Risk of Stroke From New Carotid Artery Occlusion in the Asymptomatic Carotid Surgery Trial-1

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Background and Purpose—In the Asymptomatic Carotid Surgery Trial-1 (ACST-1), 3120 patients with tight asymptomatic carotid stenosis were randomly assigned to medical treatment alone or to carotid endarterectomy and appropriate medication. Successful carotid endarterectomy significantly reduced 10-year stroke risk in younger patients. This study was undertaken to determine the risk of new occlusion and stroke during trial follow-up.

Methods—Patients with contralateral occlusion at trial entry (n=276) or incomplete duplex follow-up (n=137) were excluded. Risk of occlusion and stroke in patients with occlusion was estimated by Kaplan–Meier analysis. Cox proportional hazard regression models were used to determine risk factors for developing new occlusion and stroke.

Results—Median follow-up in 2707 patients was 80.0 months (interquartile range, 52.0–115.0). New occlusions occurred in 197 patients (1.1% per annum) but were more likely to occur in arteries with tight stenosis and in unoperated patients. Overall risk of stroke was 7.6% (95% confidence interval [CI], 6.6–8.7) and 15.5% (95% CI, 13.6–17.4) at 5 and 10 years, respectively; for patients with new occlusion, this significantly increased to 17.0% (95% CI, 11.6–22.4) and 20.8% (95% CI, 14.1–26.2), respectively ($P<0.001$). Stroke was significantly more likely to occur in patients developing occlusion (hazard ratio, 1.78; 95% CI, 1.26–2.51) irrespective of allocated treatment.

Conclusions—New occlusions were uncommon after carotid endarterectomy in ACST-1. During long-term follow-up, occlusion and stroke were commoner among patients with ≥70% stenosis, most of whom had not undergone carotid endarterectomy. Occlusion was an independent prognostic risk factor for occurrence of stroke. **(*Stroke*. 2013;44:1652-1659.)**

Key Words: carotid occlusive disease ■ carotid stenosis ■ stroke

Severe asymptomatic carotid stenosis (≥70% diameter reduction) occurs in ≤3.1% in the general population, and the stroke risk associated with this has been reported as 2% to 5% per year.[1–3]

Although modern medical management with antithrombotic, lipid-lowering, and antihypertensive medicines has reduced overall stroke risk, there is a significant long-term residual risk from established tight carotid stenosis. Two large randomized trials have shown that carotid endarterectomy (CEA) will reduce future stroke risk.[4,5] In the larger of these, the Asymptomatic Carotid Surgery Trial-1 (ACST-1), patients with ≥1 significant asymptomatic carotid artery stenosis were randomized (1993–2004) to have either immediate surgery or indefinite deferral of operation on that artery. Surgery significantly reduced 10-year stroke risk (10.8% vs 16.9%), half of this benefit involving disabling or fatal strokes.[5,6] The perioperative risk of stroke or death was 3%, but taking this into account, absolute stroke risk reduction was ≈6% for men and women ≤75 years of age at trial entry (not older patients), and importantly, for those already on lipid-lowering therapy.[5,6]

Patients with contralateral occlusion at trial entry (8%) had a similar benefit (annual event rate 1.2% in the immediate group vs 2.4% in the deferred group, 1% vs 2% all patients).[5] Previous studies suggest annual ipsilateral stroke risk from an already occluded internal carotid artery may be between 2% and 12%, but no large prospective studies have investigated stroke risk when tight carotid artery stenosis progresses to occlusion.[7–12]

Uniquely long follow-up in the large cohort of patients in ACST-1 enables us to analyze the incidence of new carotid occlusion and stroke in these patients. The aims of our study were to determine the risk of new carotid artery occlusion and associated stroke and to evaluate patient risk factors predisposing to the development of occlusion.

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Methods

In ACST-1, patients with unilateral or bilateral carotid artery stenosis that was considered to be severe (carotid artery diameter reduction of ≥60% on ultrasound) and no relevant neurological symptoms in the preceding 6 months were randomized to have immediate or deferred CEA.

Patients randomized to immediate surgery were to have this carried out as soon as routinely possible (median delay 1 month, interquartile range, 0.3–2.5), and those allocated as deferred were not to be operated on until they developed appropriate symptoms or unless some other definite indication for surgery had arisen. All were to receive appropriate medical treatment, which generally included antithrombotic, antihypertensive, and latterly, lipid-lowering therapy. The primary end point in ACST-1 was stroke or death within 30 days of carotid surgery or stroke during follow-up.[13]

Design of This Study

To determine the risk of new occlusion, patients with established contralateral internal carotid artery occlusion at baseline (n=276) or the small number of patients with incomplete follow-up (n=137) were excluded (Figure 1). For the 2707 patients in this study, the allocated treatment, perioperative morbidity, any strokes, and the use of medication during follow-up were recorded. Patients were followed up at 4 and 12 months and then yearly from 1993 to 2008, irrespective of any nonfatal strokes. Carotid artery stenosis (generally rounded to the nearest decile) was measured using Duplex Ultrasound and recorded as percentage luminal diameter reduction. Centers participating in ACST-1 were expected to have validated their own methods of measuring carotid artery stenosis, either against angiography or by recognized locally validated criteria, which were usually based on European Carotid Surgery Trial (ESCT)[14] or North American Symptomatic Carotid Endarterectomy[15] methods. There was no central reading of sonographic studies.

Outcome

The primary end point in this study was any new occlusion of the carotid artery. Patients who developed bilateral new occlusions were considered to have reached the end point at the time their first artery occluded. Occlusion was determined by Duplex Ultrasound or angiography and defined as the absence of internal carotid artery flow during regular follow-up or when found in a diagnostic work-up for patients with stroke.

The secondary outcome was the risk of stroke in patients with any new occlusion. All strokes in ACST-1 were classified and recorded by an end point review committee.[13] Strokes were defined as any stroke after randomization, either associated with occurrence of occlusion or at any time during trial follow-up. Where possible, cause, type, laterality, and disability from the stroke were recorded.

Statistical Analysis

Analysis was based on intention-to-treat principle unless otherwise specified. Kaplan–Meier life-table analyses were performed to estimate the risk of new carotid artery occlusion and the risk of stroke in patients with and without occlusion. Univariate and multivariate Cox proportional hazard regression models were used to determine the significance of risk factors for development of occlusion and for stroke. Risk of occlusion was also analyzed by allocated trial treatment. Risk factors evaluated were age at randomization (younger or older than 75), sex, stenosis at randomization of ≥70%, diabetes mellitus (DM), hypertension (patients taking antihypertensive agents or systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg), and prior known ischemic heart disease. For each of these possible risk factors, the hazard ratio and 95% confidence intervals were determined. Those with P values ≤0.20 were analyzed in a multivariate Cox regression model to identify independent risk factors for developing occlusion and for developing stroke. Significance was inferred at $P<0.05$.

Results

The study included 2707 patients; there were no differences in baseline characteristics between those allocated to the surgery group and those allocated to medical treatment alone (n=1325 vs n=1382; Table 1). Of all included patients, 1350 did not have surgery (n=1274 allocated deferral and n=76 who did not have their assigned CEA; Figure 1).

Median follow-up time was 80.0 months (interquartile range, 52.0–115.0). New occlusion of the ipsilateral (n=143) or contralateral (n=54) artery occurred in 7.3% patients

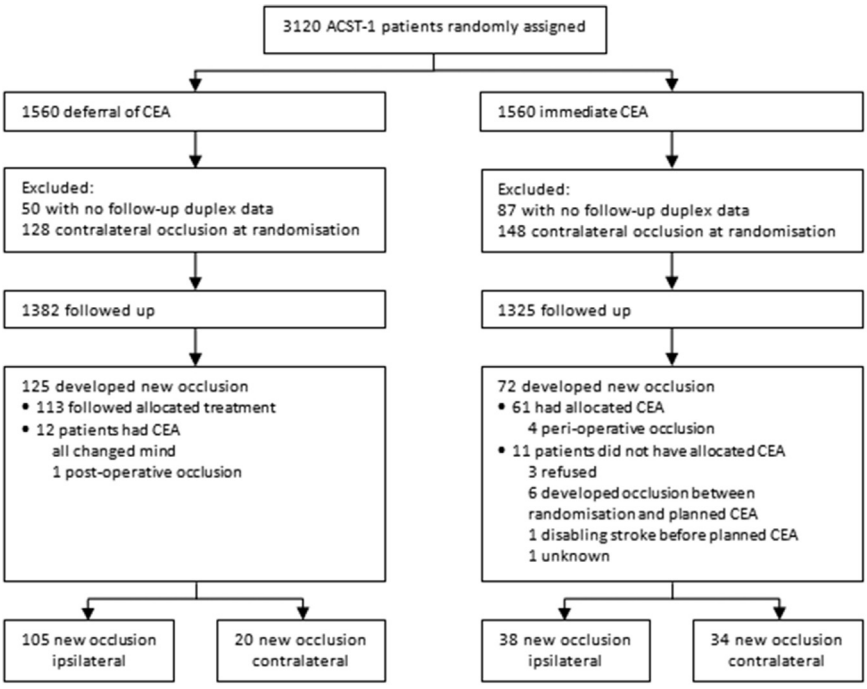

Figure 1. Flowchart. ACST-1 indicates Asymptomatic Carotid Surgery Trial-1; and CEA, carotid endarterectomy.

(n=197). The median time to occlusion was 75.0 months (immediate) and 73.0 months (deferred; interquartile range, 50.0–113.5 vs 47.0–110.3; P=0.06). The annual risk of occlusion for all patients was 1.1%.

Progression to Occlusion

In both treatment groups, an occlusion was more likely to occur in arteries that were tightly stenosed (≥70% stenosis) at trial entry. In the immediate group (most of whom had their stenosed artery successfully operated on), 41 of 72 arteries that finally occluded had tight stenosis at randomization. In the deferred group (generally unoperated), occlusion occurred in 104 of 125 previously tightly stenosed arteries (Table 1).

Risk of Occlusion

Kaplan–Meier life-table analysis showed that risk of any new occlusion was lower in the immediate CEA group (Figure 2A; log rank: P<0.001). In the deferred group, occlusion was more likely to occur in the ipsilateral (unoperated) artery (P<0.001).

A separate per-protocol analysis of all patients who did not have any surgery (n=1350) showed that their chance of developing new occlusion was somewhat higher, at 9.2% (1.4% per year).

Occlusion and Stroke

In this study, 299 of 2707 (11%) patients had a stroke during follow-up. Although most strokes (262 of 299; 87.6%) occurred in patients with tight ipsilateral stenosis, 37 patients with a new occlusion (37 of 197; 18.8%) developed stroke (Table 2).

Twenty patients (10.2%) developed a stroke with documented occlusion at that time (18 strokes were ipsilateral to the occluded artery, 1 contralateral, and 1 in whom the affected territory could not be identified). Three of the patients who had a symptomatic occlusion had a further stroke during follow-up (mean time between occlusion and second stroke, 26.7 months [±10.7]). Most of these patients had contralateral stenosis of <50% (12 of 37). More symptomatic occlusions occurred in those who had not had trial surgery (3 vs 17; P=0.04).

Twenty patients (10.2%) developed a stroke not directly related to the time of occurrence of their occlusion. Three occurred before occlusion, 2 were perioperative nondisabling strokes (1 ipsilateral and 1 contralateral to the finally occluded

Table 1. Patient Characteristics

	Immediate CEA n=1325 (48.9%)		Deferral of CEA n=1382 (51.1%)	
Variable*	New Occlusion n=72 (2.7%)	No Occlusion n=1253 (46.3%)	New Occlusion n=125 (4.6)	No Occlusion n=1257 (46.4)
Age, y, mean±SD	66.5±8.1	68.3±7.4	67.6±7.5	68.2±7.5
Sex				
Men	53 (73.6)	796 (63.5)	97 (77.6)	797 (63.4)
Stenosis at randomization				
Ipsilateral side				
0%–49%	0 (0.0)	3 (0.2)	0 (0.0)	8 (0.6)
50%–69%	5 (6.9)	112 (8.9)	4 (3.2)	131 (10.4)
70%–99%	33 (45.8)	1138 (90.8)	101 (80.8)	1118 (88.9)
Contralateral side				
0%–49%	14 (19.4)	844 (67.4)	10 (8.0)	827 (65.8)
50%–69%	12 (16.7)	264 (21.1)	7 (5.6)	276 (22.0)
70%–99%	8 (11.1)	145 (11.6)	3 (2.4)	154 (12.3)
Risk factors				
Diabetes mellitus	5 (6.9)	256 (20.4)	22 (17.6)	247 (19.6)
Prior ischemic heart disease	26 (36.1)	412 (32.9)	41 (32.8)	437 (34.8)
Hypertension	55 (76.4)	967 (77.2)	87 (69.6)	961 (76.5)
Medication use during trial FU				
Antiplatelet	68 (94.4)	1124 (89.7)	116 (92.8)	1101 (87.6)
Anticoagulation	1 (1.4)	63 (5.0)	9 (7.2)	81 (6.4)
Lipid lowering	25 (34.7)	390 (31.1)	40 (32.0)	425 (33.8)
Symptomatic at time of occlusion				
Stroke	3 (4.2)	NA	17 (13.6)	NA
Symptomatic during FU				
Stroke	7 (9.7)	104 (8.3)	13 (10.4)	158 (12.6)

CEA indicates carotid endarterectomy; FU, follow-up; and NA, not available.
*Categoric variables are presented as n (%); continuous variables as mean±SD.

side), and the third was a disabling stroke ipsilateral to a later occlusion. Nine other strokes during follow-up were ipsilateral to the occluded artery, and 4 were contralateral, 2 in unspecified territory, and 2 affected the posterior circulation. The annual risk of stroke after developing an occlusion was 2.3%. Strokes during follow-up were not clearly related to the severity of contralateral stenosis (contralateral stenosis <50% [8 of 20]; >70% [6 of 20]).

The cumulative risk of stroke in patients with and without occlusion is shown in Figure 2B. There were significantly more strokes during follow-up in those with occlusion (log-rank: $P<0.001$), particularly in those who had not had trial surgery (log-rank: $P=0.007$; Figure 2C and 2D).

Bilateral Occlusion

Two men had bilateral occlusion during follow-up; 1 allocated to medical therapy alone, developed an asymptomatic occlusion of the nonrandomized artery, and a few years later, a new ipsilateral occlusion caused stroke.

The other patient underwent allocated trial surgery, but this artery occluded asymptomatically within 2 months, and the contralateral artery occluded ≈5 years later, again without symptoms.

Risk Factor Analysis

Male sex, ≥70% stenosis at randomization, DM, hypertension, and treatment allocation were significantly associated with development of occlusion. Only male sex and deferral of CEA remained significant after multivariate analysis.

From univariate analysis of possible factors associated with development of stroke, age >75 years, DM, prior ischemic heart disease, allocated treatment, and occlusion were positively associated with stroke. All, except prior ischemic heart disease, remained significant after multivariate analysis (Table 3). A separate intention-to-treat analysis of patients allocated trial surgery showed that age >75 years, DM, and occlusion were significant risk factors for developing stroke. DM and occlusion were risk factors for stroke in patients allocated to deferral of CEA (Table 4).

Discussion

This is the only large study of patients with carotid stenosis suitable for surgery to analyze long-term risk of occlusion and the risk of stroke in association with a new occlusion.

New occlusion occurred in ≈1% of all the patients each year, but most of them did not have a stroke, either at the time of occlusion or during the 10-year follow-up. The risk of occlusion and of stroke was higher in patients in whom surgery had not been carried out, and overall, stroke-free survival was significantly worse for these patients.

The findings from the ACST-1 trial may be generally representative of patients with severe asymptomatic carotid artery stenosis, having included patients from 126 centers in 30 countries. Large vascular registries may be more reliable,

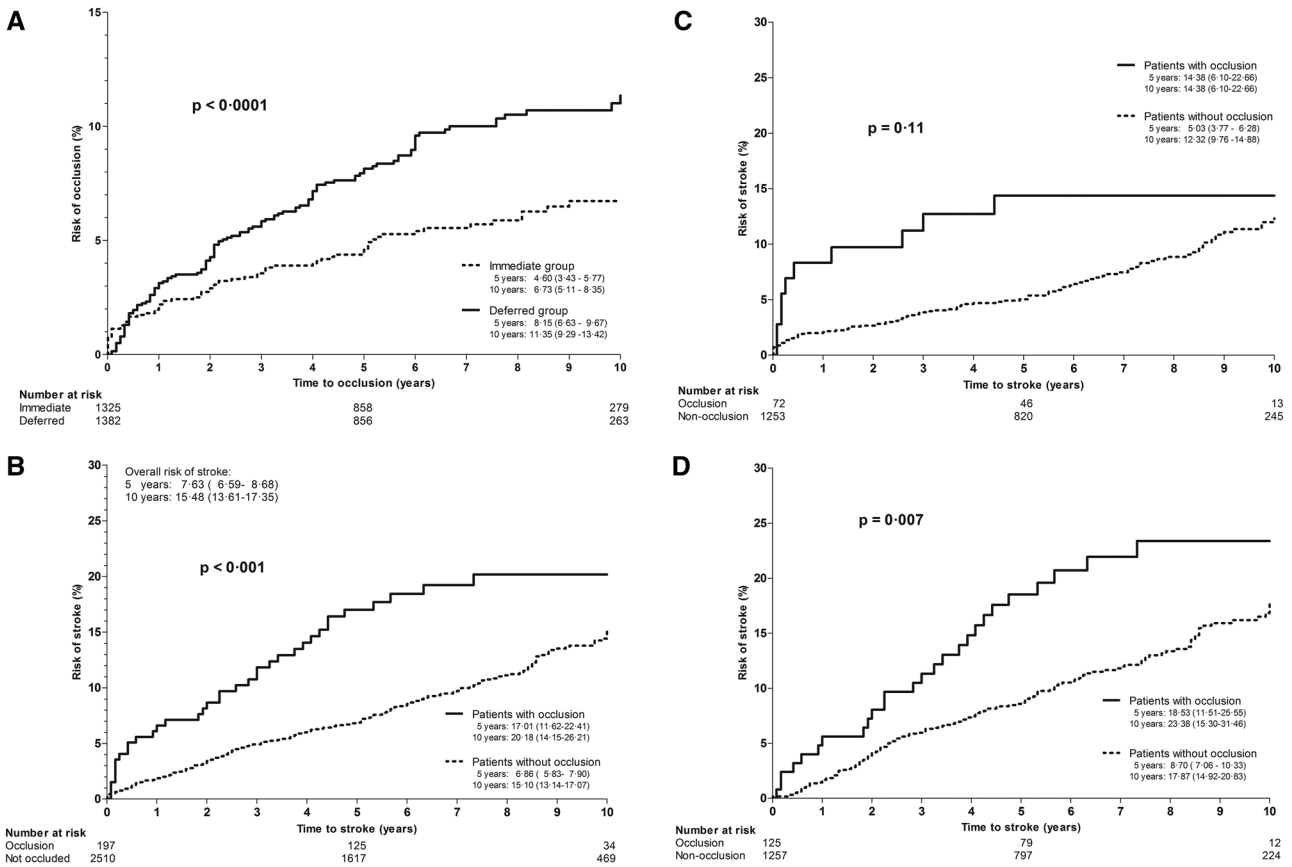

Figure 2. A, Risk of any new occlusion. **B**, Risk of stroke total study population. **C**, Risk of stroke in patients allocated immediate carotid endarterectomy (CEA). **D**, Risk of stroke in patients allocated deferral of CEA. (**Continued**)

Table 2. Strokes in Patients With New Occlusion

Allocated to	Immediate CEA n=10		Deferral of CEA n=30	
Time of Stroke	At Occlusion (n=3)	During FU (n=7)	At Occlusion (n=17)	During FU (n=13)
Territory				
Carotid	3* (30.0)	7† (70.0)	16 (53.3)	10 (33.3)
Vertebrobasilar	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.7)
Unknown	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)
Nature				
Ischemic	2 (20.0)	3 (30.0)	16 (53.3)	8 (26.7)
Hemorrhagic	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.3)
Unknown	1 (10.0)	3 (30.0)	1 (3.3)	4 (13.3)
Pathogenesis				
Arterial	2 (20.0)	4 (40.0)	16 (53.3)	9 (30.0)
Cardiac embolic	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Unknown	1 (10.0)	3 (30.0)	1 (3.3)	3 (10.0)
Laterality				
Ipsilateral‡	3 (30.0)	4 (40.0)	15 (50.0)	7 (23.3)
Contralateral	0 (0.0)	3 (30.0)	1 (3.3)	2 (6.7)
Unknown	0 (0.0)	0 (0.0)	1 (3.3)	4 (13.3)
Severity of stroke				
Nondisabling	1 (10.0)	3 (30.0)	11 (36.7)	6 (20.0)
Disabling	2 (20.0)	3 (30.0)	4 (13.3)	1 (3.3)
Fatal	0 (0.0)	1 (10.0)	1 (3.3)	4 (13.3)
Unknown	0 (0.0)	0 (0.0)	1 (3.3)	2 (6.7)

Data are presented as n (%). CEA indicates carotid endarterectomy; and FU, follow-up.
*Within 30 days after CEA n=1.
†Within 30 days after (new) CEA n=4.
‡Ipsilateral to occluded artery.

but these do not usually study populations with large numbers of unoperated patients who have tight carotid stenosis suitable for surgery.[16–18] Some natural history studies of populations with asymptomatic carotid stenosis have investigated progression of stenosis in the artery contralateral to CEA, but the natural history of severe stenosis is not usually available because so many patients with suitable (≥60% to 70%) stenosis undergo prophylactic endarterectomy leaving only some, who may be less fit for surgery, for long-term follow-up.[7,19–22]

In 1 natural history study of progression of stenosis in carotid artery disease, Lewis found there was a significantly higher risk of stroke or death (risk ratio, 3.0; 95% confidence interval, 1.3–6.7) once stenosis reached 80% stenosis or more.[23] Ballotta[7] followed up carotid stenosis contralateral to CEA and found that progression from moderate (50% to 69%) to severe (70% to 99%) stenosis was strongly associated with transient ischemic attack or stroke, >80% of the neurological events in this study occurring in this group of patients. However, these studies did not concentrate, as we have, on the specific risk of stroke in patients with occlusion.

Patients with ≥80% carotid artery stenosis in other studies were found to be at higher risk (35%; >2 years) of progression to occlusion compared with patients with lesser stenoses.[3,19,24] We also found that patients with ≥70% carotid artery baseline stenosis were more likely to develop occlusion.

Until now, there has been little information about stroke risk in patients with established occlusion. Older studies found that although acute occlusion can cause transient ischemic attack or stroke, once occlusion is established, few further events are recorded, perhaps because of poor follow-up.[4,8,25–28] In our cohort, 17 patients developed an asymptomatic occlusion and had stroke during follow-up. We identified only 3 patients who developed symptomatic occlusion and had recurrent ischemic stroke. In other studies of patients with symptomatic internal carotid artery occlusion, the annual risk of recurrent ischemic stroke is estimated to be 5%.[11,12]

Successful surgical treatment of asymptomatic carotid artery stenosis ≥70% stenosis prevents most of the risk of occlusion. After successful ipsilateral CEA, there was a low (8 of 1325) stroke rate in our patients with new (contralateral) carotid occlusion; other studies had similar findings.[29,30] Lower stroke risk in those who had unilateral surgery might be explained by improved circulation within the circle of Willis, making subsequent contralateral occlusion less hazardous.

There was a small but important risk of occlusion immediately after surgery, an observation consistent with the literature.[31] Most of these occlusions were asymptomatic and remained so over time.

Table 3. Univariate and Multivariate* Analyses of the Association Between Patient-Related Factors and Development of Occlusion

	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age at randomization >75 y	0.92 (0.61–1.38)	0.68		
Sex, men	1.85 (1.33–2.57)	<0.01	1.88 (1.35–2.61)	<0.01
Stenosis ≥70% at randomization	1.45 (0.84–2.49)	0.18	1.58 (0.92–2.73)	0.10
Risk factors				
DM	0.73 (0.48–1.09)	0.12	0.71 (0.47–1.06)	0.10
HT	0.80 (0.59–1.10)	0.17	0.82 (0.60–1.12)	0.21
Prior ischemic heart disease	1.07 (0.79–1.43)	0.67		
Allocated treatment	1.70 (1.28–2.28)	<0.01	1.72 (1.29–2.30)	<0.01

CI indicates confidence interval; DM, diabetes mellitus; HR, hazard ratio; HT, hypertension; and IHD, ischemic heart disease.
*Multivariate analysis is performed with variables proven significant (*P* value <0.20) in univariate analysis.

Some patients who had new asymptomatic occlusion and a stroke during follow-up did not always have tight contralateral carotid stenosis. When occlusion occurs, the territory of subsequent strokes is not always predictable, probably because atherosclerotic arterial disease also affects other smaller arteries, not just those in the main cerebrovascular circulation.[32,33]

Table 4. Univariate and Multivariate* Analyses of the Association Between Patient-Related Factors and Development of Stroke

	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Overall (n=2707)				
Age at randomization >75 y	1.44 (1.07–1.93)	0.02	1.51 (1.12–2.04)	<0.01
Sex, men	1.06 (0.84–1.35)	0.62		
Stenosis ≥70% at randomization	1.02 (0.70–1.48)	0.94		
Risk factors				
DM	1.52 (1.17–1.99)	<0.01	1.58 (1.20–2.06)	<0.01
HT	1.10 (0.84–1.44)	0.48		
Prior IHD	1.17 (0.92–1.49)	0.19	1.15 (0.90–1.45)	0.27
Allocated treatment	1.60 (1.27–2.02)	<0.01	1.54 (1.22–1.95)	<0.01
Occlusion	1.83 (1.30–2.59)	<0.01	1.78 (1.26–2.51)	<0.01
Immediate group (n=1325)				
Age at randomization >75 y	2.09 (1.35–3.23)	<0.01	2.19 (1.41–3.41)	<0.01
Sex, men	1.03 (0.70–1.51)	0.88		
Stenosis ≥70% at randomization	1.03 (0.55–1.92)	0.92		
Risk factors				
DM	1.55 (1.01–2.40)	0.05	1.70 (1.10–2.64)	0.02
HT	1.37 (0.86–2.19)	0.18	1.32 (0.83–2.11)	0.24
Prior IHD	1.28 (0.87–1.88)	0.21		
Occlusion	1.69 (0.89–3.24)	0.11	1.98 (1.03–3.82)	0.04
Deferral group (n=1382)				
Age at randomization >75 y	1.09 (0.72–1.64)	0.68		
Sex, men	1.09 (0.80–1.47)	0.59		
Stenosis ≥70% at randomization	1.02 (0.63–1.63)	0.94		
Risk factors				
DM	1.49 (1.06–2.10)	0.02	1.73 (1.15–2.61)	0.02
HT	0.97 (0.70–1.36)	0.87		
Prior IHD	1.08 (0.80–1.47)	0.60		
Occlusion	1.74 (1.16–2.62)	<0.01	1.73 (1.15–2.60)	<0.01

CI indicates confidence interval; DM, diabetes mellitus; HR, hazard ratio; HT, hypertension; and IHD, ischemic heart disease.
*Multivariate analysis is performed with variables proven significant (*P* value <0.20) in univariate analysis.

More strokes in ACST-1 occurred from carotid vessels that were tightly stenosed than from arteries with acute or chronic occlusions, and in the trial, some of these patients went on to have another stroke.[5] Patients not disabled by their stroke were sometimes able to have CEA, but when stroke is due to occlusion surgery is not possible. In ACST-1 about half of all strokes were disabling or fatal. Surgery to prevent future stroke therefore had limited value for those few patients with a nondisabling stroke and residual significant stenosis.

Our study shows that when occlusion occurs there is almost a 20% risk of stroke; most of this risk is around the time of occlusion, but a small residual risk is still present during longer term follow-up. So, occlusion is a risk factor for ischaemic stroke; men, who did not have an operation have a higher risk of developing occlusion, and diabetics and patients with established occlusion have a higher risk of future stroke.

In this study, the group developing occlusion was relatively small, but it is much larger than in any previous study. Analysis of adherence to medical management as a possible risk factor for occlusion would be inappropriate for this number of patients because most were on long-term antithrombotic and antihypertensive therapy, and the use of lipid-lowering therapy increased rapidly during the trial.

Conclusion

New carotid occlusions were infrequent in this cohort of asymptomatic patients (≈1% to 2% per year). Long-term follow-up shows that occlusion and stroke were commoner in patients who did not undergo CEA or in whom there was a stenosis of ≥70% stenosis before occlusion. Occlusion is an independent prognostic risk factor for the occurrence of stroke. This analysis improves our understanding of the natural history of operated and unoperated severe carotid artery disease and should enable clinicians to explain more clearly to patients with severe stenosis the future risks of carotid artery occlusion and subsequent stroke.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL:

APPENDIX:

ACST-1 Collaborative Group:

Austria (30 patients): Innsbruck (G Fraedrich, C Schmidauer); Vienna (TH Hölzenbein, I Huk, M Haumer, G Kretschmer, V Metz, P Polterauer, H. Teufelsbauer). Belgium (1 patient): Antwerp (P Cras, J Hendriks, P Lauwers, P Van Schil). Brazil (2 patients): Natal (E Barreto de Souza, M Emilio Dourado, G Gurgel, G Myrian Rocha). Bulgaria (6 patients): Sofia (V Petrov, G Slabakov [deceased]). Canada (30 patients): Halifax (ME Cooper, G Gubitz, R Holness, W Howes, R Langille, K Legg, S Nearing, G MacKean, M MacKay, SJ Phillips, J Sullivan, J Wood). Croatia (2 patients): Zagreb (L Erdelez, T Sosa [deceased]). Cyprus (13 patients): Nicosia (NS Angelides, G Christopoulos A Malikidou, A. Pesta). Czech Republic (18 patients): Pilzen (Z Ambler, J Mracek, J Polivka, V Rohan, P Sevcik, J Simaná); Prague (V Beneš, F Kramár). Finland (18 patients): Helsinki (M Kaste, M Lepäntalo, L Soinne). France (2 patients): Nimes (J-M Cardon, A Legalou). Germany (98 patients): Augsburg (B Gengenbach, K Pfadenhauer, KD Wölfle); Berlin (I Flessenkämper, BF Klumpp, J Marsch); Düsseldorf (R Kolvenbach, T Pfeiffer, W Sandmann); Freiburg (F Beyersdorf, A Hetzel, K Sarai, J Schöllhorn, G Spillner); Giessen (HJ Lutz); Heidelberg (D Böckler, N Maeder); Minden (O Busse, J Grönniger, F Haukamp); Mülheim an der Ruhr (K Balzer, HG Knoob, G Roedig, L Virreira); Würzburg (S Franke, R Moll, J Schneider). Greece (10 patients): Athens (J Dayantas, MN Sechas, S Tsiaza); Thessaloniki (D Kiskinis). Hungary (59 patients): Budapest (A Apor, C Dzinich, L Entz, K Hüttl, Z Jàrànyi, I Mogan, Z Nagy, A Szabo, D Varga); Miskolc (G Juhász, L Mátyás). Ireland (7 patients): Dublin (M Hutchinson, D Mehigan). Israel (245 patients): Ashkelon (Z Aladjem, E Harah, S Elmakias, D Gurvich , B Yoffe,); Haifa (H Ben-Meir, L Dagan, R Karmeli, G Keren, A Shimony, B Weller); Petach Tikva (R Avrahami, A Koren, JY Streifler, S Tabachnik, A Zelikovski). Italy (328 patients): Bari (D Angiletta, F Federico, G Impedovo, V Marotta, L Pascazio, G Regina); Bologna (A Andreoli, E Pozzati); Brescia (S Bonardelli, SM Giulini, B Guarneri); Caserta (P Caiazzo); Ferrara (F Mascoli); Genova (G Becchi, R Masini, E Santoro, G Simoni); L'Aquila (L Cucciolillo, C Di Girolamo, E Franceschini, E De Negeli C Spartera, C Petrassi, P Scarpelli, M Ventura); Milano (O Arena, M Collice, M Puttini, F Romani, I Santilli , V Segramora, R Sterzi); Padova (G Deriu, F Verlato); Perugia (PG Cao, E Cieri, P De Rango, L Moggi, S Ricci); Pescara (A Antico, F Spigonardo); Reggio Emilia (G Malferrari, N Tusini, E Vecchiati,); Rome (A Cavallaro, H Kasemi, M Mario, E Sbarigia, F Speziale); Savona (N Zinicola [deceased]); Torrette di Ancona (FP Alò, M Bartolini, L Carbonari, S Caporelli, C Grili-Cicilioni, G Lagalla, G Ioannidis, G Pagliariccio, M Silvestrini); Torino (D Palombo, F Peinetti); Trieste (R Adovasio, F Chiodo-Grandi, G Mase, F Zamolo); Udine (V Fregonese, N Gonano, L Mozzon). New Zealand (10 patients): Hamilton (R Blair, J Chuen, D Ferrar, M Garbowski, MJ Hamilton C Holdaway, S Muthu, F Shakibaie, TM Vasudevan). Norway (47 patients): Oslo (A Kroese, CE Slagsvold); Trondheim (T Dahl, HJ Johnsen, C Lange, HO Myhre). Poland (88 patients): Katowice (J Gniadek); Warsaw (P Andziak, M Elwertowski, J Leszczynski, A K Malek, J Mieszkowski, W Noszczyk, M Szostek, S Toutounchi). Portugal (13 patients): Porto (C Correia, MC Pereira). Russia (10 patients): Moscow (RS Akchurin). Slovenia (44 patients): Maribor (V Flis, K Miksic, B Stirn, E Tetickovic). Spain (196 patients): Barcelona (M Cairols, JM Capdevila, E Iborra-Ortega, V Obach, V Riambau, F Vidal-Barraquer, R Vila-Coll); Coruna (E Diaz-Vidal, JI Iglesias-Negreia, A Tovar-Pardo, RJ Segura Iglesias); Galdakao (AF Alfageme, A Barba-Velez, L Estallo-Laliena, JC Garcia-Monco, L Rodriguez Gonzalez); Palma (C Corominas, J Julia, P Lozano); San Sebastian (JF

Marti-Masso, RM Porta [deceased]); Vigo (A Rosendo Carrera, J Gomez). Sweden (532 patients): Göteborg (C Blomstrand, J Gelin, J Holm, L Karlström, E Mattsson); Helsingborg (S Bornhov, J Dahlstrom, G De Pedis, SM Jensen, H Pärsson, G Plate, P Qvarfordt); Kalmar (B Arvidsson, L Brattström, C Forssell, A Potemkowski [deceased], C Skiöldebrand, P Stoor); Linköping (M Blomqvist, M Calander, C Forssell, F Lundgren); Lund (H Almqvist, L Norgren, B Norrving, E Ribbe, J Thörne); Malmö (A Gottsäter, T Mätzsch, ME Nilsson); Norrkoping (C Forssell, M Lonsson, F Lundgren, B Stahre); Örebro (L Norgren, B Stenberg); Stockholm (P Konrad, L, Jarl, L Lundqvist, P Olofsson, S Rosfors, C Skiöldebrand, J Swedenborg, R Takolander); Uppsala (D Bergqvist, C Ljungman, H Pärsson). Switzerland (6 patients): Bern (HW Kniemeyer, MK Widmer); St Gallen (R Kuster, R Kaiser, W Nagel, D Sege, B Weder). The Netherlands (132 patients): Beverwijk (J De Nie, J Doelman, N Yilmaz); Eindhoven (J Buth, G Stultiens); Geldrop (J Boiten, A Boon, F van der Linden); Leeuwarden (DC Busman); Rotterdam (HAW Sinnige, TI Yo); Utrecht (GJ de Borst, BC Eikelboom, LJ Kappelle, F Moll, RWH van Reedt Dortland, TE Westra). Tunisia (11 patients): Montfleury (H Jaber, J Manaa, RB Meftah, BR Nabil, T Sraieb). United Kingdom (1069 patients): Bath (D Bateman, J Budd, M Horrocks, M Kivela, L Shaw, R Walker); Belfast (AAB Barros D'Sa [deceased], K Fullerton, R Hannon, J M Hood, B Lee, K McGuigan, J Morrow, J Reid, CV Soong [deceased]); Birmingham (M Simms); Bristol (R Baird, M Campbell, S Cole, IT Ferguson, P Lamont, D Mitchell, A Sassano, FCT Smith); Cambridge (K Blake, PJ Kirkpatrick, P Martin, C Turner); Cheshire (JF Clegg, M Crosley, J Hall); Chester (L De Cossart, P Edwards, D Fletcher, S Rosser); Dundee (PT McCollum, D Davidson, R Levison); Edinburgh (AW Bradbury, RTA Chalmers, M Dennis, J Murie, CV Ruckley, P Sandercock); Exeter (WB Campbell, T Frankel, C Gardner-Thorpe, N Gutowski, R Hardie, W Honan, P Niblett, A Peters, B Ridler, JF Thompson); Glasgow (I Bone, G Welch); Hereford (E C Grocott, P Overstall); Huddersfield (MI Aldoori, BEA Dafalla); Hull (J Bryce, C Clarke, PT McCollum, A Ming, AR Wilkinson); Leeds (J Bamford, D Berridge, J Scott); Leicester (RJ Abbott, R Naylor); Liverpool (P Harris, P Humphrey); London (M Adiseshiah, M Aukett, D Baker, CCR Bishop, A Boutin, M Brown, P Burke, KG Burnand, A Colchester, L Coward, AH Davies, M Espasandin, AEB Giddings, G Hamilton, M Harrison, C Judge, S Kakkos, A Mansfield, C McGuiness, P Morris-Vincent A Nicolaides, TS Padayachee, H Riordan, E Sullivan, P Taylor, D Thomas, M Thompson, JHN Wolfe); Manchester (CN McCollum, PA O'Neill, S Welsh); Newcastle (J Barnes, M Davis, A Gholkar, M Davis, V. Jaykishnam, AD Mendelow, JE O'Connell, MSS Siddique, G Stansby, R Vivar); Plymouth (S Ashley, C Cosgrove, J Gibson, DC Wilkins,); Southampton (ADB Chant, J Frankel, CP Shearman, J Williams); Stirling (G Hall, R Holdsworth); Truro (JN Davies, B McLean, KR Woodburn); Wakefield (G Brown, P Curley, L Loizou). USA (16 patients): Detroit (S Chaturvedi, F Diaz). Yugoslavia (77 patients): Belgrade (D Radak, PR Todorovic).

Risk of Stroke From New Carotid Artery Occlusion in the Asymptomatic Carotid Surgery Trial-1

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