

The appropriate use of carotid endarterectomy

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Abstract

FOR THE FIRST 30 YEARS AFTER CAROTID ENDARTERECTOMY WAS FIRST DEVELOPED, anecdotal evidence was used to identify patients with internal carotid artery disease for whom this procedure would be appropriate. More recently, the appropriateness of carotid endarterectomy for symptomatic patients and asymptomatic subjects has emerged from 7 randomized trials. Risk of stroke and benefit from the procedure are greatest for symptomatic patients with at least 70% stenosis of the internal carotid artery. Within this group, carotid endarterectomy is most beneficial for the following patients: otherwise healthy elderly patients, those with hemispheric transient ischemic attack, those with tandem extracranial and intracranial lesions and those without evidence of collateral vessels. Risk of perioperative stroke and death is higher in the following groups, although they still benefit: patients with wide-spread leukoaraiosis, those with occlusion of the contralateral internal carotid artery and those with intraluminal thrombus. Patients with 50% to 69% stenosis experience lesser benefit, and some other groups may even be harmed by carotid endarterectomy, including women and patients with transient monocular blindness only. The procedure is indicated for patients presenting with lacunar stroke and for those with a nearly occluded internal carotid artery, but the benefit is muted. Patients with less than 50% stenosis do not benefit. In the largest randomized trial of asymptomatic subjects, the perioperative risk of stroke and death was very low (1.5%), but the results indicated that a prohibitively high number of subjects (83) must be treated to prevent one stroke in 2 years. The subsequent literature reported higher perioperative risks (2.8% to 5.6%). In asymptomatic individuals nearly half of the strokes that occur may be due to heart and small-vessel disease. These limitations counter any potential benefit. Another trial is in progress and may identify subgroups of asymptomatic subjects who would benefit. Meanwhile, most individuals without symptoms fare better with medical care.

The prevention of ischemic stroke by surgical means goes back half a century. After initial endorsement of carotid endarterectomy, confusion arose as to the appropriate selection of patients and the allowable risk from the procedure. In the past 2 decades large randomized trials have been used to evaluate the benefit of the procedure for patients with symptomatic and asymptomatic disease of the internal carotid artery. Sufficient time has now passed since the publication of these trials to analyze their impact on practice and to make recommendations about the application of carotid endarterectomy. There is strong evidence of benefit in some symptomatic patients, whereas other patients will not benefit and may even face harm. There is weak statistical and weaker clinical evidence that asymptomatic subjects will survive longer without experiencing stroke if they undergo endarterectomy than if they do not. The evidence supporting carotid angioplasty and stenting remains anecdotal and conflicting.

The purpose of the present report is to provide a clinical roadmap to which symptomatic patients and asymptomatic subjects with carotid stenosis are candidates for endarterectomy. The risks and complications of endarterectomy are also reported. The outlook and benefit for symptomatic patients and asymptomatic subjects are so different that the evidence supporting appropriate use of endarterectomy in these 2 groups will be presented separately.

Review

Synthèse

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Symptomatic carotid artery disease

The trials and primary results

An early randomized trial to evaluate carotid endarterectomy failed because of inappropriate patient selection, excessive numbers of crossovers and an unacceptably high perioperative complication rate.¹ Two large and one small trial were launched in the 1980s, and their results were published in the 1990s.²⁻⁵ The present report uses information for 2885 patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and 3024 patients in the European Carotid Surgery Trial (ECST). Information for 2469 individuals (1255 symptomatic and 1214 asymptomatic) in the ASA and Carotid Endarterectomy (ACE) trial⁶ is also used. The ACE trial provides data about perioperative complications associated with endarterectomy.

In the NASCET and the ECST, patients were randomly assigned to receive best medical care or best medical care plus carotid endarterectomy. Severe (at least 70%) stenosis was present in 659 and 501 of the NASCET and ECST patients respectively. The remaining patients had moderate (50% to 69%) or mild (less than 50%) stenosis. A focal retinal or hemispheric transient ischemic attack or nondisabling stroke (modified Rankin score less than 3) occurring before 180 days of randomization was required for entry. The modified Rankin scale is a global functional health index with an emphasis on physical disability.⁷ Excluded were patients with potential cardioembolic abnormalities, organ failure or cancer likely to cause death within 5 years. All subsequent strokes and deaths were recorded and submitted to blind external adjudication, verifying the type, severity, and cause of stroke and the cause of death.

The results were similar in the NASCET and the ECST. Kaplan–Meier stroke-free survival curves from the NASCET depict the contrast between the 2 arms by degree of stenosis (Fig. 1). For stroke of any severity, and for disabling (Rankin score 3 or more) or fatal stroke, there was benefit for patients with stenosis of 70% or more, without overlapping confidence intervals. Reduced benefit, with overlapping confidence intervals, was observed for patients with stenosis of 50% to 69%. No benefit was apparent for patients with less than 50% stenosis.

Two conditions must be met to ensure that carotid endarterectomy prevents stroke. First, surgical skill with a low complication rate is absolutely essential. The NASCET patients with moderate stenosis (50% to 69%) had a lower medical risk, but their perioperative risk was slightly higher than that of patients with severe stenosis (70% or greater) (6.9% v. 5.8%); therefore, the number needed to treat (NNT) to prevent one stroke was 19 for patients with moderate stenosis and 6 for those with severe stenosis (Table 1).^{8,9} In contrast, the ECST perioperative risk for patients with moderate stenosis was 9.8%, and there was negative benefit (detriment), without a calculable NNT. Second, the surgical benefit must persist for several years to

justify the perioperative risk. Such durability of benefit was observed in the NASCET, as improved stroke-free survival persisted over the long term (Fig. 1).

Surgical and non-surgical complications

Surgical complications — perioperative stroke and death

The combined perioperative risk of stroke and death for the NASCET¹⁰ and the ACE trial was 6.2% (Table 2). Risk of perioperative disabling stroke or death was 2.1%. Of the 166 perioperative strokes and deaths, 107 (64.4%) occurred within 24 hours of the procedure. By the time the patient was out of bed after the surgery the subsequent risk of stroke or death was low (Fig. 1). Exclusion of patients with evidence of recent serious cardiac conditions kept perioperative myocardial infarction to a minimum.

Complications localized to the endarterectomy site

Wound hematomas and cranial nerve injuries (involving facial nerves, the superior laryngeal branch of the vagus nerve, the spinal accessory nerve or the hypoglossal nerve) were the most common complications (Table 3). They led to permanent disability or death in only a few patients.

Occlusion of the internal carotid artery occurred in 14 (1.3%) of 1060 NASCET patients who underwent an ultrasound assessment within an average of 36 days after endarterectomy. The likelihood of occlusion increased with the preoperative degree of stenosis: 0.9% with stenosis of less than 70%, 2.5% with stenosis of 70% to 94% and 5.4% with near-occlusion of the artery. Of the 14 patients in whom the artery became occluded after surgery, 3 had an ipsilateral stroke within 24 hours of the occlusion.

Medical complications during and 30 days after endarterectomy

In neither the NASCET¹¹ nor the symptomatic arm of the ACE trial did the occurrence of new angina or rhythm disorders, congestive heart failure, postoperative hypotension or hypertension requiring treatment, or respiratory disorders lead to permanent disability or death (Table 3). Subsequent blood pressure readings in the surgical patients detected no evidence that carotid endarterectomy had affected its regulation.¹² Ambulation within a few hours of the procedure was associated with avoidance of pulmonary embolism.

Use of and complications associated with conventional angiography

Patients in NASCET had to have undergone conventional angiography, and when this procedure was complicated by a disabling stroke, the patient was not eligible for entry. Among the 2885 NASCET patients, 20 (0.7%) experienced nondisabling strokes within 24 hours after an-

giography. In a systematic review of the literature, Hankey and associates¹³ found that 5 of 6 strokes complicating angiography were reported as nondisabling. Thus it can be estimated that a total of 4 disabling strokes occurred after angiography in the NASCET centres (0.1%).¹⁴

Despite advances in noninvasive imaging methods, over-reading persists,¹⁵⁻¹⁷ occurring mostly around the 50% angiographic threshold of stenosis.¹⁸ The patient then faces a 2% risk of disabling stroke from carotid endarterectomy, 20 times the risk associated with angiography (0.1%). Carotid near-occlusion was observed in 7.6% of the NASCET angiograms and is commonly misread by noninvasive methods because of reduced blood flow.¹⁹ Together,

over-reading and misreading account for approximately 15% of images. Poor agreement between conventional angiography and noninvasive modalities persists.^{15,18,20}

Patients who benefit most and least from carotid endarterectomy

From the data in these trials, the general principle emerges that patients at lowest risk of stroke are the least likely to benefit from carotid endarterectomy, whereas those at highest risk of stroke are the most likely to benefit. These findings are summarized here in the form of questions and answers.

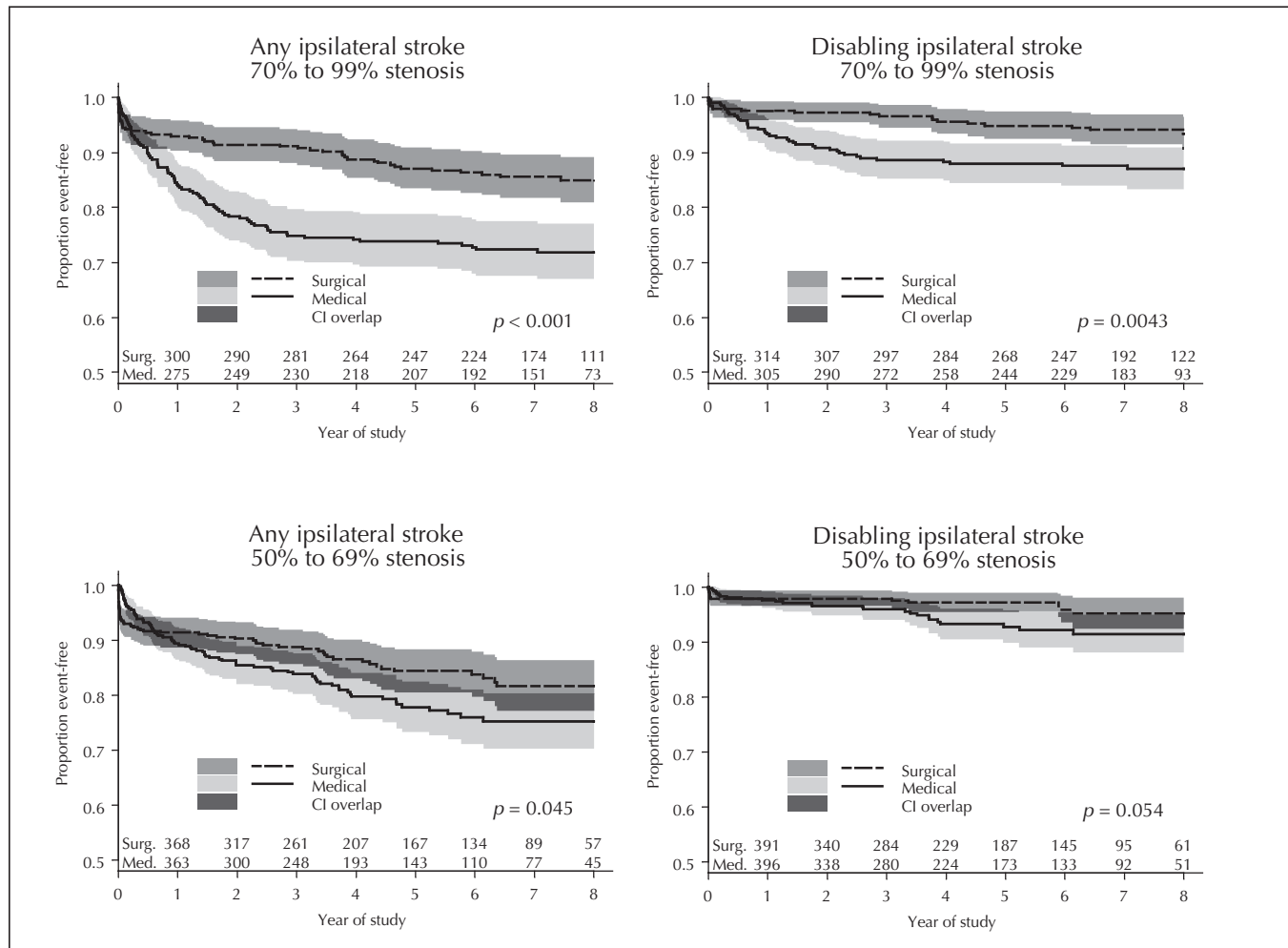


Fig. 1: Kaplan-Meier curves for event-free survival with and without carotid endarterectomy. The curves show the probability of avoiding an ipsilateral stroke of any degree of severity (left-hand panels) and a disabling or fatal ipsilateral stroke (right-hand panels) among patients with carotid stenosis of at least 70% (top panels) or 50% to 69% (bottom panels) who were randomly assigned to undergo carotid endarterectomy (surgical group) or to receive medical therapy alone (medical group). Also shown are the p values from the Mantel-Haenszel χ^2 test used to compare the survival curves, with the 95% confidence interval for each curve and the overlap between the confidence intervals indicated by bands of color. The numbers along the horizontal axis are the numbers of patients in each group who were still at risk during each year of follow-up. Reproduced with permission from Barnett HJM, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al, for the North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in symptomatic patients with moderate and severe stenosis. *N Engl J Med* 1998;339:1415-25. Copyright © 1998 Massachusetts Medical Society. All rights reserved.

Will elderly patients benefit from carotid endarterectomy?

A prejudice existed at the start of the trials that elderly patients (those at least 75 years of age) were in sufficiently poor health to warrant denying them the procedure.^{21,22} The results for 409 elderly NASCET patients showed that at all degrees of stenosis, medically treated elderly patients had the highest risk of stroke.²³ The 2-year risk of ipsilateral ischemic stroke was 36.5% for those with stenosis of at least 70% and 24.9% for those with stenosis of 50% to 69%. Because surgical risk was not higher in the elderly patients, the absolute risk reduction favouring carotid endarterectomy was 28.9% in the patients with severe stenosis (2-year NNT = 3) and 17.3% in those with moderate stenosis (2-year NNT = 6).

In conclusion, elderly patients without organ failure or serious cardiac dysfunction are ideal candidates for carotid endarterectomy.

Are women as likely to benefit from carotid endarterectomy as men?

Population studies have demonstrated that at any age women have a lower risk of stroke than men. However, women live 5 to 10 years longer than men; thus, because

the incidence of stroke increases with age, the total burden of stroke is greater in women than in men. The NASCET and the symptomatic arm of the ACE trial encompassed 1208 women and 2825 men whom all had a pre-surgery angiogram. The perioperative risk was higher for women than for men (7.6% v. 5.9%). When there were symptoms in association with 70% to 99% stenosis, the absolute reduction in risk of stroke from carotid endarterectomy at 5 years was similar: 15.1% for women and 17.3% for men. To prevent one additional stroke in 5 years requires 7 carotid endarterectomies in women and 6 in men. However, in the group with 50% to 69% stenosis, only the women with high-risk profiles benefited from the procedure. For the highest-risk profile, the absolute risk reduction at 5 years was 8.9% for women and 15.4% for men. With the lowest-risk profile, the absolute risk reduction was -2.0% for women (that is, benefit eliminated) and 7.6% for men. The 7 risk factors used in the profile were hemispheric (not retinal) index event, history of diabetes mellitus, stroke before the index event, age greater than 70 years, stroke (not transient ischemic attack) as the index event, systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 100 mm Hg, and history of myocardial infarction or evidence of myocardial infarction on electrocardiography.

Table 1: Two-year risk of ipsilateral stroke and number needed to treat (NNT) by carotid endarterectomy (symptomatic patients only)*

Degree of stenosis† and trial	No. of patients	Risk at 2 yr with medical treatment, %	Risk at 2 yr with surgical treatment, %	Absolute risk reduction, %	Relative risk reduction, %	NNT‡	Rate of perioperative stroke or death, %
70% to 99%							
NASCET	659	24.5	8.6	15.9	65	6	5.8
ECST§	501	19.9	7.0	12.9	65	8	5.6
50% to 69%							
NASCET	858	14.6	9.3	5.3	36	19	6.9
ECST	684	9.7	11.1	-1.4¶	-14	-	9.8

Note: NASCET = North American Symptomatic Carotid Endarterectomy Trial, ECST = European Carotid Surgery Trial (measurements done by NASCET method).

*Reproduced, with permission, from *BMJ*.⁶

†Patients with less than 50% stenosis are not included, as they do not benefit.

‡Number of patients that must be treated by endarterectomy to prevent one additional ipsilateral stroke in the 2-year period after the procedure, compared with medical therapy alone.

§Additional data supplied by Dr. P. Rothwell.

¶A negative risk reduction actually represents an increase in risk.

Table 2: Perioperative (30-day) outcome events in patients who underwent endarterectomy

Outcome event	Trial; % of patients			
	NASCET, symptomatic n = 1415	ACE, symptomatic n = 1255	NASCET + ACE, symptomatic n = 2670	ACE, asymptomatic n = 1214
Any stroke or death	6.5	5.9	6.2	4.4
Disabling stroke or death	2.0	2.2	2.1	2.0
Any stroke or death or MI	7.3	6.4	6.9	5.5
Nonfatal MI	0.9	0.9	0.9	1.4
Fatal MI	0.1	0.1	0.1	0.4

Note: NASCET = North American Symptomatic Carotid Endarterectomy Trial, ACE = ASA and Carotid Endarterectomy Trial, MI = myocardial infarction.

In conclusion, women with severe stenosis (at least 70%) should undergo carotid endarterectomy, but women with moderate stenosis (50% to 69%) and a low-risk profile should be treated medically.

Should patients presenting with transient monocular blindness only be recommended for carotid endarterectomy?

Transient ischemic attack was the entry criterion for 1583 (54.9%) of the patients in the NASCET.²⁴ One-third of these (496 patients) had transient monocular blindness. After medical treatment, the 3-year risk of ipsilateral stroke for patients with at least 50% stenosis and only transient monocular blindness was half that of patients with hemispheric events (Fig. 2). Univariate analyses determined that 6 risk factors in the patients with transient monocular blindness and stenosis of at least 50% more than doubled the risk of stroke: age 75 years or older, male sex, previous history of hemispheric transient ischemic attack or stroke, history of intermittent claudication, 80% to 94% stenosis and absence of collateral vessels. For patients with no risk factors or just 1 risk factor, the 3-year medical risk of ipsilateral stroke was 1.8%; for those with 2 risk factors, it was 12.3%, and for those with 3 or more risk factors, it was 24.2%. The absolute risk reduction at 3 years, in favour of surgery, was -2.2% (that is, benefit eliminated) in patients with no or only 1 risk factor, 4.9% in patients with 2 risk factors and 14.3% in patients with 3 or more risk factors. Patients with the highest degree of stenosis most commonly have several risk factors, so all of them are candidates for the surgery.

In conclusion, most patients with few risk factors who present with transient monocular blindness only are better off with medical treatment. However, patients with severe or moderate stenosis and a high-risk profile should be considered for carotid endarterectomy.

Should patients with tandem (intracranial) lesions undergo carotid endarterectomy?

Intracranial arteriosclerotic disease (IAD) has been estimated to occur in 20% to 50% of patients with extracranial carotid stenosis.²⁵⁻²⁷ At the beginning of the trials it was assumed, on the basis of anecdotal evidence, that endarterectomy could be futile in the presence of IAD. The NASCET entered 956 patients with this condition.²⁸ The risk of stroke for medically treated patients, with any degree of extracranial stenosis, was higher for those with than for those without IAD. Because the surgical risk was similar among all patients, the

number of patients needed to undergo carotid endarterectomy to prevent one ipsilateral stroke in 3 years was less among those with IAD than among those without it. When the extracranial carotid stenosis was 70% or greater, the NNT was 4 for those with IAD and 7 for those without. For patients with 50% to 69% extracranial stenosis, the NNT was 12 for those with IAD, but 26 for those without.

In conclusion, patients with mild to moderate intracranial disease and severe symptomatic extracranial stenosis are ideal candidates for carotid endarterectomy. For those with moderate stenosis and IAD, endarterectomy is recommended, but for those without IAD, endarterectomy is unlikely to be beneficial.

Can ipsilateral strokes of any cause be prevented by carotid endarterectomy?

Stroke data banks^{29,30} have recorded 4 categories of ischemic stroke: strokes of large-artery origin (carotid disease being the commonest), small-vessel disease (lacunar), cardioembolic stroke, and a combined category of miscellaneous and cryptogenic strokes. During an average follow-up period of 5 years, 749 NASCET patients had 1039 strokes.³¹ Primary intracerebral hemorrhage accounted for 17 of these and subarachnoid hemorrhage for 1. The 1021 ischemic strokes consisted of 698 of large-artery origin, 211 lacunar strokes and 112 cardioembolic strokes. Because the NASCET excluded patients with serious cardiac conditions, the proportion of cardioembolic strokes was presumably

Table 3: Perioperative (30-day) complications after endarterectomy

Complication	Trial and severity of complication,* % of patients			
	NASCET + ACE, symptomatic n = 2670		ACE, asymptomatic n = 1214	
	Mild or moderate	Severe	Mild or moderate	Severe
Surgical				
Wound hematoma	6.6	0.3†	5.7	0
Wound infection	1.2	0	0.2	0
Other wound complication	0.3	0	2.9	0
Cranial nerve injury	6.8	0	2.9	0
Medical				
Arrhythmia	1.6	0	2.1	0.2‡
Congestive heart failure	0.9	0	1.1	0.1‡
Angina pectoris	1.2	0	0.2	0
Hypertension	1.1	0	0.6	0
Hypotension	2.9	0	3.3	0.2‡
Respiratory disorder	1.6	0.1‡	1.6	0.2‡
Confusion	0.9	0	0.7	0

*Mild or moderate complications were transient complications that did not result in permanent disability; severe complications were those that resulted in permanent functional disability or death.

†Three of 7 fatal.

‡All fatal.

lower than would be the case among carotid endarterectomy patients in community hospitals. Even among patients with 70% to 99% carotid stenosis causing initial symptoms, 20% of subsequent strokes were not of large-artery origin. The proportion of strokes other than those of large-artery origin was higher (35%) when the carotid stenosis was moderate.

In conclusion, many future strokes will be unrelated to the stenosed intracranial carotid artery and will not be prevented by carotid endarterectomy. Vigilant attention to risk-factor management and ongoing scrutiny of cardiac function must be pursued in all patients.

Should patients presenting with lacunar stroke be considered for carotid endarterectomy?

Large-artery disease is commonly associated with intracranial small-vessel disease, the site of lesions causing lacunar stroke. NASCET entered 1158 patients with hemispheric stroke, of whom 493 (42.6%) had clinicoradiologic features of lacunar stroke: 283 defined as possible and 210 as probable.³² With medical treatment these lacunar stroke patients had a lower risk of large-artery stroke than did those presenting with large-artery stroke and conversely a

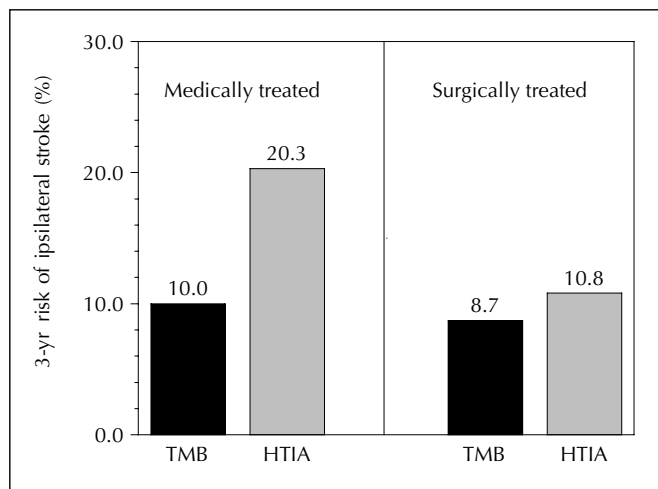


Fig. 2: Kaplan–Meier 3-year risk of ipsilateral stroke in patients with at least 50% stenosis and transient monocular blindness (TMB) or hemispheric transient ischemic attack (HTIA). The difference in risk between medical and surgical therapy for patients presenting with hemispheric events is impressive (20.3% v. 10.8%), but for patients presenting with retinal events it is only modest (10.0% v. 8.7%). The number of patients were as follows: 142 with TMB treated medically, 215 with HTIA treated medically, 142 with TMB treated surgically and 197 with HTIA treated surgically. Reproduced, with permission, from Benavente O, Eliasziw M, Streifler JY, Fox AJ, Barnett HJM, Meldrum H, for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators. Prognosis after transient monocular blindness associated with carotid artery stenosis. *N Engl J Med* 2001;345:1084-90. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

higher risk of further lacunar stroke. Lacunar strokes were more likely to be observed in patients with mild to moderate stenosis. Among patients with stroke other than lacunar stroke who had 50% to 99% stenosis of the internal carotid artery, the risk of stroke associated with medical treatment at 3 years was reduced by carotid endarterectomy from 24.9% to 9.7%, an absolute risk reduction of 15.2%. Among patients with “probable” lacunar stroke at entry, risk of subsequent stroke was reduced from 25.5% to only 16.5%, an absolute risk reduction of 9.0%.

In conclusion, the benefit from carotid endarterectomy is lower for patients with a lacunar stroke and a stenosing carotid artery lesion. There is no evidence that these patients should be denied the procedure, but the lesser benefit should be recognized.

Does leukoaraiosis alter the decision to recommend carotid endarterectomy?

In the mid-1980s CT and MRI of the brain led to the recognition of a white matter condition called leukoaraiosis.³³ It is characterized by poorly delineated, hypodense lesions unlike the sharply defined, low-density lesions within a specific arterial territory that are characteristic of an infarct. The cause is uncertain, the pathology is nonspecific and the pathogenesis is the subject of considerable speculation.³⁴⁻³⁶ Leukoaraiosis occurs most commonly in elderly subjects and has been associated with a higher risk of stroke, vascular death and dementia. The reasons for this higher risk are unknown. Beginning as focal changes in the white matter, the condition becomes widespread in some of those affected. Among 2618 NASCET patients with entry CT scans, 354 had restricted and 139 had widespread evidence of leukoaraiosis.³⁷ Among patients with 50% to 99% stenosis, the 3-year risk of stroke was greater with more extensive leukoaraiosis than without the condition. In addition, the perioperative risk of stroke and death was 5.3% among patients with no leukoaraiosis, 10.6% among those with restricted leukoaraiosis and 13.9% among those with widespread leukoaraiosis. Despite the higher perioperative risk, endarterectomy reduced the absolute 3-year risk of stroke (ipsilateral to the symptomatic artery in patients with 50% to 99% stenosis) by 11.6% for patients with widespread leukoaraiosis, by 7.6% for patients with restricted leukoaraiosis and by 10.9% for patients with no leukoaraiosis.

In conclusion, leukoaraiosis has emerged as a significant risk factor for stroke. Although its presence increased the perioperative risk, the medical risk alone was sufficiently high to recommend carotid endarterectomy. Such patients must be made aware of the increased operative risk.

Should patients undergo carotid endarterectomy when the contralateral artery is occluded?

In the early days of carotid endarterectomy it was recognized that the risk associated with the procedure was higher among patients with occlusion of the contralateral internal

carotid artery than among those whose contralateral artery was normal.³⁸⁻⁴¹ The NASCET examined the risk of stroke in the artery ipsilateral to the one with severe symptomatic stenosis in 3 groups of patients: 43 patients with occlusion of the artery contralateral to the symptomatic one, 57 with severe patent contralateral stenosis and 559 with only mild to moderate contralateral stenosis.⁴² With medical treatment alone, the hazard rate of an ipsilateral stroke at 2 years in patients with occlusion of the contralateral artery was very high, at 69.4% (Fig. 3). Among those without occlusion, the degree of stenosis of the contralateral artery made no difference to the lower risk of stroke. Although the perioperative risk of ipsilateral stroke in the presence of contralateral occlusion was high for surgically treated patients (14.3%), the absolute risk reduction at 2 years favouring carotid endarterectomy was 45.1%. When NASCET patients with moderate stenosis were aggregated with the aforementioned severe-stenosis patients, the perioperative rate of stroke and death was 14.8% among patients with contralateral occlusion and 6.1% among those whose contralateral artery was stenosed but patent (Fig. 4).⁴³ For the symptomatic ACE patients the rates were 9.8% and 6.2% respectively (Fig. 4).

In conclusion, occlusion of the contralateral internal carotid artery is not a contraindication to carotid endarterectomy of the symptomatic artery. However, the patient must be informed that the perioperative risk is almost double that for patients with a patent contralateral artery. The long-term benefit of carotid endarterectomy still justifies the immediate surgical risk and outweighs the risk from medical therapy alone.

Is carotid endarterectomy beneficial in cases of near-occlusion of the carotid artery?

The severest form of carotid stenosis reduces the diameter of the artery beyond the stenosing plaque. The condition may be so severe that it is accompanied by narrowing of the ipsilateral common carotid artery. This phenomenon, called near-occlusion, occurred in the internal carotid artery of 7.6% of the NASCET patients. This amount of stenosis is accompanied by evidence of collateral circulation to the supply of the intracranial portion of the internal carotid artery. In addition, the flow of contrast agent to the intracranial territory is delayed relative to the arrival of contrast in the distal portions of the external carotid artery, and there is dilution of the contrast from collateral blood entering the internal carotid intracranially.⁴⁴ In the NASCET, near-occlusion did not impose an additional perioperative risk, but the medical risk was lower.¹⁹ Thus the absolute benefit of carotid endarterectomy was reduced to the equivalent of that observed in patients with lesser degrees of stenosis (absolute risk reduction of stroke of 7.9%).

In conclusion, patients with near-occlusion should be considered for endarterectomy but should be advised that the benefit will be muted.

Is carotid endarterectomy beneficial for patients with collateral pathways visualized on angiography?

Collateral filling through anterior or posterior communicating vessels and retrograde filling through ophthalmic arteries was determined angiographically for all patients on entry into the NASCET.⁴⁵ Blood supply through collateral pathways improves regional cerebral blood flow and protects against ischemic events. The evidence of collateral vessels supplying the symptomatic internal carotid artery increased with severity of stenosis, and they were visualized in approximately one-half of the patients with severe stenosis. The 2-year risk of hemispheric stroke in medically treated patients with severe stenosis of the internal carotid artery was 27.8% for those without and 11.3% for those with collateral vessels. For surgically treated patients, the 2-year risk was 8.4% for those without and 5.9% for those with collateral vessels. Therefore, the absolute risk reduction was 19.4% among patients without and 5.4% for patients with collateral vessels.

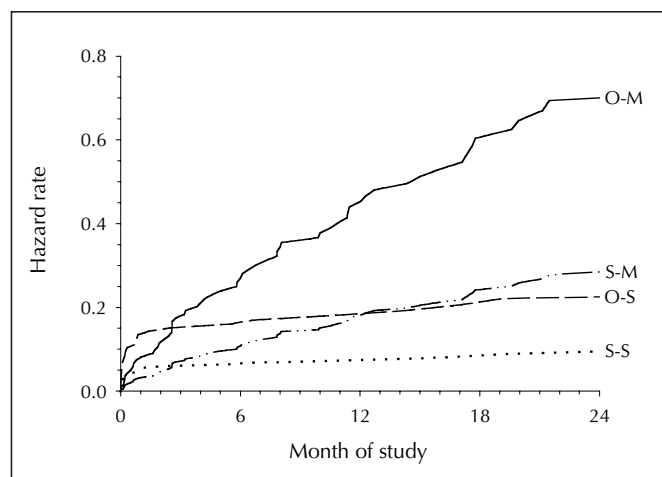


Fig. 3: Cumulative hazard curves showing risk (hazard rate) of ipsilateral stroke for medically and surgically treated patients with either an occluded contralateral carotid artery or a stenosed but patent contralateral carotid artery. When the artery contralateral to the symptomatic side is occluded, patients treated medically (O-M = Occluded Medical) face a formidable risk at 2 years (69.4%). When the contralateral artery is stenosed but not occluded the risk with medical treatment is considerably lower (S-M = Stenosed Medical). Despite a high perioperative risk, patients undergoing surgical treatment in the presence of contralateral occlusion (O-S = Occluded Surgical) still benefit, as do patients with contralateral stenosis short of occlusion (S-S = Stenosed Surgical). Reproduced, with permission, from Gasecki AP, Eliasziw M, Ferguson GG, Hachinski V, Barnett HJM, for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. *J Neurosurg* 1995;83:778-82.

In conclusion, the absence of collateral vessels was associated with a high risk of hemispheric stroke in both medically and surgically treated patients. The high absolute risk reduction commends carotid endarterectomy for these patients. However, patients with collaterals and severe stenosis experience a muted benefit.

Does carotid endarterectomy benefit patients with intraluminal thrombi?

The finding on an angiogram of an intraluminal thrombus beyond the stenosis is ominous. The likelihood of such an occurrence increases with increasing degree of stenosis. Intraluminal thrombus was present in 5.5% of NASCET patients with at least 85% stenosis.⁴⁶ The 30-day risk of stroke or death for medically treated patients with a clot was triple the risk for medically treated patients without a clot. For surgically treated patients, the risk among those with a

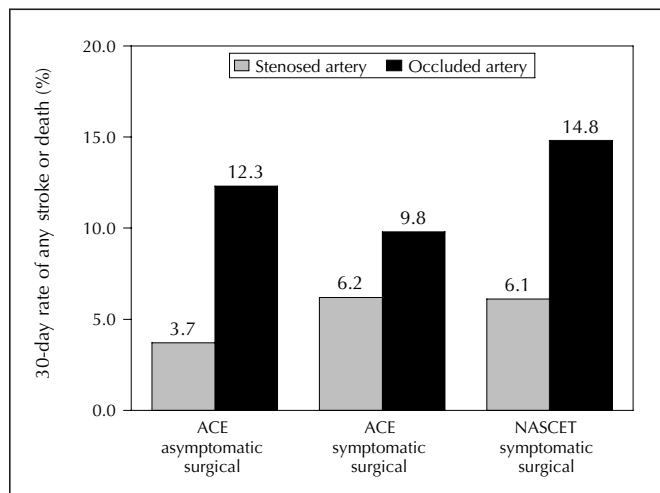


Fig. 4: Thirty-day rate of perioperative stroke or death in surgically treated patients with contralateral occlusion and those with only contralateral stenosis. Data are for patients with either asymptomatic or symptomatic stenosis in the ASA and Carotid Endarterectomy (ACE) trial⁶ and symptomatic patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).³ The high risk (12.3%) for asymptomatic patients with contralateral occlusion would recommend strongly against carotid endarterectomy for patients with this combination of lesions. The numbers of patients were as follows: asymptomatic patients in ACE trial, 1358 with stenosed and 154 with occluded contralateral artery; symptomatic patients in ACE trial, 1210 with stenosed and 82 with occluded contralateral artery; symptomatic patients in NASCET, 1354 with stenosed and 61 with occluded contralateral artery. Reproduced, with permission, from Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RKT, Meldrum HE, et al, for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. The causes and risk of stroke in subjects with an asymptomatic internal carotid artery. *N Engl J Med* 2000;342:1693-700. Copyright © 2000 Massachusetts Medical Society. All rights reserved.

clot was double that among those without a clot. At 1 year, the risk of ipsilateral stroke was 16.0% among surgically treated patients and 25.3% among those treated medically.

In conclusion, endarterectomy can be advised despite intraluminal thrombi. Patients must be informed of the greater risk. It is not known whether a preliminary course of prophylactic platelet inhibitors or anticoagulants diminishes the surgical risk.

Conclusions

Patients with symptomatic severe stenosis (at least 70%) of the internal carotid artery

All patients with symptoms related to severe carotid stenosis fare better with carotid endarterectomy than with medical care alone. In the absence of life-threatening disease they should undergo the procedure. Symptomatic patients with the conditions listed below face a much greater risk of stroke when treated medically than those without these conditions. Therefore, carotid endarterectomy is most beneficial in the following patients:

- otherwise healthy elderly patients (75 years or older)
- patients presenting with hemispheric transient ischemic attack
- patients with tandem extracranial and intracranial lesions
- patients without angiographic evidence of collateral pathways.

Although the perioperative risk is higher in patients with the following conditions, they still benefit from the procedure:

- widespread leukoaraiosis
- occlusion of the contralateral carotid artery
- intraluminal thrombus.

Patients with symptomatic moderate stenosis (50% to 69%) of the internal carotid artery

Many, but not all, patients with moderate stenosis benefit from carotid endarterectomy. For most such patients the benefit is much smaller than for patients with severe stenosis. Furthermore, the following patients may be harmed:

- patients with transient monocular blindness only, especially those with few risk factors
- women with few risk factors.

Other patients with symptomatic stenosis of the internal carotid artery

A separate category involves 2 types of patients: those presenting with both lacunar stroke and stenosis of at least 50% and those presenting with near-occlusion of the symptomatic artery. For both conditions, medical treatment carries a lower risk of stroke than for patients without these conditions. Carotid endarterectomy is still indicated and there is no increase in perioperative risk, but the benefit is muted.

Caveats

To achieve optimal benefit of carotid endarterectomy for stroke-threatened symptomatic patients, the following 4 caveats must be borne in mind:

Surgical expertise must be no less than that of the surgeons in the NASCET and ACE trials, achieving a perioperative stroke and death rate close to 6%. Institutional audits of the procedure should be readily available to referring physicians and patients.

The measurements from arterial images must be exact, because the carotid endarterectomy imposes a 2% risk of disabling stroke or death. In addition, the stroke rate associated with angiography must be kept below 1%. Because noninvasive methods may be suggesting endarterectomy for patients who will not benefit from the procedure and preventing the procedure for others who *would* benefit, such technology is not appropriate in all instances.

The trials discussed here had strict exclusion criteria: patients with impending organ failure, serious forms of cardiac dysfunction and late-stage cancer. It is dubious if patients with any of these condition should undergo carotid endarterectomy.

Best medical management should be given scrupulous attention: control of blood pressure, glycemic control, reduction of lipids, smoking cessation, control of heart disease if it develops and antithrombotic medication in the form of acetylsalicylic acid.

Asymptomatic carotid artery disease

Committees of the American Heart Association and the National Stroke Association have endorsed the use of carotid endarterectomy for asymptomatic subjects.^{47,48} Some, including us, question this enthusiasm.⁴⁹⁻⁵²

Four randomized trials have been conducted.⁵³⁻⁵⁶ Two were flawed in design and conduct and yielded negative results. The third also had a negative result: a 4.6% rate of perioperative stroke or death and no difference in stroke-free survival between the medically and surgically treated groups. The fourth study, the Asymptomatic Carotid Atherosclerosis Study (ACAS),⁵³ reported a statistically significant benefit favouring carotid endarterectomy and provided the impetus for the recent burst of activity in the performance of carotid endarterectomy.

Although the relative reduction in the risk of stroke in favour of carotid endarterectomy in the ACAS was reported as 53%, the average annual absolute risk reduction was only 1%, and this was dependent on a low perioperative risk of 1.5% (excluding the 1.2% rate of angiographic complications). Because of the low medical risk faced by the asymptomatic subjects, in spite of excellent surgical skill, the NNT to prevent one additional stroke in 2 years was 83, too high to be accepted without question. Examination of the stroke-free survival curves in the ACAS, with its paucity of patients ($n = 149$) at 5 years and few outcome

events in either the medical or the surgical arm, reveals that the absolute risk reduction of 5.9% would not have been achieved except for a small burst of strokes in the fifth year of the trial (Fig. 5). Had the ACAS been analyzed at 4 years, no statistically significant difference would have emerged.

A reliably reproducible operative risk, below the medical risk, has been hard to achieve. The annual risk of stroke in the medical arms of the 2 large trials of asymptomatic subjects was only about 2.5%. In a few surgical series the risk has been close to or just below this figure, at 2.8%.⁵⁷⁻⁵⁹ This 2.5% to 2.8% range, on the other hand, is exceeded by the operative morbidity and mortality rates (3.6% to 5.6%) in several large nonrandomized series, which included surveys of regional Medicare records, single surgeons' case series and regional centre series.⁶⁰⁻⁶⁵

In the ACE trial, the NASCET surgeons operated on 1214 patients with no symptoms and with characteristics similar to those of the ACAS patients. The 30-day perioperative rate of stroke or death was 4.4% (Table 2). When this perioperative rate is superimposed upon the stroke-free survival curves of the ACAS, it becomes clear that the 1214 asympto-

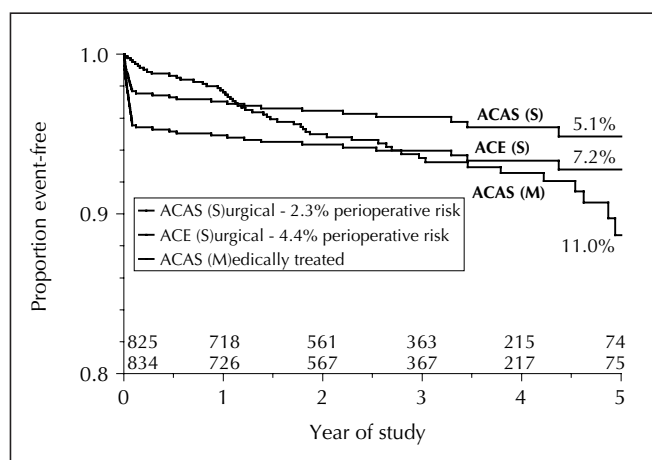


Fig. 5: Five-year Kaplan-Meier curves of event-free survival (no ipsilateral stroke or perioperative stroke or death) for the Asymptomatic Carotid Atherosclerosis Study (ACAS) indicate a 5.9% difference in projected risk, favouring endarterectomy, at 5 years.⁵³ However, between years 4 and 5 a series of strokes of unknown cause occurred in the medical treatment arm. The numbers of patients available for analysis at each year of follow-up appear along the horizontal axis (top and bottom numbers at each time point represent ACAS patients who underwent surgical and medical treatment respectively). At year 5 these numbers were very small. Superimposed on the graph (adapted from Barnett and colleagues⁵²) is the projected outcome for 1214 asymptomatic subjects in the ASA and Carotid Endarterectomy (ACE) trial, based on the 30-day perioperative rate of stroke or death (4.4%) extrapolated to 5 years. For this group the projected risk at 5 years is 7.2%, so the difference between this group and ACAS patients treated medically would be 3.8% — only 0.8% benefit per year. Clearly no benefit was present for the first 4 years of follow-up in the ACE subjects.

matic subjects in the ACE trial did not achieve benefit until at least 4 years after the procedure and, at least until then, would have fared better with medical treatment (Fig. 5).

Some clinicians suggest that carotid endarterectomy for asymptomatic subjects be done only when the contralateral asymptomatic artery is occluded. This condition was met for the 154 asymptomatic subjects in the ACE trial, but the perioperative complication rate was a forbidding 12.3% (Fig. 4).⁴³

The NASCET's study of 1820 subjects with asymptomatic stenosis contralateral to the symptomatic side (the latter of which was used for randomization) showed that 45% of the strokes in the initially asymptomatic territory were of cardioembolic or lacunar origin.⁴³ Future strokes of cardioembolic origin will not be prevented by carotid endarterectomy; this procedure is less effective in preventing lacunar strokes than in preventing large artery strokes. In the ACAS several strokes occurring in the fifth year of the trial influenced the statistical results.⁵³ The cause of these strokes was unknown, but approximately half of them could have been cardioembolic or lacunar.

When the ACAS results were published there was sufficient skepticism about the conclusions that another randomized trial was launched in Europe.⁶⁶ It is now close to its goal of recruiting 3500 patients.

Conclusions

Carotid endarterectomy for subjects with an asymptomatic stenosed carotid artery has marginal benefit and questionable safety, and large numbers of individuals must be treated to prevent a single stroke. In our view, until new data support or contradict these conclusions in an evidence-based manner, best management for subjects with asymptomatic carotid stenosis is to treat hypertension, diabetes mellitus and hyperlipidemia, to encourage smoking cessation, to administer prophylactic therapy with acetylsalicylic acid and to monitor for the development of treatable cardiac conditions. There may be a subgroup of subjects who clearly benefit from endarterectomy, but the characteristics of such a subgroup cannot be determined from existing evidence.

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