

PROGNOSIS AFTER TRANSIENT MONOCULAR BLINDNESS ASSOCIATED WITH CAROTID-ARTERY STENOSIS

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ABSTRACT

Background Transient monocular blindness associated with internal-carotid-artery stenosis is a risk factor for stroke. The effect of carotid endarterectomy in patients who present with transient monocular blindness has not been determined.

Methods We compared the risk of stroke among patients presenting with transient monocular blindness with the risk among patients presenting with hemispheric transient ischemic attack. The effect of endarterectomy was assessed in patients with transient monocular blindness. The analyses were based on data from the North American Symptomatic Carotid Endarterectomy Trial.

Results A total of 198 medically treated patients with transient monocular blindness had a three-year risk of ipsilateral stroke that was approximately half of that among 417 medically treated patients with hemispheric transient ischemic attack (adjusted hazard ratio, 0.53; 95 percent confidence interval, 0.30 to 0.94). Six factors were associated with a higher risk of stroke in patients with monocular blindness — an age of 75 years or more, male sex, a history of hemispheric transient ischemic attack or stroke, a history of intermittent claudication, stenosis of 80 to 94 percent of the luminal diameter, and the absence of collateral circulation. The three-year risk of stroke with medical treatment for patients with zero or one risk factor was 1.8 percent, with two risk factors 12.3 percent, and with three or more risk factors 24.2 percent ($P=0.003$). The three-year absolute reduction in the risk of stroke associated with endarterectomy was -2.2 percent (i.e., a 2.2 percent increase in risk) among patients with zero or one risk factor, 4.9 percent among those with two risk factors, and 14.3 percent among those with three or more risk factors ($P=0.23$ by a test for interaction).

Conclusions Among patients with internal-carotid-artery stenosis, the prognosis was better for those presenting with transient monocular blindness than for those presenting with hemispheric transient ischemic attack. Among patients with transient monocular blindness, carotid endarterectomy may be beneficial when other risk factors for stroke are also present. (N Engl J Med 2001;345:1084-90.)

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TRANSIENT monocular blindness, also known as amaurosis fugax, accounts for approximately 25 percent of transient ischemic attacks involving the anterior cerebral circulation, and approximately 50,000 new cases occur annually in the United States.¹ It is a common phenomenon among patients who consult primary care physicians, internists, ophthalmologists, neurologists, and vascular surgeons.² Transient monocular blindness, when caused by ischemia of the retina, is considered to be evidence of an attack in the vascular territory of the internal carotid artery and a risk factor for ischemic stroke.^{3,4} Among patients with transient monocular blindness, the risk factors for ischemic stroke, the risk of ischemic stroke, and its natural history are different from those among patients with transient ischemic attacks involving the cerebral hemisphere.⁵⁻¹⁴

Two large clinical trials reported that endarterectomy is effective in reducing the risk of stroke in patients with symptomatic internal-carotid-artery stenosis.^{15,16} The effect of endarterectomy in patients with only transient monocular blindness is unclear, since both trials reported their results in aggregate form by combining patients who presented with transient monocular blindness with patients who presented with hemispheric transient ischemic attacks or nondisabling stroke.

We undertook a study to compare the risk of stroke among patients presenting with transient monocular blindness with the risk among those presenting with hemispheric transient ischemic attack and to assess the effectiveness of carotid endarterectomy in patients with transient monocular blindness. The present study was a predefined research project of the North American Symptomatic Carotid Endarterectomy Trial.

METHODS

Eligibility and Randomization

Patients were enrolled in the North American Symptomatic Carotid Endarterectomy Trial if they had had a transient ischemic attack or nondisabling ischemic stroke associated with carotid-artery

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stenosis within the previous 180 days. Between December 1987 and December 1996, 2885 patients were randomly assigned to receive optimal medical therapy or optimal medical therapy plus endarterectomy and were followed until the end of December 1997. Patients were not eligible if they had a probable cardiac source of embolism or a serious disease likely to cause death within five years. All patients underwent a detailed evaluation at base line, including electrocardiography, chest radiography, imaging of the brain, and conventional carotid angiography. Follow-up consisted of clinical examinations every four months. The protocol was approved by the appropriate institutional review boards, and all patients gave written informed consent.

Clinical Analysis

Clinical details of the episodes of transient monocular blindness and the hemispheric transient ischemic attacks, including their duration and number, were collected as part of the trial protocol. Transient monocular blindness was defined as a partial or complete visual-field loss in one eye that was of ischemic origin and lasted less than 24 hours with complete recovery. A hemispheric transient ischemic attack was defined as a transient, focal cerebral dysfunction of ischemic origin lasting less than 24 hours. The ischemic event that had occurred most recently before randomization was considered the qualifying (presenting) event for the purposes of the trial.

Computed tomographic scans of the brain were evaluated for the presence of infarcts and to rule out other causes of hemispheric symptoms. The degree of internal-carotid-artery stenosis was calculated from the angiogram with the use of strict criteria.^{17,18} Near-occlusion of the carotid artery was defined by the presence of severe stenosis that was associated with one or more of the following: a narrowed distal internal carotid artery beyond the diseased portion (considered narrowed if it was only slightly wider than, the same width as, or narrower than the external carotid artery or if it was narrower than the contralateral internal carotid artery); evidence of intracranial collateral supply (a visible collateral flow or evidence of the dilution of intracranial vessels by unopacified blood from collateral sources); or slower progress of contrast material from the internal carotid artery into the cranium than into the distal branches of the external carotid artery.

All strokes were evaluated by the outcomes committee to establish the type, cause, territory, and level of disability. Strokes were considered to be disabling if they received a modified Rankin score of 3 or more (on a scale on which 0 indicates normal and independent functioning and 6 indicates death)¹⁹ 90 days after the onset of symptoms. Further details of the trial methods have been published previously.²⁰

Statistical Analysis

The base-line characteristics of the patients were compared with the use of the chi-square test. The three-year risk of stroke ipsilateral to the symptomatic internal-carotid-artery stenosis was analyzed according to the intention-to-treat principle. The estimates of risk were derived from Kaplan–Meier event-free survival curves and were evaluated for statistical significance by means of a log-rank test. The Kaplan–Meier analyses included all deaths and any strokes (regardless of location) that occurred during the 30-day perioperative period among patients who underwent endarterectomy and during the 32 days after randomization among the patients who were treated medically. A Cox proportional-hazards regression model was used to adjust the analyses of risk for the base-line characteristics of the patients and to test for interactions.

To identify base-line characteristics that could increase the risk of an ipsilateral stroke and influence the effectiveness of endarterectomy, we analyzed the risk factors among the medically treated patients with transient monocular blindness and stenosis of at least 50 percent of the diameter of the internal carotid artery. Patients with stenosis of less than 50 percent of the arterial diameter were not included in the analysis of risk factors because they do not benefit from endarterectomy.¹⁵ Univariate Kaplan–Meier analyses were used to identify important risk factors among the base-line charac-

teristics we analyzed, and patients were then grouped into three categories of risk — those with zero or one risk factor (low risk), those with two risk factors (moderate risk), and those with three or more risk factors (high risk). The three-year risk of ipsilateral stroke among the medically treated patients with transient monocular blindness, as determined by the Kaplan–Meier analysis, was compared with the three-year risk among the surgically treated patients with transient monocular blindness in an analysis stratified according to the category of risk. We defined a variable with scores of 0, 1, and 2, corresponding to the three categories of risk, and performed a test of interaction (with 1 df) between the treatment-group assignment and the number of risk factors using a Cox regression model.

RESULTS

A total of 2885 patients were enrolled in the trial. Transient ischemic attack was the qualifying event in 1583 patients (54.9 percent), and the remaining 1302 patients had a nondisabling stroke. A total of 496, or approximately one third, of the qualifying transient ischemic attacks were episodes of transient monocular blindness, and 397 of the patients with transient monocular blindness (80.0 percent) had no history of hemispheric transient ischemic attack or stroke in the vascular territory ipsilateral to the transient monocular blindness.

In the first analysis, we compared two clinically homogeneous groups. One group consisted of the 397 patients who had only ever had transient monocular blindness, and the other consisted of 829 patients who had only ever had hemispheric transient ischemic attack. Patients who had had a previous ipsilateral stroke or who had ever had a transient ischemic attack different from the qualifying event were excluded from the analysis.

The base-line characteristics of the patients are shown in Table 1. The patients with transient monocular blindness were more likely to have smoked in the year before they entered the study, were roughly twice as likely to have stenosis of at least 70 percent of the diameter of the internal carotid artery or near-occlusion of the carotid artery, and were more than three times as likely to have evidence of collateral circulation. The patients with hemispheric transient ischemic attack tended to be older and were more likely to have a history of hypertension and diabetes mellitus and to have evidence of brain infarcts on imaging. Among those with cerebral infarcts on brain imaging, the patients with hemispheric transient ischemic attack were twice as likely as those with transient monocular blindness to have infarcts of 1 cm or larger. All other vascular risk factors, including the presence of irregular or ulcerated plaque in the ipsilateral internal carotid artery and the presence of ipsilateral intracranial artery disease, were evenly distributed between the two groups.

The medically treated patients with transient monocular blindness had a three-year risk of ipsilateral stroke that was approximately half of that among the medically treated patients with hemispheric transient ischemic attack (Fig. 1). The adjusted hazard ratio, after all base-line characteristics had been controlled

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	TRANSIENT MONOCULAR BLINDNESS (N=397)	HEMISPHERIC TRANSIENT ISCHEMIC ATTACK (N=829)	P VALUE
	%		
Assigned to carotid endarterectomy	50.1	49.7	0.89
Age			<0.001
<65 yr	46.4	39.6	
65–74 yr	46.3	46.2	
≥75 yr	7.3	14.2	
Male sex	66.0	68.0	0.48
Medical history			
Hypertension	55.4	60.6	0.09
Diabetes mellitus	14.4	20.1	0.01
Myocardial infarction or angina	40.3	41.3	0.75
Intermittent claudication	15.9	17.0	0.65
Hyperlipidemia	36.3	35.9	0.91
Smoking in the past year	53.2	43.3	<0.001
Degree of stenosis of the internal carotid artery			<0.001
<50%	28.5	50.3	
50–69%	30.5	29.8	
70–94%	31.7	16.2	
Near-occlusion	9.3	3.7	
Irregular or ulcerated plaque in the ipsilateral internal carotid artery	52.9	53.3	0.89
Appropriate infarct on brain imaging*	19.9	30.8	<0.001
Ipsilateral intracranial artery disease	32.5	30.8	0.54
Collateral circulation†	24.2	6.9	<0.001

*Infarcts were deemed appropriate if they were in the anterior circulation and ipsilateral to the internal carotid artery in which the presenting episode occurred.

†Collateral circulation was identified on angiography by the filling of the anterior communicating, posterior communicating, or ophthalmic artery with contrast material after a carotid or vertebral injection.

for in a Cox regression analysis, was 0.53 (95 percent confidence interval, 0.30 to 0.94). Higher degrees of internal-carotid-artery stenosis (50 percent or more of the luminal diameter as compared with less than 50 percent) doubled the risk in both groups (adjusted hazard ratio, 2.29; 95 percent confidence interval, 1.37 to 3.83).

Thirty-one percent of the strokes that occurred in the medically treated patients who had presented with transient monocular blindness were retinal, and the remaining 69 percent were hemispheric; of the hemispheric strokes, 18 percent were disabling or fatal (Fig. 2). Among the medically treated patients who had presented with a hemispheric transient ischemic attack, most of the strokes that occurred (94 percent) were hemispheric, and 28 percent of these were disabling or fatal.

The three-year risk of ipsilateral stroke was similar among the surgically treated patients with transient blindness and among those with hemispheric attack ($P=0.35$) (Fig. 1). The rate of stroke or death within 30 days of surgery among surgically treated patients

with transient monocular blindness was 3.6 percent, as compared with 7.4 percent among surgically treated patients with hemispheric transient ischemic attack ($P=0.06$). After all base-line characteristics had been controlled for, surgically treated patients with transient monocular blindness were still half as likely as surgically treated patients with hemispheric attack to have a stroke or die within 30 days of surgery (adjusted hazard ratio, 0.51; 95 percent confidence interval, 0.21 to 1.22).

Among the 397 patients who had only ever had transient monocular blindness (including patients in both the medically and surgically treated groups), the median number of episodes of transient monocular blindness that occurred within the 180 days before randomization was 3 (interquartile range, 1 to 7; 5 percent of these patients had 45 or more episodes within that period). The median duration of the qualifying episode of transient monocular blindness was 4 minutes (interquartile range, 1 to 10 minutes; 5 percent had had episodes lasting 60 minutes or more). There were no significant differences according to the degree of stenosis in the number or duration of the episodes of transient monocular blindness. In the 198 medically treated patients who had presented with transient monocular blindness, the three-year risk of ipsilateral stroke was similar regardless of whether the patient had had a single episode of transient monocular blindness or two or more such episodes (risks of 10.4 percent and 8.2 percent, respectively; $P=0.44$). Similarly, the duration of the episode of transient monocular blindness — less than five minutes or five or more minutes — did not influence the risk of ipsilateral stroke (which was 8.6 percent and 9.3 percent, respectively; $P=0.70$).

In a subgroup analysis, we examined the relation between the higher prevalence of angiographically visualized collateral vessels in patients with transient monocular blindness and the risk of ipsilateral stroke. Because collateral vessels are seldom present in patients with stenosis of less than 70 percent of the diameter of the internal carotid artery,²¹ the analysis was restricted to medically treated patients with stenosis of 70 to 94 percent of the diameter or near-occlusion of the internal carotid artery (both patients with transient monocular blindness and patients with hemispheric transient ischemic attacks). The three-year risk of ipsilateral stroke among the 35 patients with transient monocular blindness and evidence of collaterals was lower (2.9 percent) than the risk among the 30 patients with hemispheric transient ischemic attack and evidence of collaterals (16.7 percent; $P=0.06$). The three-year risk of ipsilateral stroke among the 44 patients with transient monocular blindness and no collaterals was 16.0 percent, as compared with 34.4 percent among the 69 patients with hemispheric transient ischemic attack and no collaterals ($P=0.03$). A P value of 0.42 was derived from a Cox regression model for the test of the inter-

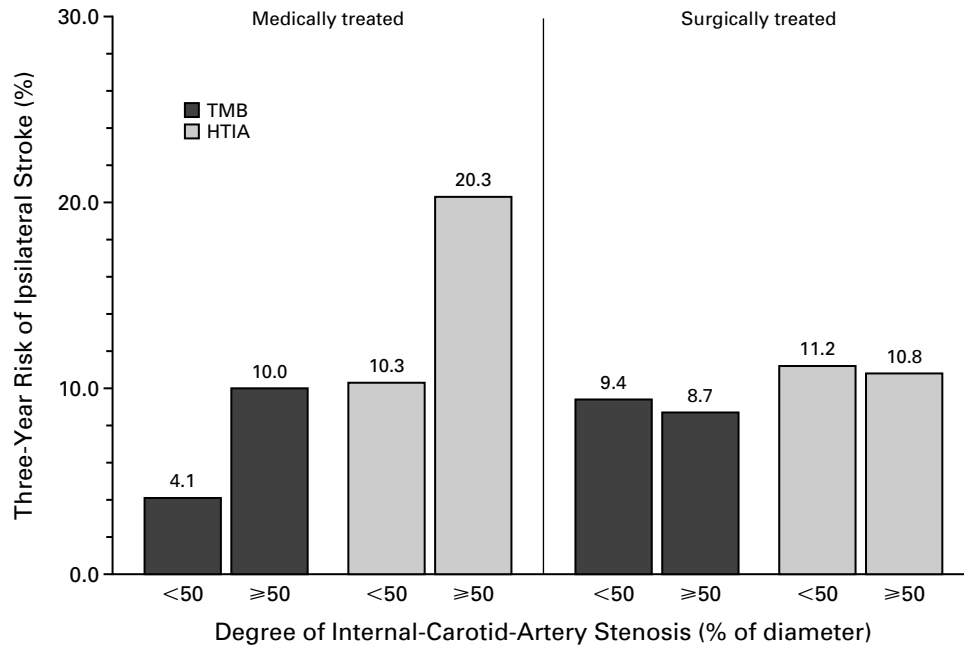


Figure 1. Kaplan–Meier Analysis of the Three-Year Risk of Ipsilateral Stroke among Patients with Transient Monocular Blindness (TMB) and Hemispheric Transient Ischemic Attack (HTIA), According to Treatment Group and Degree of Internal-Carotid-Artery Stenosis.

The risk estimates (as percentages) are shown above the bars. The numbers of patients represented by the bars are, from left to right, 56, 142, 202, 215, 57, 142, 215, and 197.

action between the type of transient ischemic attack and the presence or absence of collaterals.

To identify the risk factors that were predictive of ipsilateral stroke in patients with transient monocular blindness, we performed an analysis that included all patients with stenosis of at least 50 percent of the diameter of the internal carotid artery, including those with a history of stroke or hemispheric transient ischemic attack. With the use of univariate Kaplan–Meier analyses, all the variables listed in Table 1 were examined. Six of these variables were strongly associated with the occurrence of stroke in medically treated patients, each more than doubling the risk (Table 2). Patients with stenosis of 70 to 79 percent of the diameter of the internal carotid artery were grouped together with those who had stenosis of 50 to 69 percent of the diameter or near-occlusion of the artery, since the three-year risk of ipsilateral stroke was similar in these three subgroups (10.1 percent, 9.8 percent, and 9.1 percent, respectively). According to the Kaplan–Meier analysis, the risk of ipsilateral stroke among medically treated patients classified as at low risk, moderate risk, and high risk was 1.8 percent, 12.3 percent, and 24.2 percent, respectively ($P=0.003$ for the comparison of all three groups) (Table 3). The absolute

reduction in the three-year risk of stroke associated with endarterectomy was -2.2 percent in the low-risk group (indicating a 2.2 percent increase in risk), 4.9 percent in the moderate-risk group, and 14.3 percent in the high-risk group ($P=0.23$ for the test of interaction between the treatment group and the category of risk) (Table 3).

DISCUSSION

Attacks of transient monocular blindness represent a common manifestation of internal-carotid-artery stenosis and are warnings of impending stroke. They were the presenting symptoms in 20 percent of the patients who underwent randomization in three large trials of carotid endarterectomy.^{15,16,22}

The results of the present study were based on data from a large sample of patients with transient monocular blindness associated with carotid-artery stenosis, consisting of a total of 1057 person-years of prospective follow-up. The three-year risk of ipsilateral stroke was lower and the strokes less disabling among patients who presented with transient monocular blindness than among those who presented with hemispheric attacks. The perioperative rate of stroke and death was also lower among patients with monocular blindness.

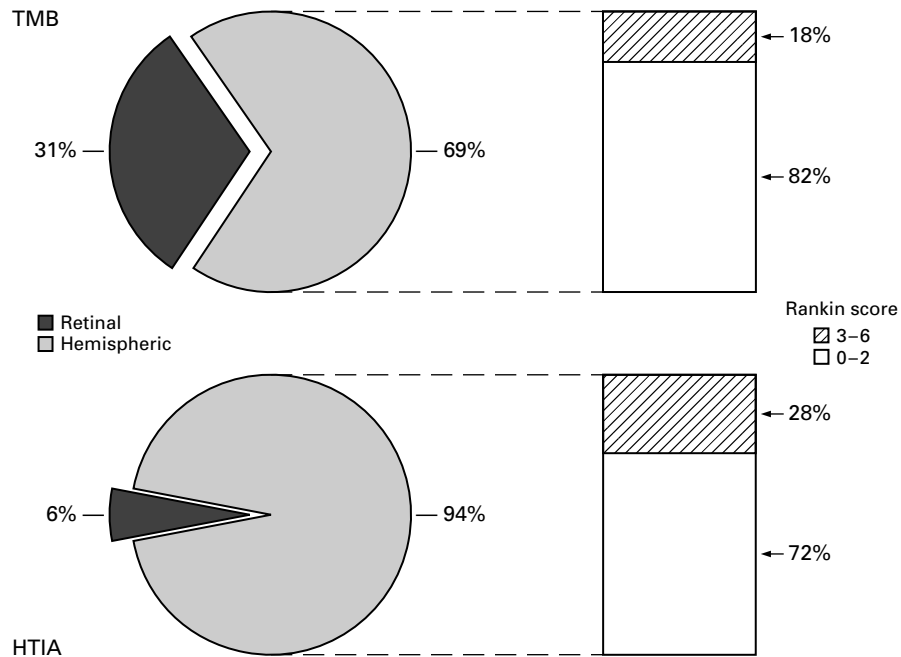


Figure 2. Distribution of the Territory of Strokes Occurring during Follow-up in Medically Treated Patients Presenting with Transient Monocular Blindness (TMB) and in Those Presenting with Hemispheric Transient Ischemic Attack (HTIA) and the Level of Disability Caused by Hemispheric Strokes.

Among patients with transient monocular blindness there were 16 strokes, and among the patients with hemispheric transient ischemic attack there were 62 strokes. A Rankin score of 3 or higher indicates a disabling or fatal stroke.

TABLE 2. UNIVARIATE PREDICTORS OF THE THREE-YEAR RISK OF IPSILATERAL STROKE AMONG THE 174 MEDICALLY TREATED PATIENTS WITH TRANSIENT MONOCULAR BLINDNESS AND STENOSIS OF AT LEAST 50 PERCENT OF THE DIAMETER OF THE INTERNAL CAROTID ARTERY.*

RISK FACTOR	RISK WITH FACTOR PRESENT	RISK WITH FACTOR ABSENT	RELATIVE RISK (95% CI)
	%		
Age \geq 75 yr	32.5	11.2	2.9 (0.9 to 10.6)
Male sex	15.3	6.8	2.2 (0.8 to 7.0)
History of hemispheric transient ischemic attack or stroke	22.7	10.0	2.3 (1.0 to 6.1)
History of intermittent claudication	22.5	10.4	2.2 (0.8 to 5.6)
Ipsilateral stenosis of 80 to 94% of internal carotid artery†	21.1	9.8	2.2 (0.9 to 5.5)
No collaterals on angiography	14.8	6.2	2.4 (0.7 to 8.3)

*CI denotes confidence interval.

†The absence of this risk factor is defined for this analysis as stenosis of 50 to 79 percent or near-occlusion of the internal carotid artery.

The frequency and duration of monocular ischemic attacks bore no relation to the risk of stroke.

Despite their having, on average, a higher degree of stenosis (Table 1), patients with transient monocular blindness had, paradoxically, a lower risk of hemispheric stroke, and the strokes that did occur were less disabling. One possible explanation is that there was a higher prevalence of collateral circulation in these patients, which has been shown to be associated with a better prognosis.²¹ Good collateral circulation was identified in almost one quarter of the patients with transient monocular blindness but in less than 7 percent of the patients with hemispheric transient ischemic attack. Another explanation for the difference in prognosis between patients with transient monocular blindness and those with hemispheric transient ischemic attack is that each small group of cells in the retina is more sensitive than a group of cells of similar size in the brain. This means that a small platelet-fibrin embolus will more readily become clinically manifest in the retina than it would in the brain and that transient monocular blindness may frequently result from small emboli that would be less likely to cause brain infarction. The patients with transient monocular blindness were more likely to have retinal strokes than were those who presented with hemispheric transient ischemic

TABLE 3. THREE-YEAR RISK OF IPSILATERAL STROKE AND THE NUMBER NEEDED TO TREAT ACCORDING TO AN ANALYSIS OF 360 PATIENTS WITH TRANSIENT MONOCULAR BLINDNESS AND STENOSIS OF AT LEAST 50 PERCENT OF THE DIAMETER OF THE INTERNAL CAROTID ARTERY, STRATIFIED ACCORDING TO THE CATEGORY OF RISK.*

VARIABLE	NO. OF PATIENTS		THREE-YR RISK OF IPSILATERAL STROKE		ABSOLUTE REDUCTION IN RISK (95% CI)	NO. NEEDED TO TREAT AT THREE YEARS†
	MEDICAL	SURGICAL	MEDICAL	SURGICAL		
	percent					
All patients with transient monocular blindness	174	186	12.3	7.2	5.1 (-0.4 to 10.6)	20
Category of risk						
Low (0 or 1 risk factor)	56	51	1.8	4.0	-2.2 (-8.7 to 4.3)	NA
Moderate (2 risk factors)	67	83	12.3	7.4	4.9 (-4.9 to 14.7)	20
High (≥3 risk factors)	51	52	24.2	9.9	14.3 (-0.2 to 28.8)	7

*The six risk factors were an age of at least 75 years, male sex, a history of hemispheric transient ischemic attack or stroke, a history of intermittent claudication, stenosis of 80 to 94 percent of the internal carotid artery, and the absence of collateral circulation on angiography. P=0.003 for the comparison of the risk estimates among the medically treated patients in the categories of risk; P=0.50 for the comparable comparison among the surgically treated patients. P=0.23 by a test of interaction between the treatment group and the category of risk, with 1 df. CI denotes confidence interval, and NA not applicable.

†The number needed to treat is the number of patients who must undergo carotid endarterectomy to prevent one additional stroke over a three-year period.

attacks, probably as a consequence of the phenomenon of intraluminal streaming.^{23,24}

Approximately 30 percent of the patients with transient monocular blindness associated with stenosis of at least 50 percent of the diameter of the internal carotid artery were in the high-risk group (had three or more risk factors). Nearly half of these patients had stenosis of 80 to 94 percent of the diameter of the internal carotid artery. In the high-risk group, only seven patients would have to undergo endarterectomy in order to prevent one additional stroke over a three-year period. In the moderate-risk group (with two risk factors), which included approximately 40 percent of the patients, there was a moderate three-year risk of ipsilateral stroke in medically treated patients, and endarterectomy appeared to be less effective (number needed to treat, 20). The remaining 30 percent of the patients had zero or one risk factor; endarterectomy was ineffective in these patients. Although the test of interaction did not find a statistically significant association, there was a clinically important relation between the number of risk factors and the effectiveness of endarterectomy in patients with transient monocular blindness.

We conclude that, as compared with hemispheric transient ischemic attack, transient monocular blindness associated with carotid-artery stenosis carries a better prognosis with respect to subsequent stroke. Among patients with monocular blindness, carotid endarterectomy may improve the outcome in those with other risk factors for stroke.

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