatic bruits followed for a mean period of 3.8 years.[6] Both the mean age of their patients (65.7 years) and the stroke rates were quite similar to those in our study of patients with ≥50% disease at 4 years (Fig. 5). Other authors, in follow-ups ranging from 2 to 13 years, report strokes developing in from 12 to 19% of patients with bruits.[7,28-30] Contrary to other reports, the presence or absence of bruit was not correlated with the incidence of stroke in our study.[7,28,30]

Although diabetes has been a strong risk factor in most studies, it did not affect the stroke incidence in our series.[11,20,23,24] In younger individuals, the reported stroke risk in males exceeds that in females, but in the older age groups the risk becomes roughly equal and may even reverse.[19-21] The stroke incidence in males appears to peak in the seventh decade while that in females peaks in the eighth.[31] Although the females in the present study tended to have less stenosis, the incidence of stroke in the two sexes was roughly equivalent. Females with stroke in the asymptomatic group were somewhat older than their male counterparts.

TABLE 10. *Neurologic Complications Related to Degree of Carotid Stenosis at Initial Noninvasive Examination of Asymptomatic Patients*

Author	Tests†	Per Cent Developing Symptoms: Positive Tests (≥50% Stenosis) Stroke	Positive Tests (≥50% Stenosis) TIA	Negative Tests (<50% Stenosis) Stroke	Negative Tests (<50% Stenosis) TIA	Follow-up (months) Mean	Follow-up (months) Range
Kartchner and McCrae*[8]	OPG-K	8	4	2	2	24	6–70
Busuttil et al.[9]	OPG-G, SOD	7	29	0	7	31	>6
Barnes et al.[38]	CW-Doppler	3‡	14‡	0	1	11	1–28
Roederer et al.[11]	Duplex	3§	4§	0.5§	1§	—	<36

* Approximately half of the patients had nonhemispheric symptoms.

† OPG-K = pulse-delay oculoplethysmography; OPG-G = oculopneumoplethysmography; SOD = supra-orbital Doppler; CW-Doppler = direct Doppler examination; Duplex= combined B-mode imaging and Doppler spectrum analysis.

‡ Positive test and/or bruit.

§ Calculated on basis of individual arteries rather than patients.

Carotid Stenosis as a Risk Factor

Most reports in the literature concerning the prognosis of asymptomatic carotid disease have been restricted to patients who had a carotid endarterectomy on one side, while the contralateral "asymptomatic" side was not treated surgically.[32–37] Before their surgery, many of the patients included in these reports had definite neurologic symptoms or TIA's related to the operated vessel. In this respect, the present review may not be comparable, since none of our patients had a history of any neurologic deficit. Furthermore, it is arguable that the low incidence of stroke in long-term follow-up recorded by these reports (0–4%) should be compared with the surgical patients in our series rather than the nonsurgical group, since it is possible that endarterectomy may reduce the risk of stroke on the side of the unoperated stenotic vessel.

Although it is popularly assumed that severe stenosis and deeply ulcerated plaques at the carotid bifurcation have a significantly more ominous prognosis than minor smooth lesions, there has been, until recently, little data to support this concept. Table 10 summarizes four reports from the literature that compare the incidence of neurologic complications developing in asymptomatic patients with the results of noninvasive tests performed at initial presentation.[8,9,11,38] It appears that the annual incidence of stroke ranges from 3 to 4% in patients with ≥50% and is less than 1% in those with <50% disease. TIA's also appear to correlate with the degree of stenosis.

Our results are comparable. Stenoses reducing the diameter of one or both internal carotid arteries by more than 50%, as estimated by pulsed Doppler flow-mapping, predicted an increased risk of stroke. By 2 years, 15% of these patients had developed a stroke—an incidence significantly greater than that associated with lesser lesions. At 5 years, the cumulative stroke risk was 21%, or approximately 4% per year. Patients in whom either no disease or 1–49% stenosis was found at the initial examination did not, however, have a benign prognosis. Although the risk of stroke was well under 5% at 2 years, by the fifth year 9% of those who initially had no detectable disease and 14% of those with 1–49% stenosis had experienced a stroke. It is interesting that the stroke risk associated with 1–49% stenosis began to climb during the third year, while that associated with "no disease" did not become appreciable until the fourth year (Fig. 1). Similar findings were reported by Cullen and her associates.[39] Javid et al.[40] noted that 55% of carotid lesions with diameter reductions < 60% progressed during an average period of 3 years; Hennerici et al.[41] reported an 85% progression rate; and Roederer and her associates[11,37] estimated a mean annual progression rate of 8% from <50% to >50% stenosis. Moreover, she documented a very close relationship between disease progression and stroke. Based on Roederer's figures, 40% of the patients in our study with <50% stenosis would have had ≥50% stenosis at the end of 5 years and would, therefore, be expected to have an increased risk of stroke. Unfortunately, few patients in our study were reexamined during the 5-year period.

Strokes, however, may occur in patients with minimal or no disease even without disease progression. In the series reported by Thiele et al., 17% of strokes were associated with <50% stenosis of the ipsilateral carotid artery and 10% occurred in the absence of angiographically detectable disease.[42] But based on autopsy studies, almost all men and women between 65 and 69 years of age have fibrous plaques at the carotid bifurcation, and approximately 20% of women and 40% of men have complicated plaques.[43] Since bifurcation disease is so prevalent, the incidence of stroke associated with minimal disease must be quite low.

Other explanations for the occurrence of strokes in our patients with minimal or no disease are possible. Pulsed Doppler imaging is sensitive only to stenosis; ulcers in arteries with little or no stenosis will not be detected. The annual risk of stroke associated with type A and B ulcers is reported to range from 1 to 4.5%.[44,45] On this basis, some of the patients coded as 0% disease may have had

ulcerated plaques that could have produced later symptoms. Moreover, we did not identify a strong association of stroke with the carotid artery having the greater degree of stenosis (Table 5). Strokes were, however, more frequent in patients with bilateral lesions. Although most of the strokes were felt to represent thromboembolic events related to carotid disease, in this retrospective study we could not eliminate other causes, such as intracranial hemorrhage, lacunar strokes, posterior circulation events, or cardiac emboli.

Lastly, due to the less than perfect accuracy of pulsed Doppler imaging, the true prevalence of disease in the three stenosis categories will differ from that predicted. Based on the known sensitivity and specificity of the test at the time the patients were admitted to the study, the "true" prevalence of disease is estimated to be 113 patients with no stenosis, 124 with 1–49% stenosis, and 57 patients with ≥50% stenosis. From this data, one can estimate that the "true" incidence of strokes during the 5-year period would be: no disease, 2.7%; 1–49% lesions, 16.1%; and ≥50% lesions, 22.8% (see Appendix). Thus the "true" incidence would be less than the apparent incidence in those patients with no disease and would be greater in the disease categories.

Information on TIA's was considered less reliable than that on stroke. Only one of the 36 strokes in this series was preceeded by a TIA, a finding at variance with other reviews.

Combination of Risk Factors

Hypertensive patients who are also ≥70 years old represent a subgroup of patients with a high risk of strokes, TIAs, and fatal cardiac events (Table 7). Within this hypertensive subgroup, internal carotid stenosis ≥ 50% increases the risk of neurologic deficits and total vascular events, but the differences are not statistically significant. At the other end of the spectrum, patients with no hypertension who are under the age of 70 have a low incidence of strokes, regardless of degree of stenosis. In between, patients with hypertension under the age of 70 and those over 70 without high blood pressure have comparable stroke rates, which are only slightly higher in patients with hemodynamically significant lesions.

Both Javid and Moll have shown that hypertension accelerates the progression of disease.[40,46] Hypertension may also play a role in intraplaque hemorrhage, which appears to correlate well with the development of symptoms.[47–49] Through these mechanisms, hypertension, acting over a 5-year period, may have minimized the differences in stroke incidence between the two stenosis categories. It is possible, therefore, that the use of B-mode imaging, which can identify plaque hemorrhage, may provide better prognostic information than those tests that merely reveal the degree of stenosis.[49,50]

Survival is more clearly predictable on the basis of carotid stenosis (Fig. 4 and Table 7). Seven (54%) of fatal strokes and 14 (48%) of cardiac deaths recorded in the whole group were in the ≥50% category, resulting in a cardiovascular fatality rate of 25% in this group *versus* 10% in the patients with <50% disease ($p < 0.005$). There was no difference in the nonvascular related deaths according to degree of stenosis (7%). The combination of age > 70, hypertension, and ≥50% disease was associated with a cardiovascular mortality of 41%.

Surgical Study

Asymptomatic and nonhemispheric patients in the surgical and nonsurgical groups were not randomized, but there were no significant differences in the incidence of hypertension, previous myocardial infarction, carotid bruits, diabetes, or sex distribution. Since carotid endarterectomy is usually performed only on patients with hemodynamically significant lesions, the study was restricted to those patients with ≥50% stenoses. Because the surgical group was slightly younger than the nonsurgical group, the younger and older patients were considered separately (Fig. 6).

A significant difference in stroke rate was noted after the first year of follow-up with a 13% difference in favor of surgery becoming apparent by the fifth year. The 8% cumulative stroke rate in the surgically treated patients is disturbing, since obviously not all strokes were prevented during follow-up, and a third of the deficits occurred perioperatively. These results, however, are comparable to those from other series.[6,13,14] Overall, two-thirds of the late strokes occurred on the side of the operated vessel.

The deleterious effects of both old age and hypertension upon long-term incidence of stroke in nonsurgical subjects appear to be significantly mitigated by carotid endarterectomy (Figs. 6 and 7). Conversely, surgery appears to confer little benefit in the younger group and in normotensive patients. Surgical patients over 70 years old have a stroke risk at 5 years (8%) identical to that of surgical patients under 70 years old. Likewise, while the stroke rate in the surgically treated hypertensive patients is higher at 5 years than it is in surgically treated normotensive subjects, the difference is not statistically significant.

No significant difference in survival rates was found in surgical subjects compared to their matched population (Fig. 8). The difference at 5 years approached significance, possibly due to a sharp fall-off in the numbers of patients followed at this interval. On the other hand, members of the nonsurgical group, who were slightly older, fared considerably worse. Survival rates were significantly lower

than their matched population rates at all stages of follow-up and were also significantly worse than that of the surgical patients at the second, third, and fourth intervals ($p < 0.05$).

The survival of patients following carotid endarterectomy is comparable to the results published by Bernstein et al.,[14] Moore et al.,[13] and Thompson et al.[6] All three reports describe a 70% 5-year survival for asymptomatic bruit patients at 5 years after surgery. Unlike our study, however, the survival rate in Moore's study was significantly lower than that of an age-matched male population.

The fact that the present series describes a restoration of normal life expectancy in patients treated by carotid endarterectomy is interesting and may reflect the fact that seven of the strokes in the nonsurgical patients with ≥ 50% disease were fatal and might have been prevented by endarterectomy. Only one (6%) of the late surgical deaths was stroke related. The frequency of cardiac-related deaths was similar in both groups. Forty-four per cent of the surgical group died from myocardial infarction despite the fact that 10 patients had undergone myocardial revascularization procedures immediately following their carotid endarterectomy. The high incidence of fatal heart disease in patients with significant carotid stenosis has been well documented in reports from the Cleveland Clinic[51] and Tufts University.[52]

Conclusion

The incidence of stroke in patients with carotid arterial disease who are either asymptomatic or have vague nonhemispheric symptoms is strongly influenced by age and hypertension. Although noninvasive detection of hemodynamically significant stenosis initially defines a subset who are at greater risk for stroke, the risk associated with less severe stenosis increases substantially with time. Elderly, hypertensive patients with ≥50% stenosis have a very high incidence of stroke, TIA, and fatal cardiac events over a 5-year period. This group appears to benefit most from prophylatic carotid endarterectomy. Conversely, young patients without hypertension but with isolated significant carotid stenosis do not appear to gain much by carotid endarterectomy in terms of stroke-free survival. This subgroup might best be managed nonoperatively with regular follow-up to examine for disease progression.

Acknowledgments

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Appendix

The "true" prevalence (p) of disease in a population can be estimated from the apparent prevalence ($\hat{p}$), provided the sensitivity (x) and specificity (y) are known of the test used to determine the apparent prevalence: $p = (\hat{p} + y - 1)/(x + y - 1)$.

The "true" incidence of an event can be calculated by assuming that the frequencies of the event in the true negative and false positive categories are equal and that the frequencies of the event in the true positive and false negative categories are also equal. Authors will supply complete formula on request.

Discussion

DR. JESSE E. THOMPSON (Dallas, Texas): The problem of management of asymptomatic carotid bruit or stenosis remains a difficult one.

Several years ago we presented our data on asymptomatic bruits to this Association and concluded that certain individuals were at increased risk for stroke, and that this risk could be reduced from 17.4% to 4.6% by prophylactic carotid endarterectomy. Our studies have continued, and we have found no reason to change our original basic concepts.

The problem was and remains how to identify those patients at increased risk so that unnecessary invasive arteriograms and operations can be avoided. Dr. Moore's nice study addresses this problem of identifying such patients by using the noninvasive technique of ultrasonic arteriography. One very important aspect and strong point of this study is the length of clinical follow-up, which is 5 years or more for the entire group. Because of the rate of progression of atherosclerotic disease, a follow-up of this length is obligatory if any significant conclusions are to be drawn. Our own follow-up studies extend over 16 years with an average of 5 years.

Dr. Moore's over-all 5-year incidence of stroke was 13%, while in the subset of patients with greater than 50% ICA stenosis it was 21%. Our own incidence was 17.4%, and our more recent data have shown a 22% long-term stroke incidence.

In addition to the degree of stenosis, Dr. Moore has identified hypertension and age over 70 as additional risk factors. There are a number of other factors, however, that come into play, such as contralateral carotid occlusion, other impending operations, and cardiac status, all of which make the decision for prophylactic endarterectomy a difficult one.

At present, we are using both real time B-mode imaging and the OPG in addition to clinical considerations to evaluate and follow asymptomatic patients.

Management must be individualized, and I do not think that there will ever be an absolute dictum on management of asymptomatic lesions because of the variability of the course of the disease and the difficulty of applying statistics to an individual patient. But the more factors we