Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial

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Lancet Neurol 2009; 8: 908–17

Published Online August 29, 2009 DOI:10.1016/S1474-4422(09)70227-3

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Summary

Background In the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), early recurrent carotid stenosis was more common in patients assigned to endovascular treatment than it was in patients assigned to endarterectomy (CEA), raising concerns about the long-term effectiveness of endovascular treatment. We aimed to investigate the long-term risks of restenosis in patients included in CAVATAS.

Methods 413 patients who were randomly assigned in CAVATAS and completed treatment for carotid stenosis (200 patients had endovascular treatment and 213 patients had endarterectomy) had prospective clinical follow-up at a median of 5 years and carotid duplex ultrasound at a median of 4 years. We investigated the cumulative long-term incidence of carotid restenosis after endovascular treatment and endarterectomy, the effect of the use of stents on restenosis after endovascular treatment, risk factors for the development of restenosis, and the effect of carotid restenosis on the risk of recurrent cerebrovascular events. Analysis was by intention to treat. This study is registered, number ISRCTN01425573.

Findings Severe carotid restenosis (≥70%) or occlusion occurred significantly more often in patients in the endovascular arm than in patients in the endarterectomy arm (adjusted hazard ratio [HR] 3·17, 95% CI 1·89–5·32; p<0·0001). The estimated 5-year incidence of restenosis was 30·7% in the endovascular arm and 10·5% in the endarterectomy arm. Patients in the endovascular arm who were treated with a stent (n=50) had a significantly lower risk of developing restenosis of 70% or greater compared with those treated with balloon angioplasty alone (n=145; HR 0·43, 0·19–0·97; p=0·04). Current smoking or a history of smoking was a predictor of restenosis of 70% or more (2·32, 1·19–4·54; p=0·01) and the early finding of moderate stenosis (50–69%) up to 60 days after treatment was associated with the risk of progression to restenosis of 70% or more (3·76, 1·88–7·52; p=0·0002). The composite endpoint of ipsilateral non-perioperative stroke or transient ischaemic attack occurred more often in patients in whom restenosis of 70% or more was diagnosed in the first year after treatment compared with patients without restenosis of 70% or more (5-year incidence 23% *vs* 11%; HR 2·18, 1·04–4·54; p=0·04), but the increase in ipsilateral stroke alone was not significant (10% *vs* 5%; 1·67, 0·54–5·11).

Interpretation Restenosis is about three times more common after endovascular treatment than after endarterectomy and is associated with recurrent ipsilateral cerebrovascular symptoms; however, the risk of recurrent ipsilateral stroke is low. Further data are required from on-going trials of stenting versus endarterectomy to ascertain whether long-term ultrasound follow-up is necessary after carotid revascularisation.

Funding British Heart Foundation; UK National Health Service Management Executive; UK Stroke Association.

Introduction

Atherosclerotic carotid artery stenosis is a main cause of transient ischaemic attack and stroke. In patients with recent cerebrovascular symptoms associated with severe carotid stenosis, the risk of recurrent stroke can be reduced by more than a half after carotid endarterectomy.[1] Endovascular treatment of carotid stenosis by percutaneous transluminal balloon angioplasty or insertion of a stent is an alternative to endarterectomy. However, a recent meta-analysis found a higher risk of stroke or death within 30 days after endovascular treatment than after endarterectomy, with some uncertainty about this result, and endarterectomy has remained the treatment of choice for carotid stenosis.[2]

The long-term efficacy of endovascular treatment for preventing stroke is unknown. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was a large multicentre randomised trial with the aim of comparing endovascular treatment (angioplasty with or without stenting) with endarterectomy in patients with predominantly symptomatic moderate or severe carotid stenosis.[3] The initial report from CAVATAS showed no difference in the primary endpoint of disabling stroke or death, or in ipsilateral stroke in the first 3 years after

treatment. However, 1 year after treatment, severe stenosis or occlusion of the carotid artery was seen more often after endovascular treatment than after endarterectomy.[4] Concern remained that the proportion of patients with restenosis after endovascular treatment would increase over time and that the high rate of restenosis might restrict the long-term efficacy of endovascular treatment for stroke prevention.

The long-term follow-up of patients in CAVATAS has recently been completed, 10 years after the last patient was randomised. In the analysis of clinical outcome events, which is reported in this issue,[5] there was a non-significant difference in the incidence of ipsilateral non-perioperative stroke or TIA that favoured endarterectomy (hazard ratio 1·29, 95% CI 0·78–2·14).

In this follow-up study, we analysed the available long-term carotid ultrasound data from CAVATAS with the following aims: to compare the cumulative long-term incidence of carotid restenosis after endovascular treatment and endarterectomy; to investigate the effect of the use of stents on restenosis after endovascular treatment; to identify risk factors for the development of restenosis; and to investigate the effect of carotid restenosis on the risk of recurrent cerebrovascular events.

Methods

Patients

CAVATAS was a randomised, open, multicentre trial with outcome adjudication by investigators masked to treatment allocation. The trial methodology has been described in detail in the initial report.[3] For the present study, we selected patients who had completed endovascular treatment or endarterectomy of the stenotic internal carotid artery and had follow-up data from carotid duplex ultrasound. The study population differs from that in a previous report on residual and early recurrent stenosis in CAVATAS, which was restricted to ultrasound examinations done 1 month and 1 year after treatment and included both patients who had completed treatment and those with incomplete treatment.[4] A few patients with stenosis of the common carotid artery were enrolled in CAVATAS, but these patients were excluded from this analysis owing to the absence of uniform criteria for grading stenosis of the common carotid artery with ultrasound.

Procedures

In the first phase of the study, patients randomly assigned to endovascular treatment were treated by percutaneous transluminal angioplasty with balloon catheters. Stents became available in the second half of the recruitment period; collaborating interventionalists were subsequently permitted to use Wallstents, Palmaz, and Strecker stents at their discretion. Stents were most commonly deployed if the reduction in stenosis achieved with previous balloon angioplasty was unsatisfactory. In a few patients, primary stenting was done without first attempting full balloon dilatation. Endovascular treatment was defined as complete if a balloon was dilated across the stenosis or a stent was successfully deployed.[3] Collaborating surgeons used their preferred technique for endarterectomy, either with primary closure of the arteriotomy or closure with surgical patches. Completed endarterectomy was defined as an operation in which removal of the atheromatous plaque and closure of the arteriotomy was achieved.

The protocol recommended endovascular or surgical treatment for recurrent stenosis after initial treatment only if the patient developed relevant new symptoms. Asymptomatic restenosis was not deemed an indication for re-treatment because the risk of recurrent cerebrovascular events after restenosis was unknown. No recommendation as to the type of retreatment (endovascular or endarterectomy) was made.

Patients in CAVATAS were examined at baseline by neurologically trained investigators not involved in the endovascular treatment or endarterectomy and followed up at 1 month, 6 months, and 1 year after treatment and annually thereafter. There was no predefined maximum length of follow-up, but centres were encouraged to follow up patients for as long as the centre and individual patients were willing to do so. Follow-up ended in 2007, 10 years after the end of recruitment. Outcome events, including stroke, transient ischaemic attack, and amaurosis fugax, were independently adjudicated by use of standard definitions[5] in the central trial office by two investigators (LHB and JE) who were masked to treatment allocation. Amaurosis fugax was included in the category of transient ischaemic attack. In case of disagreement, a third independent investigator made the final adjudication.

Carotid imaging before randomisation required either selective digital subtraction angiography (DSA) or consistent findings on carotid duplex ultrasound and non-invasive angiography (magnetic resonance angiography [MRA] or computer tomography angiography [CTA]). Assessment of the rate of restenosis after treatment was a predefined objective of CAVATAS. The protocol included carotid duplex ultrasound follow-up 1 year after treatment and every year thereafter. In many centres, additional ultrasound examinations were done at 1 and 6 months after treatment. In the event of recurrent cerebrovascular events during follow-up, additional carotid imaging was done at the discretion of the local investigators.

The peak systolic velocities of the common carotid and the internal carotid arteries and the end diastolic velocity of the internal carotid artery were recorded with carotid duplex ultrasound and reported to the central trial office. One investigator (LHB), who was masked to treatment allocation, ascertained the degree of stenosis during follow-up, on the basis of predefined, standardised flow velocity criteria, which equate well with the severity of carotid stenosis measured on catheter angiography with the North American Symptomatic Carotid Endarterectomy

	PSV ICA (m/s)	EDV ICA (m/s)	PSV ICA/PSV CCA
0–29%	<1·1	<0·4	<3·2
30–49%	1·1–1·3	<0·4	<3·2
50–59%	>1·3–2·1	<0·4	<3·2
60–69%	>1·3–2·1	0·4–1·1	3·2–4·0
70–79%	>2·1	>1·1–1·4	>4·0
80–95%	>2·1	>1·4	>4·0
96–99%	String flow	String flow	String flow
100%	Occluded	Occluded	Occluded

PSV=peak systolic velocity. ICA=internal carotid artery. EDV=end diastolic velocity. CCA=common carotid artery. NASCET=North American Symptomatic Carotid Endarterectomy Trial.

Table 1: **Duplex ultrasound velocity criteria equivalent to NASCET angiography measures used for grading the degree of carotid stenosis**

Trial (NASCET) method (table 1).[4,6] The severity of stenosis seen on carotid angiography (MRA, CTA, or DSA) done in addition to ultrasound for recurrent symptoms was measured according to the NASCET method. A second investigator made the final classification of stenosis when measurements from more than one imaging modality were conflicting. Stenosis was classified as: not significant (0–49% stenosis), moderate (50–69%), severe (70–99%), or occluded (100%). Velocity measurements were not available for a few centres, and the degree of stenosis reported by the local ultrasonographer at the participating centre was used in these cases.

The primary outcome of this analysis (≥70% restenosis) was defined as any residual or recurrent severe stenosis or occlusion of the carotid artery detected at any stage during follow-up after completed treatment. The secondary outcome (≥50% restenosis) was defined as any residual or recurrent moderate or severe carotid stenosis or occlusion after completed treatment. We compared the incidence of the primary and secondary outcomes between patients randomly assigned to endovascular treatment versus endarterectomy and between patients who were treated with balloon angioplasty alone (without use of a stent) and patients treated with a stent in those randomly assigned to endovascular treatment. Because the use of stents was not randomised in CAVATAS, the analysis of patients treated with stents and those treated with balloon angioplasty is a comparison of two subsets of patients in the endovascular treatment arm and is based on post-randomisation information (ie, which endovascular treatment technique the patient actually received).

We investigated whether the following baseline characteristics were independently associated with restenosis of 70% or more: age at randomisation, sex, smoking, hypertension, hypercholesterolaemia, diabetes, history of coronary heart disease, history of peripheral vascular disease, and the degree of ipsilateral carotid stenosis at randomisation according to the NASCET method. In a separate analysis, we assessed whether the moderate (50–69%) residual or early recurrent stenosis diagnosed up to 60 days after treatment was associated with long-term risk of restenosis of 70% or more.

To assess the association between restenosis and recurrent cerebrovascular events during long-term follow-up, we compared the incidence of the composite endpoint of ipsilateral stroke or transient ischaemic attack, and only ipsilateral stroke between patients with and without 70% or more restenosis diagnosed in the first year after treatment. Only cerebrovascular events that occurred after the first 1-year carotid duplex ultrasound that confirmed 70% or more restenosis or less than 70% restenosis were included. Events that occurred within 30 days of initial treatment were excluded because they were defined as perioperative complications of treatment. To ascertain the natural risk of cerebrovascular events with restenosis, patients who had endovascular treatment or endarterectomy for recurrent stenosis after their initial treatment were censored at the time of retreatment.

Statistical analysis

Data analysis was primarily done according to the randomly assigned treatment (intention to treat). A second, per-protocol analysis, which excluded patients who did not receive their assigned treatment, was also done. The incidence of restenosis after stenting compared with angioplasty alone could only be calculated from the per-protocol analysis. To check whether the length of carotid duplex ultrasound follow-up was similar in both treatment arms, the time to censoring was compared by use of the log-rank test. When comparing the risks of 70% or more and 50% or more restenosis between the treatment groups, the exact date of restenosis was not known (ie, restenosis was only known to have occurred at some point between the previous normal ultrasound and the examination at which restenosis was diagnosed). Data in this form are known as interval-censored data and require appropriate analysis methods. Because the scheduled ultrasound examinations did not always take place at the planned times, and because some patients missed their scheduled appointments, an analysis method in which observation times can differ among individuals was used.[7] This method assumes proportional hazards and is based on a non-linear model for a set of binary response variables (a generalised non-linear model). The resulting parameter estimates, such as the treatment effect estimate, can be interpreted as log hazard ratios. For these models, patients without restenosis were censored at the time of their last carotid duplex ultrasound. Censoring was assumed to be non-informative. The proportionality of hazards was assessed by interactions with follow-up time periods. There was some suggestion that the hazard ratio of endovascular treatment versus carotid endarterectomy for the 50% or greater restenosis outcome might decrease over the course of the study, but

the test for non-proportionality of hazards was not significant (p=0·1). The hazard ratios and their 95% CIs throughout the follow-up period are reported. Life-table analyses were used to estimate the cumulative incidences of restenosis at the scheduled examination times after treatment, with predefined interest in the incidences at 1 year and 5 years. For the patients diagnosed with restenosis who were missing from the previous scheduled ultrasound examination, restenosis was assumed to have occurred during the life-table interval, half way between diagnosis and the last available normal ultrasound examination. Cumulative incidences for later than 5 years after treatment were not calculated because the patients who continued to have ultrasound follow-up was small. Multivariable generalised non-linear models that were adjusted for treatment were used to test whether 70% or more restenosis during follow-up was associated with the above defined baseline covariates and early 50–69% stenosis. Hazard ratios calculated for restenosis were adjusted for age, sex, and the independent baseline predictors of restenosis identified in the multivariable model. Cox regression analysis was used to compare time until ipsilateral cerebrovascular events between patients with and without 70% or more restenosis detected within the first year after treatment (including ultrasound examinations done up to 1·5 years after treatment because the scheduled 1-year examinations did not always take place exactly 1 year after treatment) and were adjusted for allocated treatment, age, and sex. This study is registered, number ISRCTN01425573.

Role of the funding source

The study sponsors had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 1, 1992, and July 31, 1997, 504 patients were randomly assigned to endovascular treatment (n=251) or endarterectomy (n=253) by telephone or fax from the randomisation service at the Oxford Clinical Trials Unit. Figure 1 shows the trial profile. Of the patients randomly assigned to endovascular treatment, 240 had initial treatment as allocated, six crossed over to endarterectomy, and five received neither endovascular treatment nor endarterectomy. Among the patients randomly assigned to endarterectomy, 246 received the treatment they were assigned, two crossed over to endovascular treatment, and five received neither of the two treatments. Endovascular treatment was not

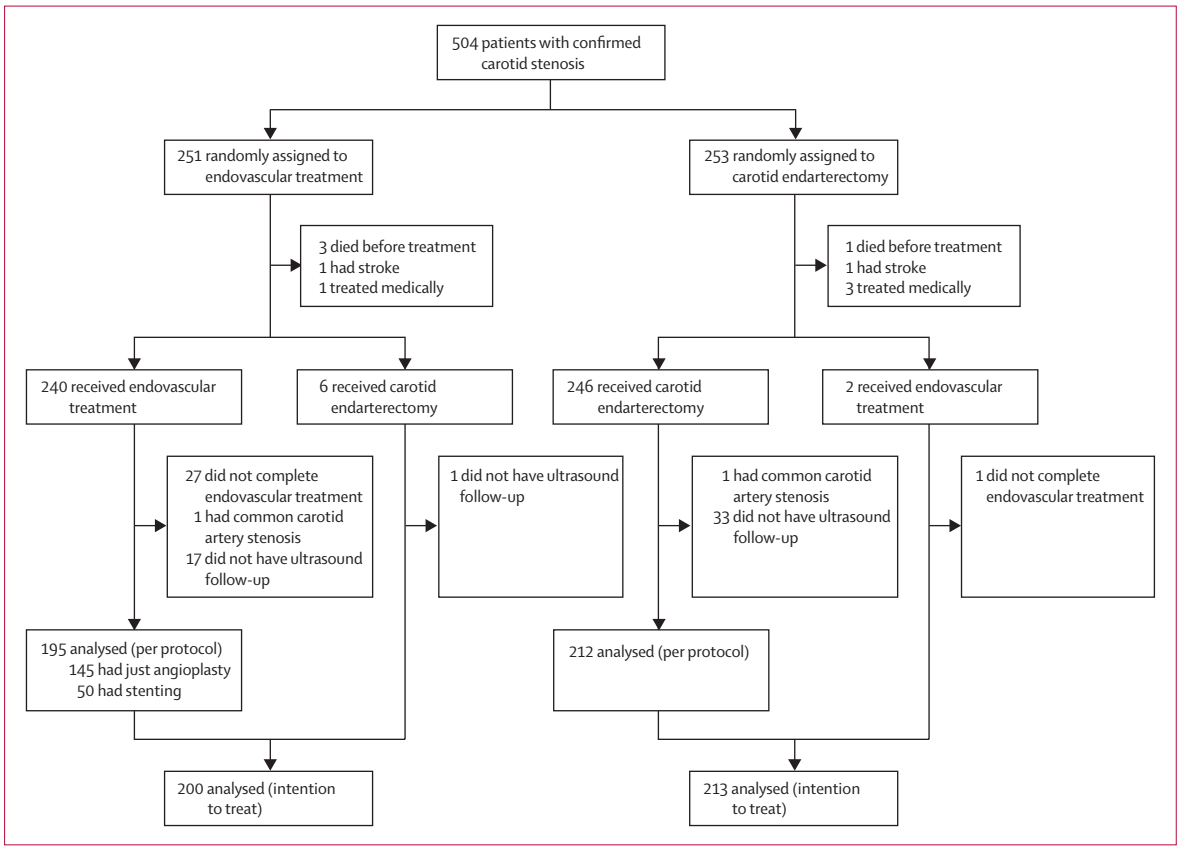

Figure 1: **Trial profile**

	CAVATAS all patients (n=504)	CAVATAS analysis of restenosis (n=413)*	EVT (n=200)*	EVT by stenting (n=50)†	EVT by angioplasty alone (n=145)†	CEA (n=213)*
Age (years)	67·0 (8·4)	67·0 (8·4)	66·5 (8·5)	66·6 (9·2)	66·6 (8·1)	67·4 (8·3)
Men	352 (70%)	286 (69%)	142 (71%)	33 (66%)	104 (72%)	144 (68%)
Vascular risk factors						
Smoking (past or present)	383 (76%)	307 (74%)	151 (76%)	36 (72%)	114 (79%)	156 (73%)
History of hypertension	276 (55%)	224 (54%)	103 (52%)	24 (48%)	77 (53%)	121 (57%)
History of hypercholesterolaemia	129 (26%)	107 (26%)	53 (27%)	13 (26%)	40 (28%)	54 (25%)
History of diabetes	67 (13%)	57 (14%)	28 (14%)	8 (16%)	20 (14%)	29 (14%)
History of coronary heart disease	187 (37%)	155 (38%)	78 (39%)	19 (38%)	57 (39%)	77 (36%)
History of peripheral vascular disease	111 (22%)	86 (21%)	42 (21%)	4 (8%)‡	38 (26%)‡	44 (21%)
Ipsilateral cerebrovascular events within 6 months before randomisation	452 (90%)	394 (95%)	192 (96%)	48 (96%)	139 (96%)	202 (95%)
Mean degree of ipsilateral carotid stenosis before treatment§	77·2% (14·2)	76·8% (14·3)	77·0% (14·2)	77·3% (12·1)	76·8% (15·1)	76·6% (14·5)
Median duration of clinical follow-up (years)	5·0 (2·6–6·1)	5·0 (2·9–6·1)	5·0 (3·0–6·2)	5·0 (2·2–6·5)	5·0 (3·0–6·1)	5·0 (2·9–6·1)
Median duration of ultrasound follow-up (years)	..	4·0 (1·8–5·5)	4·0 (1·9–5·4)	3·2 (1·0–5·3)	4·0 (2·0–5·4)	4·1 (1·3–5·5)

Data are mean (SD), number (%), or median (IQR) at the time of randomisation. EVT=endovascular treatment. CEA=carotid endarterectomy. ..=not available. *Numbers are intention-to-treat analysis of restenosis of patients randomly assigned to endovascular therapy versus patients randomly assigned to endarterectomy. †Numbers are non-randomised per-protocol comparison of restenosis of patients who received endovascular treatment by stenting versus patients who received endovascular treatment by angioplasty alone. ‡p<0·005. §Degree of stenosis measured on angiography at study entry according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) method.[6]

Table 2: **Clinical characteristics**

completed in 27 of the patients assigned to this treatment and in one patient who was allocated to endarterectomy but crossed over to the other treatment arm. Endarterectomy was completed in each patient who had surgery. The reasons for not receiving the randomly allocated treatment or for incomplete treatment were specified in the initial report.[3] One patient in each treatment arm was treated for stenosis of the common carotid artery and was thus excluded from the present analysis. Among the patients who completed treatment, 18 patients in the endovascular group and 33 patients in the endarterectomy group did not have carotid duplex ultrasound follow-up. Therefore, the intention-to-treat analysis of those patients who completed treatment comprised 200 patients who had endovascular treatment and 213 patients who had endarterectomy; the per-protocol analysis comprised 195 patients treated with the endovascular approach (angioplasty alone n=145; stenting n=50) and 212 patients treated with endarterectomy.

	Endovascular treatment (n=200)	Endarterectomy (n=213)
≥70% restenosis		
Number of patients with outcome	53	20
Cumulative 1-year incidence*	21·7% (3·0)	7·5% (1·9)
Cumulative 5-year incidence*	30·7% (3·7)	10·5% (2·4)
Unadjusted hazard ratio†	3·14, 1·87–5·26‡	
Adjusted hazard ratio†	3·17, 1·89–5·32‡	
≥50% restenosis		
Number of patients with outcome	109	59
Cumulative 1-year incidence*	48·5% (3·6)	20·7% (2·9)
Cumulative 5-year incidence*	58·6% (3·9)	31·5% (3·5)
Unadjusted hazard ratio†	2·57, 1·87–3·53‡	
Adjusted hazard ratio†	2·58, 1·87–3·55‡	

Data are number, cumulative incidence (SE), or hazard ratio, 95% CI. *Cumulative incidence of restenosis estimated from life-table analysis. †Restenosis after endovascular treatment compared with carotid endarterectomy to the end of available follow-up (generalised non-linear model: unadjusted and adjusted for sex, age, and smoking). ‡p<0·0001.

Table 3: **Carotid restenosis after endovascular treatment compared with endarterectomy**

Baseline clinical characteristics of patients included in the present analysis of restenosis were similar to the whole population of CAVATAS and there were no significant differences between those assigned to endovascular treatment and those assigned to endarterectomy (table 2). More than 90% of patients had a cerebrovascular event in the territory of the ipsilateral carotid artery within 6 months before randomisation. The duration of the carotid duplex ultrasound follow-up (median 4·0 [IQR 1·9–5·4] years in the endovascular arm *vs* 4·1 [1·3–5·5] years in the surgery arm) and clinical follow-up (5·0 [3·0–6·2] years *vs* 5·0 [2·9–6·1] years) were similar in the two arms, and there was no evidence of a difference in time to censoring (log rank p=0·9). In the endovascular arm, patients who were treated with stenting were less likely to have a history of peripheral vascular disease than were patients treated with angioplasty alone (4 of 50 [8%] *vs* 38 of 145 [26%]; p=0·005). Other clinical characteristics were similar between the two endovascular treatment subgroups.

The primary outcome (≥70% restenosis) occurred significantly more often in patients who had endovascular treatment than in patients who had endarterectomy (53 *vs* 20 patients [adjusted HR 3·17, 95% CI 1·89–5·32;

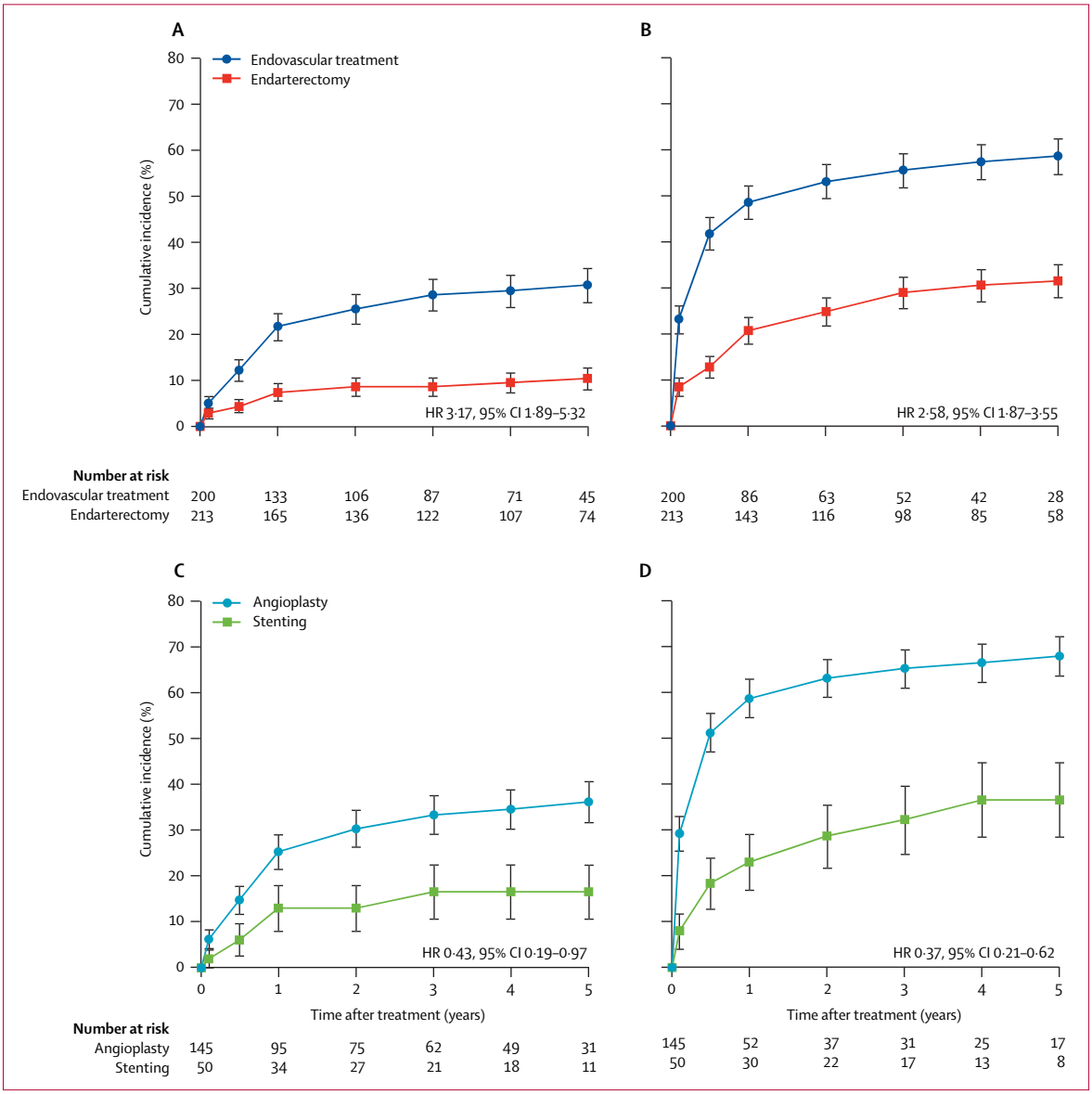

Figure 2: **Cumulative incidence of restenosis estimated from life-table analysis**
Data are the cumulative incidence of restenosis after endovascular treatment compared with endarterectomy (A,B), and for stenting compared with balloon angioplasty alone (C,D), respectively, to the end of available follow-up, from generalised non-linear models. (A,C) 70% or more restenosis. (B,D) 50% or more restenosis. Vertical bars are SE.

p<0·0001]; table 3, figure 2). 1 and 5 years after treatment, the cumulative incidences of 70% or greater restenosis were 21·7% (SE 3·0) and 30·7% (3·7), respectively, in the endovascular arm and 7·5% (1·9) and 10·5% (2·4), respectively, in the surgery arm.

The secondary outcome (≥50% restenosis) also occurred more frequently in the endovascular arm than in the surgery arm (109 *vs* 59; adjusted HR 2·58, 95% CI 1·87–3·55; p<0·0001). The cumulative 1-year and 5-year incidences of 50% or more restenosis were 48·5% (SE 3·6) and 58·6% (3·9), respectively, in the endovascular arm, compared with 20·7% (2·9) and 31·5% (3·5), respectively, in the endarterectomy group.

Similar results were obtained in the secondary per-protocol analysis: adjusted HR 3·40 (95% CI 2·10–5·77) for 70% or more restenosis and 2·72, (1·97–3·75) for 50% or more restenosis after endovascular treatment compared with endarterectomy.

Of the patients who were assigned to endovascular treatment, the risks of 70% or more restenosis (adjusted HR 0·43, 0·19–0·97; p=0·04) and 50% or more restenosis (0·37, 0·21–0·62; p=0·0003) were significantly lower in those patients treated with a stent than in those treated by angioplasty alone (table 4, figure 2).

Of all the covariates tested at baseline, smoking (either at baseline or in the past) was the only independent predictor

	Stenting (n=50)	Angioplasty (n=145)
≥70% restenosis		
Number of patients with outcome	7	46
Cumulative 1-year incidence*	13·1% (5·0)	25·3% (3·7)
Cumulative 5-year incidence*	16·6% (5·9)	36·2% (4·5)
Unadjusted hazard ratio†	0·41, 0·19–0·92‡	
Adjusted hazard ratio†	0·43, 0·19–0·97§	
≥50% restenosis		
Number of patients with outcome	16	93
Cumulative 1-year incidence*	23·0% (6·1)	58·8% (4·2)
Cumulative 5-year incidence*	36·6% (8·1)	68·1% (4·3)
Unadjusted hazard ratio†	0·36, 0·21–0·61¶	
Adjusted hazard ratio†	0·37, 0·21–0·62‖	

Data are number, cumulative incidence (SE), or hazard ratio, 95% CI. *Cumulative incidence of restenosis estimated from life-table analysis. †Restenosis after stenting compared with balloon angioplasty alone to the end of available follow-up (generalised non-linear model: unadjusted and adjusted for sex, age, and smoking). ‡p=0·03. §p=0·04. ¶p=0·0002. ‖p=0·0003.

Table 4: **Carotid restenosis after endovascular treatment with stenting compared with balloon angioplasty alone**

	≥70% restenosis (n=52)	<70% restenosis (n=344)
Ipsilateral stroke or transient ischaemic attack		
Number of patients with endpoint	10	35
Cumulative 5-year incidence*	22·7% (6·4)	10·9% (1·9)
Unadjusted hazard ratio†	2·19, 1·08–4·43‡	
Adjusted hazard ratio†	2·18, 1·04–4·54§	
Ipsilateral stroke		
Number of patients with endpoint	4	17
Cumulative 5-year incidence*	9·7% (4·7)	5·4% (1·4)
Unadjusted hazard ratio†	1·73, 0·58–5·16¶	
Adjusted hazard ratio†	1·67, 0·54–5·11‖	

Data are number, cumulative incidence (SE), or hazard ratio, 95% CI. *Cumulative incidence of events estimated from Kaplan–Meier analysis. †Cox hazard ratio for ipsilateral cerebrovascular events during follow-up in patients with 70% or more restenosis in the first year after treatment compared with patients with less than 70% restenosis in the first year after treatment to the end of available follow-up: unadjusted and adjusted for treatment, sex, and age. Only events that occurred after the first ultrasound examination to show 70% or more stenosis or less than 70% restenosis are included. ‡p=0·03. §p=0·04. ¶p=0·3. ‖p=0·4.

Table 5: **Ipsilateral non-perioperative cerebrovascular events during follow-up in patients with 70% or more restenosis compared with patients with less than 70% restenosis diagnosed in the first year after treatment**

of 70% or more restenosis (HR 2·32, 95% CI 1·19–4·54; p=0·01 [adjusted for treatment in current or ex-smokers compared with those who never smoked]). There was no significant interaction between treatment and the effect of smoking on restenosis (p=0·86). Residual or recurrent stenosis of between 50–69% seen on early ultrasound at any time up to 60 days after treatment was associated with a significant increase in the risk of subsequent progression to 70% or more restenosis (HR 3·76, 95% CI 1·88–7·52; p=0·0002) compared with 0–49% stenosis seen on early carotid duplex ultrasound, adjusted for treatment. There was no significant interaction between treatment and the effect of early moderate stenosis on progression to severe restenosis or occlusion (p=0·91).

The incidence of ipsilateral non-perioperative stroke or transient ischaemic attack was significantly higher in patients with 70% or more restenosis that was diagnosed within the first year after treatment compared with those who had less than 70% restenosis in the first year. 10 of 52 patients (cumulative 5-year incidence 22·7%) with 70% or more restenosis had subsequent ipsilateral cerebrovascular events compared with 35 of 344 patients (10·9%) with less than 70% restenosis (adjusted HR 2·18, 95% CI 1·04–4·54; p=0·04; table 5, figure 3). In three patients without 70% or more restenosis in the first year who had an ipsilateral cerebrovascular event, carotid duplex ultrasound done after the event detected severe restenosis. There was a higher incidence of ipsilateral stroke in patients with 70% or more restenosis (four patients [9·7%]) compared with patients without 70% or more restenosis (17 patients [5·4%]) but the difference was not statistically significant (1·67, 0·54–5·11; p=0·4).

Seven patients in the endovascular arm had repeat endovascular treatment for restenosis (6 patients who were symptomatic and 1 patient who was asymptomatic). One of these patients had an ipsilateral non-disabling stroke during the procedure. In the endarterectomy arm, one patient had repeat endarterectomy for symptomatic restenosis and one patient had repeat endarterectomy for asymptomatic restenosis; these were done without complications.

Discussion

This study provides several key findings: the long-term risk of developing severe (≥70%) carotid restenosis or occlusion was about three times higher after endovascular treatment than it was after endarterectomy; smoking and moderate residual or early recurrent stenosis were independent predictors of severe carotid restenosis or occlusion during follow-up; and severe carotid restenosis or occlusion was associated with an increased risk of ipsilateral cerebrovascular events during follow-up.

CAVATAS was a large randomised trial to assess the long-term risk of restenosis after revascularisation of symptomatic carotid stenosis. The previous large trials of endarterectomy for symptomatic stenosis (ie, NASCET and the European Carotid Surgery Trial [ECST]) did not include carotid ultrasound follow-up.[6,8] In CAVATAS, 31% of patients in the endovascular group developed severe (≥70%) carotid restenosis or occlusion by the fifth year after treatment compared with only 11% of the patients treated with endarterectomy. The secondary outcome (moderate or worse [≥50%] restenosis) was estimated to occur in 59% of patients in the first 5 years after endovascular treatment compared with 32% of patients in the first 5 years after endarterectomy. The cumulative long-term incidence of restenosis seen in the endarterectomy arm of CAVATAS was similar to that seen in case series, in which incidences of up to 9% for severe restenosis or occlusion at 5 years and up to 32%

for moderate or worse restenosis at 7 years after treatment were reported.[9–12]

Most of the patients randomly assigned to endovascular treatment in CAVATAS had angioplasty without stents. In the endovascular arm, the long-term incidences of 70% or more and 50% or more restenosis were lower after stenting than they were after balloon angioplasty alone. However, restenosis among patients who had a stent in CAVATAS was still more common than it was in case series of primary stenting, which have reported moderate restenosis in up to 16% of patients and severe restenosis in 6% of patients at 5 years.[13–15] This might indicate better ascertainment of the restenosis outcome within the context of a clinical trial and highlights differences in patient selection, stenting technique (in CAVATAS, most stenting procedures were done after balloon dilatation was attempted), and ultrasound criteria for grading restenosis. Our study therefore provides some evidence that stenting might be superior to angioplasty alone for the prevention of restenosis. The investigators in one trial that compared primary stenting with endarterectomy have published the incidence of carotid restenosis after a comparatively short follow-up period: the 2-year cumulative risk of severe restenosis or occlusion was 11% after stenting compared with 5% after endarterectomy.[16] Long-term follow-up data on restenosis from recent trials of primary stenting versus endarterectomy are needed to assess the long-term efficacy of carotid stenting for the prevention of restenosis.[17–19]

Restenosis up to about 2 years after endarterectomy is commonly attributed to neointimal hyperplasia, whereas recurrent atherosclerosis is thought to cause later restenosis.[20–22] Neointimal hyperplasia and smooth muscle cell proliferation have also been seen in a patient in CAVATAS who had symptomatic restenosis after endovascular treatment.[23] This observation, and the fact that in both arms of CAVATAS most restenoses occurred within the first year of treatment, suggests that similar mechanisms are involved in restenosis after endovascular treatment and endarterectomy.

We found that smoking at study entry or past smoking was an independent predictor of restenosis. There was no significant interaction between treatment received and smoking for the prediction of restenosis, suggesting that smoking had a similar effect in both treatment arms. Smoking has previously been indentified as a predictor of restenosis after endarterectomy.[21] Smoking did not predict restenosis after carotid stenting in previous case series,[24–26] but these studies had median follow-up times of only 2 years or less. Additionally, patients in whom moderate residual or early recurrent stenosis was found within 60 days of treatment were at significantly elevated risk for progression to severe restenosis or occlusion during follow-up compared with patients without significant early stenosis. These observations might be helpful when selecting patients for long-term ultrasound follow-up.

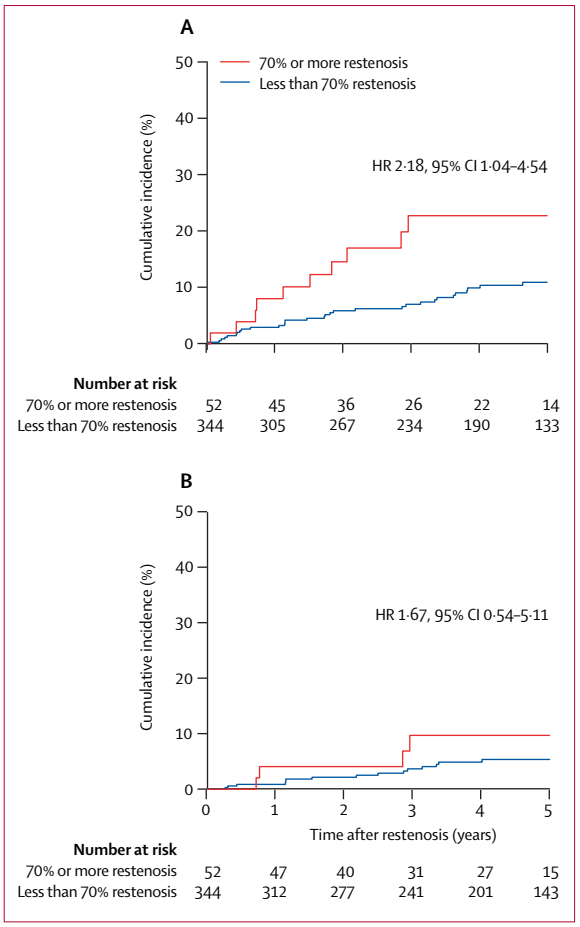

Figure 3: **Kaplan–Meier estimates of ipsilateral stroke or transient ischaemic attack**

(A) Ipsilateral stroke or transient ischaemic attack. (B) Ipsilateral stroke. Hazard ratio calculated from adjusted Cox hazard ratio for ipsilateral cerebrovascular events during follow-up in patients with 70% or more restenosis in the first year after treatment compared with patients with less than 70% restenosis in the first year after treatment to the end of available follow-up. Time is from the first ultrasound examination done within the first year after treatment that confirmed 70% or more restenosis or less than 70% restenosis.

Severe carotid restenosis or occlusion diagnosed within the first year after treatment was associated with an increased risk of subsequent ipsilateral cerebrovascular events (ipsilateral stroke or transient ischaemic attack) during long-term follow-up. There was no significant increase in the risk of ipsilateral stroke in patients with 70% or more restenosis compared with those with less than 70% restenosis; however, owing to the small number of patients that reached this endpoint, the confidence interval for the estimated hazard ratio was wide. As reported in the companion article on the long-term clinical outcome of CAVATAS,[5] there were more patients with non-perioperative ipsilateral stroke or transient ischaemic attack (HR 1·29, 95% CI 0·78–2·14) and more patients with non-perioperative ipsilateral stroke (1·22, 0·59–2·54) in the endovascular arm than there were in the endarterectomy arm during follow-up, although these

differences were not statistically significant. The increase in events in the endovascular arm might be partly explained by the high incidence of restenosis after endovascular treatment.

Because more than half of the recurrent cerebrovascular symptoms that occurred in patients with severe restenosis were transient, and because of the small number of outcome events, our data do not support routine elective carotid reinterventional treatment for asymptomatic severe carotid restenosis after endovascular treatment or endarterectomy. Any decision on potential reintervention in patients with asymptomatic severe carotid restenosis seen on routine carotid duplex ultrasound or angiographic screening should take into account the low risk of ipsilateral stroke in these patients (about 2% per year in our study).

Our study has several limitations. Owing to financial constraints and the restricted availability of ultrasound at the beginning of the trial, ultrasound follow-up was not available or was only done at 1 year after treatment at some centres. However, at the centres that recruited the most patients, annual ultrasound follow-up was usually continued after 1 year, and the median length of follow-up in CAVATAS is similar to that reported in open registries of the long-term risk of carotid restenosis. Therefore, the performance of ultrasound follow-up and its duration primarily depended on the centre where the patient was randomly assigned, rather than selection criteria at the patient level. Because equal proportions of patients were randomly assigned to each arm at the centres, any concerns about selection bias in the comparison of restenosis between treatments might be reduced. Stenting in the endovascular group was not randomly assigned in the trial, and only a few patients were treated with stents. Although the baseline characteristics were similar in those patients treated with and those treated without stents (with the exception of a history of peripheral artery disease), differences in unmeasured risk factors might have been present. Additionally, most of the patients treated with stents received them after balloon angioplasty had not reduced the degree of stenosis sufficiently. The primary carotid stenosis in these patients might therefore have differed from the stenosis in the patients in whom balloon angioplasty was successful, in a way that might have systematically altered their risk of restenosis. The strength of evidence from CAVATAS with regard to the efficacy of stenting for preventing restenosis compared with angioplasty alone is therefore limited. Without broadly accepted criteria for ultrasound of stented carotid arteries, and for reasons of consistency with previous reports from CAVATAS, the same ultrasound criteria were applied in those patients treated with and without stents. This approach might have led to the overestimation of restenosis in the patients who received stents because of reduced compliance in the vessel wall.

Our study was underpowered to detect any effect of carotid restenosis on ipsilateral stroke. Optimum medical treatment has improved since CAVATAS was designed. In particular, the use of lipid-lowering therapy in patients with symptomatic carotid artery stenosis is likely to have increased in recent years, and antiplatelet treatment regimens to be given around the time of stenting have been developed. These factors might possibly influence the risk of restenosis after treatment, and information on lipid-lowering therapy was not systematically collected in CAVATAS. Finally, primary stenting has replaced balloon angioplasty as the endovascular treatment of choice for severe carotid stenosis.

In conclusion, restenosis is about three times more common after endovascular treatment than it is after endarterectomy and seems to cause recurrent cerebrovascular events. More data from ongoing randomised trials that compare primary carotid stenting with endarterectomy are needed to assess whether modern stenting techniques are as effective as surgery for preventing restenosis in the long term and to determine accurately the relation between restenosis and recurrent stroke over time. In particular, whether patients treated with endovascular methods require long-term follow-up with carotid duplex ultrasound to detect restenosis before it becomes symptomatic remains uncertain.

Contributors

LHB classified the degree of stenosis on carotid duplex ultrasound and angiography, adjudicated clinical outcome events, did statistical analysis, and wrote the first draft of the manuscript. JE adjudicated clinical outcome events and reviewed the manuscript. JD did interval-censored analysis with the generalised non-linear model and supervised all statistical analyses. DMC was involved in the study design, data interpretation, and reviewed the manuscript. RLF assisted with database queries and reviewed the manuscript. The remaining authors contributed most of the patients to the study and reviewed the manuscript. Collaborators at individual centres were given the opportunity to comment on a draft of the manuscript. MMB had the final responsibility for the study and the manuscript content as the chief investigator in CAVATAS.

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Conflicts of interest

We have no conflicts of interest.

Acknowledgments

CAVATAS was funded by grants from the British Heart Foundation, the UK National Health Service Management Executive, and the UK Stroke Association. The ultrasound laboratory at the central trial office was funded by the UK Wellcome Trust and the UK Neurosciences Research Foundation. LHB was supported by a grant from the Swiss National Science Foundation (PBBSB-116873). JE and RLF were supported by a grant from the UK Medical Research Council. MMB holds a chair in stroke medicine that is supported by the Reta Lila Weston Trust for Medical Research. This work was done at University College London Hospitals/University College London, which receives a proportion of its funding from the UK Department of Health National Institutes for Health Research Biomedical Research Centres funding scheme.

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