Long-term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: a preplanned pooled analysis of individual patient data

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Summary

Background The risk of periprocedural stroke or death is higher after carotid artery stenting (CAS) than carotid endarterectomy (CEA) for the treatment of symptomatic carotid stenosis. However, long-term outcomes have not been sufficiently assessed. We sought to combine individual patient-level data from the four major randomised controlled trials of CAS versus CEA for the treatment of symptomatic carotid stenosis to assess long-term outcomes.

Methods We did a pooled analysis of individual patient-level data, acquired from the four largest randomised controlled trials assessing the relative efficacy of CAS and CEA for treatment of symptomatic carotid stenosis (Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial, Stent-Protected Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy trial, International Carotid Stenting Study, and Carotid Revascularization Endarterectomy versus Stenting Trial). The risk of ipsilateral stroke was assessed between 121 days and 1, 3, 5, 7, 9, and 10 years after randomisation. The primary outcome was the composite risk of stroke or death within 120 days after randomisation (periprocedural risk) or subsequent ipsilateral stroke up to 10 years after randomisation (postprocedural risk). Analyses were intention-to-treat, with the risk of events calculated using Kaplan-Meier methods and Cox proportional hazards analysis with adjustment for trial.

Findings In the four trials included, 4775 patients were randomly assigned, of whom a total of 4754 (99·6%) patients were followed up for a maximum of 12·4 years. 21 (0·4%) patients immediately withdrew consent after randomisation and were excluded. Median length of follow-up across the studies ranged from 2·0 to 6·9 years. 129 periprocedural and 55 postprocedural outcome events occurred in patients allocated CEA, and 206 and 57 for those allocated CAS. After the periprocedural period, the annual rates of ipsilateral stroke per person-year were similar for the two treatments: 0·60% (95% CI 0·46–0·79) for CEA and 0·64% (0·49–0·83) for CAS. Nonetheless, the periprocedural and postprocedural risks combined favoured CEA, with treatment differences at 1, 3, 5, 7, and 9 years all ranging between 2·8% (1·1–4·4) and 4·1% (2·0–6·3).

Interpretation Outcomes in the postprocedural period after CAS and CEA were similar, suggesting robust clinical durability for both treatments. Although long-term outcomes (periprocedural and postprocedural risks combined) continue to favour CEA, the similarity of the postprocedural rates suggest that improvements in the periprocedural safety of CAS could provide similar outcomes of the two procedures in the future.

Funding None.

Introduction

Randomised controlled trials of patients with recently symptomatic carotid stenosis have compared treatment with carotid artery stenting (CAS) with carotid endarterectomy (CEA).[1–5] Individual studies have shown higher risk for the composite of periprocedural stroke and death and subsequent ipsilateral stroke 2–3 years after CAS than after CEA. Because life expectancies for men and women, in the general population, of ages similar to those in these trials exceed 10–15 years, differences in the occurrence of stroke beyond 2–3 years are clinically meaningful.[6]

The imprecision of the long-term data from individual studies does not provide clinicians and patients with the information they need to make treatment decisions and to adjudge long-term prognosis. Few patients were followed up for more than 5 years in individual trials: 363 patients in the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial,[7] 596 in the International Carotid Stenting Study (ICSS),[3] and 700 symptomatic patients in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).[8] No patients in the Stent-Protected Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial[2] were followed up to 5 years. Accordingly, investigators representing the four major randomised trials—EVA-3S, SPACE, ICSS, and CREST—have

Research in context

Evidence before this study

Over the past two decades, four large randomised controlled trials compared carotid artery stenting (CAS) to carotid endarterectomy (CEA) for prevention of stroke in symptomatic patients with moderate to severe carotid stenosis: the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial (n=527), the Stent-Protected Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial (n=1200), the International Carotid Stenting Study (ICSS, n=1713), and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST, n=1321 symptomatic patients). The Carotid Stenosis Trialists' Collaboration (CSTC) previously reported short-term outcomes from pooled data on 3433 patients from the three largest European-based trials, EVA-3S, SPACE, and ICSS. The risk of stroke or death within 120 days of the procedure was 8·9% for CAS and 5·8% for CEA (risk difference 3·2% [95% CI 1·4–4·9]). Another randomised controlled trial that included more than 300 patients comparing CAS with CEA in symptomatic patients was the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial (n=334). This study was not included in our analysis because it was performed in a different type of patient population (patients deemed at high risk for CEA, and only 96 were symptomatic).

Added value of this study

In this study, the CSTC-pooled patient-level data were expanded to include data from CREST (in the USA and Canada), increasing the sample cohort to 4754 patients. The previously reported treatment difference at 120 days after randomisation is numerically unchanged by the addition of CREST. Subsequent to the 120-day periprocedural period, the ipsilateral stroke rates were similar (approximately 0·6% per person-year) for patients allocated CAS and CEA for symptomatic carotid stenosis. The annual rates of ipsilateral stroke are lower than the annual rates of stroke outside the distribution of the target artery and are also lower than the postprocedural rates reported for patients with symptomatic and asymptomatic patients in earlier randomised trials. However, the combined periprocedural and postprocedural risks favoured CEA.

Implications of all the available evidence

This pooled analysis provides evidence that for both CEA and CAS, if performed safely, most patients who are revascularised can anticipate freedom from stroke up to 10 years after either CEA or CAS. Nonetheless, the net long-term superiority of CEA over CAS, as performed at the time of the four trials, warrants the ongoing efforts to improve the safety of CAS. Improvements in the periprocedural safety of CAS could provide similar outcomes of the two procedures in both the short and long term.

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combined long-term outcome data of individual patients in a pooled analysis, which are reported in this paper. The main durability outcome is the occurrence of ipsilateral stroke during the postprocedural period, beyond 120 days and up to 10 years. The periprocedural and postprocedural outcomes combined, the outcomes approximating the primary endpoints of the individual trials, are also analysed. Although the analyses were preplanned, no published protocol is available.

Methods

Overview

EVA-3S, SPACE, ICSS, and CREST were multicentre, randomised controlled trials that compared outcomes after CAS and CEA of patients with moderate or severe atherosclerotic symptomatic stenosis at the carotid bifurcation.[9] The Carotid Stenosis Trialists' Collaboration requested, received, and harmonised the individual patient-level data for each of these trials. These data have served as the bases for a series of reports, including the current analysis. CREST also enrolled patients with asymptomatic carotid stenosis who are not included in this analysis. Stenosis eligibility was 60% or more in EVA-3S, 50% or more in SPACE, more than 50% in ICSS, and 70% or more in CREST, all stenosis identified by duplex ultrasound and corresponding to angiographical values obtained with methods used in previous trials (CREST also allowed enrolment of patients with 50% or more stenosis identified by catheter angiogram). Patients were randomly assigned from November, 2000, through July, 2008. Enrolment in EVA-3S was halted in September, 2005, per recommendation of the safety committee.[1] Enrolment in SPACE was also stopped prematurely after an interim analysis because of futility and lack of funding.[2] Each of the trials contributing data were reviewed and approved by the appropriate ethics committees.

Credentialing and device use varied for carotid stenting. Interventionists had to have performed at least 12 carotid stenting procedures in EVA-3S, ten in ICSS, and 30 in CREST, and additional criteria varied. In SPACE, interventionists had to have performed at least 25 successful consecutive angioplasty or stent procedures, not necessarily of the carotid artery. Choice of stenting devices was at the discretion of the interventionist in EVA-3S, SPACE, and ICSS. The use of approved cerebral protection devices was optional in SPACE and ICSS. Protection devices were made mandatory in EVA-3S after an interim analysis showed a higher risk of procedural stroke with unprotected stenting than with protected stenting.[7] CREST required use of the ACCUNET protection device (Abbott, Temecula, CA, USA) and the ACCULINK stent (Abbott, Temecula, CA, USA).[8]

Outcomes

We predefined the main long-term outcome as ipsilateral stroke during the postprocedural period. Treatment

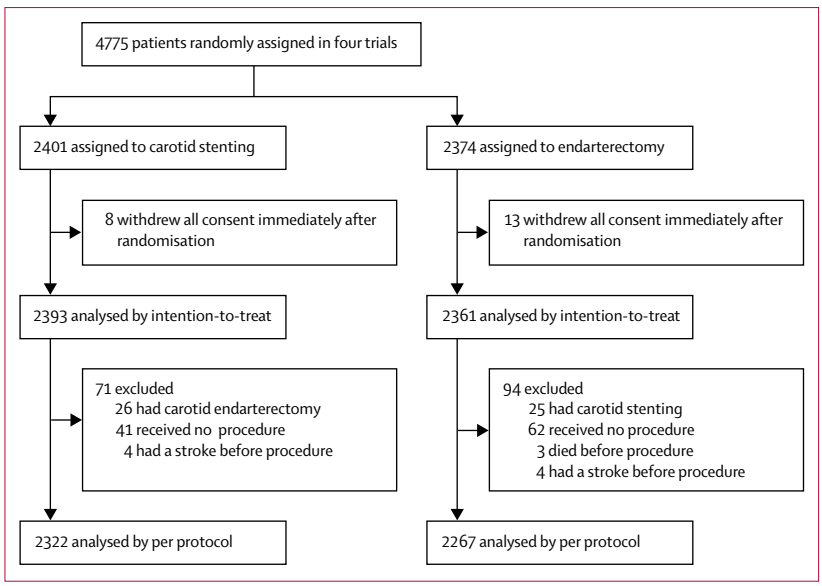


Figure 1: **CONSORT diagram**

differences at 1, 3, 5, 7, 9, and 10 years after randomisation are reported. These points were chosen arbitrarily without consideration of the specific pattern of treatment differences. The predefined primary outcome is the composite of stroke or death, occurring within 120 days after randomisation, or subsequent ipsilateral stroke.[5] In the original reports of the individual trials, the periprocedural period was 0–30 days after CEA or CAS in EVA-3S, 0–30 days after randomisation in SPACE and CREST, and 0–120 days after randomisation in ICSS. The cutoff point for the periprocedural and postprocedural periods at 120 days after randomisation was chosen for the analyses here because in each contributing trial, nearly all patients received their treatment within 3 months of randomisation and received their post-treatment follow-up appointment within 4 months after randomisation. Accordingly, outcomes during this periprocedural period of 0–120 days are also reported. In addition to examining treatment differences at the above fixed timepoints, the hazard ratio (HR) over the entire follow-up period extending to the end of follow-up was considered. Secondary outcomes include major stroke, minor stroke, and stroke in any distribution; for brevity the treatment differences for these secondary outcomes are provided only for the 5-year point in follow-up. Additionally, analysis was performed for ipsilateral and non-ipsilateral stroke outcomes showing similar patterns to those reported herein, but these results are not reported in detail for reasons of brevity.

Stroke was defined as an acute neurological event with focal symptoms and signs, lasting for 24 h or more, that were consistent with focal cerebral ischaemia; visual loss resulting from retinal ischaemia that lasted for longer than 24 h was included within the category of stroke. None of the four trials used a tissue-based definition of stroke, and therefore patients with symptoms less than 24 h in duration with positive MRI scans were not classified as stroke. Major stroke was defined in EVA-3S, SPACE, and ICSS as any stroke resulting in a modified Rankin Scale score of 3 or higher 30 days or more after stroke onset. In CREST, major stroke was defined on the basis of clinical data or if the National Institutes of Health Stroke Scale score was 9 or higher 90 days after the randomisation. Patients were assessed neurologically after the procedure and had follow-up assessments at 30–36 days, 6 months, and at least annually thereafter. Potential outcome events were adjudicated by independent committees. Medical treatments followed standard of care, and patients continued to be followed up for stroke events after any carotid revasularisation procedure.

Data analysis

Analyses were intention-to-treat (ITT) and included all patients randomly assigned, with the exception of 21 patients who immediately withdrew consent after randomisation. For both the periprocedural and postprocedural periods, we assessed the crude differences in the proportion of patients with events with Kaplan-Meier methods, and we used Cox proportional hazards analysis to estimate CAS to CEA HRs after adjustment for the contributing trial. Throughout the paper, we refer to the risk of events, with the cumulative incidence representing the risk. For the ITT analysis, we defined the periprocedural period as the first 120 days after randomisation. We omitted all patients who had an event (stroke or death) or who withdrew from the studies during the periprocedural period from the postprocedural analysis, which started at 121 days after randomisation. We assessed the potential for heterogeneity of treatment effect between studies by the introduction of a treatment-by-study interaction term to the proportional hazards model. We did an additional per-protocol analysis, including only those patients in whom the first initiated revascularisation procedure after randomisation was the randomly allocated treatment. We excluded from the per-protocol analysis patients crossing over to the alternative procedure, those remaining on medical treatment only, and patients who died before treatment. For the per-protocol analysis, we defined the periprocedural period as the first 30 days after revascularisation, and the postprocedural period started at 31 days after revascularisation.

We performed subgroup analysis in which patients were stratified by covariates that potentially could affect treatment differences between CEA and CAS, with treatment differences assessed for the entire follow-up (including both periprocedural and postprocedural periods) and for the postprocedural period alone. Within each stratum, we used proportional hazards analysis to calculate the CAS to CEA HR after adjustment for the contributing trial, and we assessed the significance of potential treatment effect modification by covariates through the addition of an interaction term to the

	Overall		Source trial			
	CEA (N=2361)	CAS (N=2393)	EVA-3S (N=527)[7]	SPACE (N=1196)[2]	ICSS (N=1710)[3]	CREST (N=1321)[8]
Age, years	70 (63–77)	70 (63–76)	72 (64–78)	68 (62–75)	71 (64–77)	70 (62–76)
Sex						
Women	702/2361 (30%)	735/2393 (31%)	130/527 (25%)	338/1196 (28%)	503/1710 (29%)	446/1321 (35%)
Men	1659/2361 (70%)	1658/2393 (69%)	397/527 (75%)	858/1196 (72%)	1207/1710 (71%)	875/1321 (65%)
Hypertension	1782/2350 (76%)	1792/2381 (75%)	383/527 (73%)	904/1196 (76%)	1183/1694 (70%)	1104/1314 (84%)
Diabetes	602/2356 (26%)	591/2390 (25%)	126/527 (24%)	326/1196 (27%)	372/1710 (22%)	369/1313 (28%)
Dyslipidaemia	1231/1757 (70%)	1186/1771 (67%)	300/527 (57%)	NA	1085/1694 (64%)	1032/1307 (79%)
Current smoking	613/2340 (26%)	606/2373 (26%)	126/527 (24%)	325/1196 (27%)	403/1694 (24%)	365/1296 (28%)
Previous ischaemic heart disease	656/2303 (28%)	637/2338 (27%)	93/527 (18%)	269/1196 (22%)	467/1694 (28%)	464/1224 (38%)
Severe ipsilateral stenosis	1896/2361 (80%)	1939/2393 (81%)	491/527 (93%)	741/1196 (62%)	1542/1710 (90%)	1061/1321 (80%)
Severe contralateral stenosis or occlusion	314/2115 (15%)	312/2139 (15%)	69/527 (13%)	100/927 (11%)	301/1697 (18%)	156/1103 (14%)
Modified Rankin Scale score of 0	1172/2335 (50%)	1200/2370 (51%)	288/527 (55%)	635/1196 (53%)	675/1680 (40%)	774/1302 (59%)
Length of follow-up, years						
Mean	4·2 (2·9)	4·0 (3·0)	6·2 (3·2)	1·7 (0·7)	4·0 (2·1)	5·6 (3·4)
Median	3·6 (2·0–6·4)	3·4 (2·0–6·2)	6·9 (3·8–8·6)	2·0 (2·0–2·0)	4·1 (3·0–5·2)	6·2 (2·7–8·6)

Data are k/n (%), where k is the number of patients with the characteristic and n is number of patients with data available, median (IQR), or mean (SD). CEA=carotid endarterectomy. CAS=carotid artery stenting. EVA-3S=Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis. SPACE=Stent-Protected Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy. ICSS=The International Carotid Stenting Study. CREST=Carotid Revascularization Endarterectomy versus Stenting Trial. NA=data not available.

Table 1: **Description of the study population by treatment assignment and by contributing study**

proportional hazards model (statistical testing for interactions was done using an a-priori α=0·10). Statistical analyses were done using SAS 9.4 (Cary, NC, USA).

Role of the funding source

There was no funding source for this study.

Results

For the 4754 patients who were randomly assigned in the four trials (excluding those who withdrew consent immediately after randomisation; figure 1), maximum follow-up was 12·4 years in EVA-3S, 4·1 years in SPACE, 10·0 years in ICSS, and 10·2 years in CREST. Median follow-up ranged between 2·0 and 6·9 years (table 1). About 30% of patients were women, three-quarters had hypertension, and about 70% were dyslipidaemic. About a quarter were current smokers and 15% had severe (≥50–70%) contralateral carotid stenosis or occlusion (table 1).

In EVA-3S, SPACE, and ICSS, the previously estimated treatment difference in risk between CEA and CAS in the periprocedural 120-day period for stroke or death was 3·2% (95% CI 1·4–4·9).[5] In this analysis, which included data from the CREST trial,[8] this estimate is unchanged (3·2%), but with the increased sample size the 95% CI tightened (1·7–4·7; table 2; figure 2A).

Beyond 120 days, the occurrence of stroke in the long term was infrequent, and risks did not differ between CAS or CEA treatment at 5 years (table 2), nor did the proportion of patients with events (table 3; figure 2B). The absolute CAS versus CEA treatment difference in postprocedural stroke risk at years 1, 3, 5, 7, or 9 never exceeded 1%, ranging from –0·6% (95% CI –1·6 to 0·4) at year 3 to 0·6% (–0·7 to 2·0) at year 7 (table 3). In the postprocedural period, 57 ipsilateral strokes occurred in the CAS cohort and 55 ipsilateral strokes occurred in the CEA cohort (HR 1·06 [95% CI 0·73 to 1·54]; table 2). The annual rate of postprocedural ipsilateral stroke per person-year was similar for CEA (0·60% [0·46 to 0·79]) and CAS (0·64% [0·49 to 0·83]; table 2). The rates of major stroke and minor stroke were also less than 1% per year (table 2). These results of up to 5 years (table 2) are consistent with the results up to 9 years (table 3) and the Kaplan-Meier curves (figure 2A–H).

With the similarity of postprocedural stroke risk for patients assigned to CAS and CEA, the 3·2% periprocedural stroke risk difference was carried forward over the entire follow-up period, never differing from this initial treatment difference by more than 1% (table 3; figure 2A–B). Over the entire follow-up, the hazard for the primary outcome (periprocedural and postprocedural events combined) was 1·45 times (95% CI 1·20–1·75) higher for those assigned to CAS (table 2; figure 2A) than those assigned to CEA.

The postprocedural CAS versus CEA treatment differences were also quite small for major ipsilateral stroke (at 5 years –0·3% [95% CI –1·1 to 0·6]; HR 0·86 [95% CI 0·48 to 1·56]), minor ipsilateral stroke (0·3% [–0·6 to 1·3]; 1·21 [0·75 to 1·96]), and stroke in any distribution (0·4% [–1·5 to 2·3]; 1·08 [0·84 to 1·38]; table 2). Among

	All events (CEA, n=2361; CAS, n=2393)				Periprocedural events (within 120 days) (CEA, n=2361; CAS, n=2393)				Postprocedural events (after 120 days) (CEA, n=2168; CAS, n=2121)				
	Events	Risk at 5 years	Absolute risk difference at 5 years	Hazard ratio (CAS *vs* CEA)	Events	Risk at 120 days	Absolute risk difference at 120 days	Hazard ratio (CAS *vs* CEA)	Events	Risk at 5 years	Absolute risk difference at 5 years	Hazard ratio (CAS *vs* CEA)	Annual event rate per person-years
Any stroke or death within 120 days and ipsilateral stroke afterwards													
CEA	184 (7·8%)	8·3% (7·2 to 9·6)	3·0% (1·2 to 4·8)	1·45 (1·20 to 1·75)	129 (5·5%)	5·5% (4·7 to 6·5)	3·2% (1·7 to 4·7)	1·61 (1·29 to 2·01)	55 (2·5%)	3·1% (2·3 to 4·1)	0·1% (−1·2 to 1·3)	1·06 (0·73 to 1·54)	0·60% (0·46 to 0·79)
CAS	263 (11·0%)	11·4% (10·1 to 12·8)	..	..	206 (8·6%)	8·7% (7·6 to 9·9)	..	..	57 (2·7%)	3·2% (2·3 to 4·2)	..	..	0·64% (0·49 to 0·83)
Any major stroke within 120 days and major ipsilateral afterwards													
CEA	79 (3·4%)	3·7% (2·9 to 4·6)	0·7% (−0·5 to 2·0)	1·23 (0·91 to 1·66)	55 (2·3%)	2·4% (1·8 to 3·1)	1·0% (−0·0 to 1·9)	1·39 (0·98 to 1·97)	24 (1·1%)	1·4% (0·9 to 2·2)	−0·3% (−1·1 to 0·6)	0·86 (0·48 to 1·56)	0·26% (0·18 to 0·39)
CAS	96 (4·0%)	4·4% (3·6 to 5·4)	..	..	76 (3·2%)	3·3% (2·6 to 4·1)	..	..	20 (0·9%)	1·2% (0·7 to 1·9)	..	..	0·22% (0·14 to 0·35)
Any minor stroke within 120 days and minor ipsilateral afterwards													
CEA	88 (3·7%)	4·1% (3·3 to 5·1)	2·2% (0·9 to 3·6)	1·67 (1·28 to 2·17)	57 (2·4%)	2·5% (1·9 to 3·2)	2·2% (1·1 to 3·2)	1·91 (1·39 to 2·63)	31 (1·4%)	1·7% (1·2 to 2·4)	0·3% (−0·6 to 1·3)	1·21 (0·75 to 1·96)	0·34% (0·24 to 0·48)
CAS	145 (6·1%)	6·3% (5·3 to 7·5)	..	..	108 (4·5%)	4·7% (3·9 to 5·6)	..	..	37 (1·7%)	2·0% (1·4 to 2·9)	..	..	0·41% (0·30 to 0·57)
Stroke in any distribution													
CEA	238 (10·1%)	11·1% (9·8 to 12·7)	3·1% (0·9 to 5·2)	1·35 (1·15 to 1·60)	112 (4·7%)	4·8% (4·0 to 5·7)	3·0% (1·6 to 4·4)	1·66 (1·32 to 2·10)	126 (5·8%)	6·9% (5·7 to 8·3)	0·4% (−1·5 to 2·3)	1·08 (0·84 to 1·38)	1·38% (1·16 to 1·65)
CAS	318 (13·3%)	14·2% (12·7 to 15·9)	..	..	185 (7·7%)	7·8% (6·8 to 9·0)	..	..	133 (6·3%)	7·3% (6·0 to 8·8)	..	..	1·49% (1·25 to 1·76)

Data are n (%) or risk or hazard ratio (95% CI). For the periprocedural period, risks are estimated at 120 days after randomisation. For the postprocedural period, risks are estimated at 5 years from Kaplan-Meier analysis. CEA=carotid endarterectomy. CAS=carotid artery stenting.

Table 2: **Risk of events over the entire follow-up, within the periprocedural period and during the postprocedural period**

all strokes (both major and minor), 112 (43%) of 259 postprocedural strokes were in the distribution of the artery targeted for CAS or CEA, and 147 (57%) were outside that distribution (ie, either contralateral or in the posterior circulation).

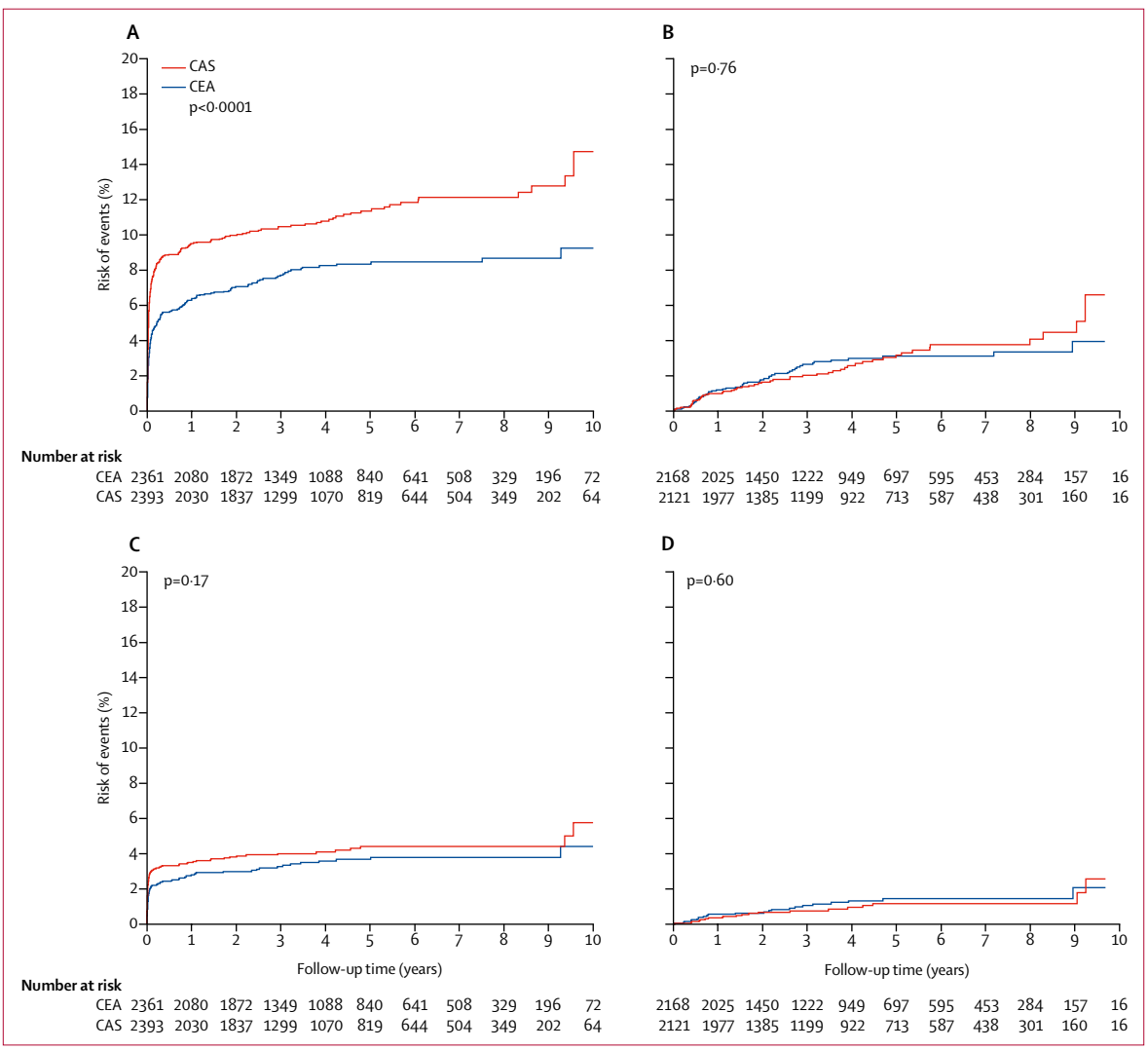
The homogeneity of treatment effects across studies was assessed by the addition of a trial-by-treatment interaction term to the proportional hazards models. A total of 12 interaction terms were considered for four outcomes (primary outcome, major stroke, minor stroke, and all stroke outcome) for three periods (periprocedural and postprocedural periods, periprocedural, and postprocedural). Of these 12 analyses, there was weak evidence for one interaction (p=0·040) for the overall period, which was probably a spurious finding arising from multiple testing.

The results of the subgroup analysis are shown in figure 3. The analysis of the entire follow-up period (periprocedural stroke or death or postprocedural ipsilateral stroke) supports the previously reported lower risk of treatment by CEA than CAS in patients aged 65 years or older, with similar risks in younger patients ($p_{interaction}$=0·003). There was evidence of a significant interaction between treatment effect and smoking ($p_{interaction}$=0·022) and the presence of contralateral severe stenosis ($p_{interaction}$=0·040). We found no evidence of a treatment difference for smokers (HR 0·93 [95% CI 0·61–1·41]), whereas among non-smokers the risk was higher for treatment with CAS (1·61 [1·30–1·99]) than with CEA. Likewise, we found no evidence of a treatment effect for patients with a severe contralateral stenosis (1·01 [0·65–1·58]), whereas among those without a contralateral stenosis the risk was higher for treatment with CAS (1·69 [1·35–2·13]) than with CEA. During the postprocedural period, the CAS to CEA treatment differences were not significant within any stratum defined by any covariate, and there was no evidence to support treatment effect modification (or interaction with treatment) by any covariate ($p_{interaction}$ ≥0·134).

Results of the per-protocol analysis were generally similar to those of the ITT analysis. With the use of the significance of associations as criteria, no differences were found between the ITT and per-protocol analyses that would affect interpretation of results for the primary outcome, minor stroke, or stroke in any distribution. However, for major stroke, the per-protocol analysis showed a significant treatment difference for all events (HR 1·41 [95% CI 1·02–1·94]) and during the periprocedural period (1·63 [1·10–2·43]); conversely, the ITT analysis for major stroke was not significant for either all events (1·23 [0·91–1·66]) or for the periprocedural period (1·39 [0·98–1·97]).

Discussion

This pooled analysis shows that the long-term (ie, postprocedural) durabilities of CAS and CEA are remarkably



(Figure 2 continues on next page)

similar, with the annual rate of ipsilateral stroke per person-year at 0·60% for CEA and 0·64% for CAS. Hence, patients remaining event-free during the periprocedural period are similarly served by the CAS and CEA interventions. Nonetheless, the higher early risks after CAS are such that the primary outcome of any stroke or death up to 120 days, and ipsilateral stroke thereafter, favours CEA, even up to 10 years (HR 1·45 [95% CI 1·20–1·75]).

These results support the importance of ongoing improvements in the periprocedural safety of CAS,[10] including changes in CAS technology and stenting techniques and the careful selection of appropriate patients for the procedure. For example, we have previously reported[11] that most excess risk among patients assigned to CAS is at older ages. As such, preferentially using CAS in younger patients (ie, <65 years) could improve periprocedural safety.

The rates of long-term postprocedural events reported here are low compared with previous trials for stroke preventions. If the estimated risks from the Kaplan-Meier curves of the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[12] were annualised, the postprocedural annual risk for any stroke would be 4·5%. The comparable risk in the four trials reported here is 1·4% for CEA and 1·5% for CAS. Comparable data are not available for the patients with symptomatic carotid stenosis reported in the European Carotid Surgery Trial.

We do not suggest that the low long-term stroke rates herein result solely from revascularisation with CAS or CEA. Risk factor control probably has a more important role.[13] In the Asymptomatic Carotid Surgery Trial (ACST),[14] patients on lipid-lowering drugs at baseline had an annual rate of stroke after the periprocedural period of 0·6% compared with 1·5% for those not on lipid-lowering

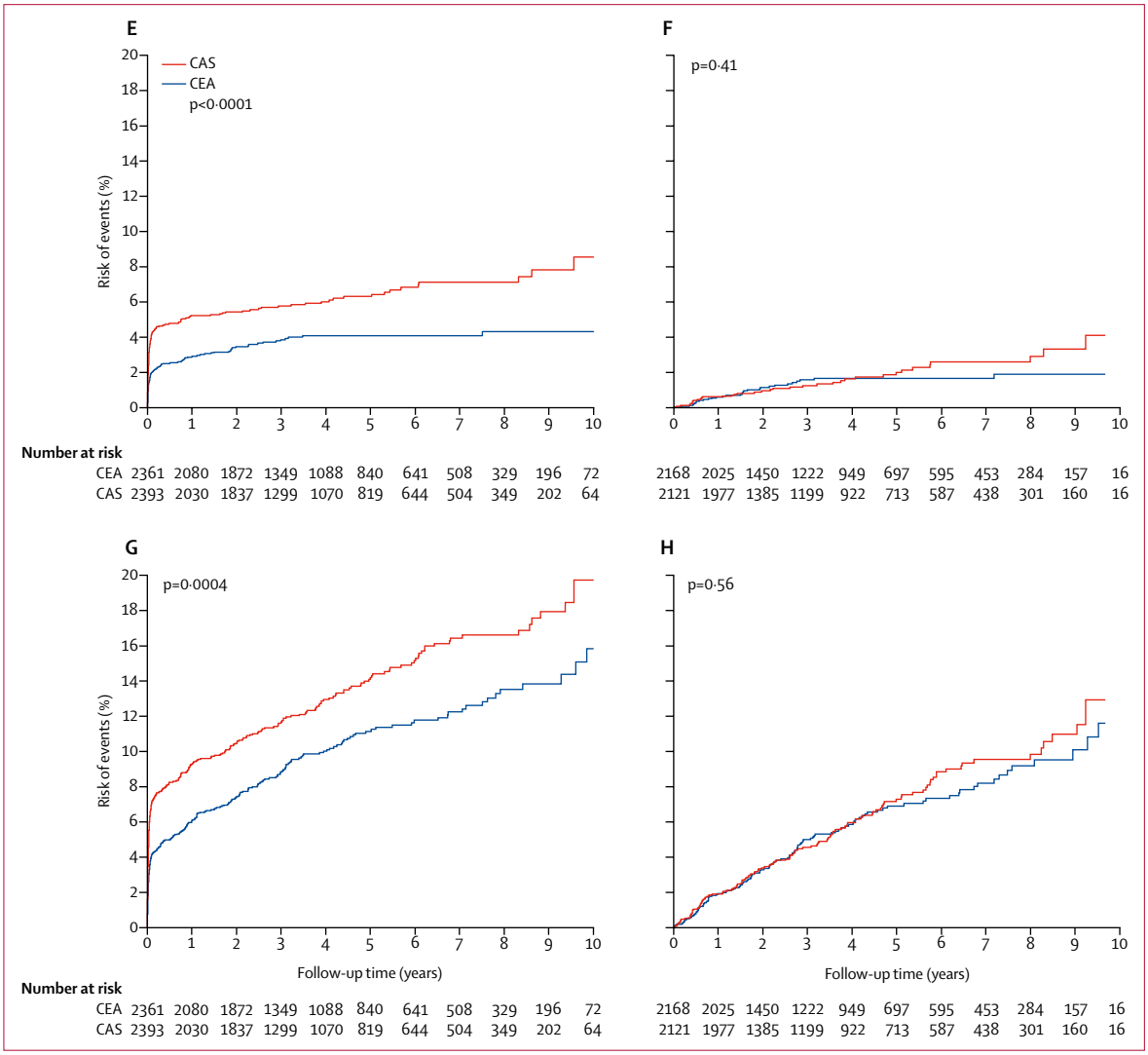


Figure 2: **Kaplan-Meier estimates of risk of events for the primary outcome, postprocedural ipsilateral stroke, and the secondary outcomes of major stroke, minor stroke, and all stroke**

(A) Primary outcome. (B) Postprocedural ipsilateral stroke. (C,D) Major stroke. (E,F) Minor stroke. (G,H) All stroke. The risk of events estimates are provided for all outcomes, including both periprocedural and postprocedural events on the left of the figure (A, C, E, G) and for postprocedural events only (ie, >120 days; B, D, F, H) on the right of the figure. p values are for treatment differences using the log-rank test. CAS=carotid artery stenting. CEA=carotid endarterectomy.

	1 year after randomisation	3 years after randomisation	5 years after randomisation	7 years after randomisation	9 years after randomisation
Long-term outcome (periprocedural and postprocedural risks)					
CEA	6·4% (5·4 to 7·4)	7·7% (6·7 to 8·9)	8·3% (7·2 to 9·6)	8·4% (7·3 to 9·7)	8·7% (7·5 to 10·0)
CAS	9·5% (8·4 to 10·8)	10·5% (9·3 to 11·8)	11·4% (10·1 to 12·8)	12·1% (10·7 to 13·7)	12·5% (11·2 to 14·6)
Difference (CAS *vs* CEA)	3·1% (1·6 to 4·7)	2·8% (1·1 to 4·4)	3·0% (1·2 to 4·8)	3·7% (1·8 to 5·6)	4·1% (2·0 to 6·3)
Postprocedural durability (ipsilateral postprocedural stroke risk)					
CEA	1·2% (0·8 to 1·7)	2·6% (2·0 to 3·5)	3·1% (2·3 to 4·1)	3·1% (2·3 to 4·1)	3·9% (2·7 to 5·8)
CAS	1·0% (0·6 to 1·5)	2·0% (1·5 to 2·8)	3·2% (2·3 to 4·2)	3·7% (2·8 to 5·0)	4·5% (3·2 to 6·2)
Difference (CAS *vs* CEA)	–0·2% (–0·8 to 0·4)	–0·6% (–1·6 to 0·4)	0·1% (–1·2 to 1·3)	0·6% (–0·7 to 2·0)	0·5% (–1·6 to 2·7)

Data are risk (95% CI). CEA=carotid endarterectomy. CAS=carotid artery stenting.

Table 3: **Risk of events for primary outcome and ipsilateral postprocedural stroke by treatment assignment and differences in treatment at 1, 3, 5, 7, and 9 years**

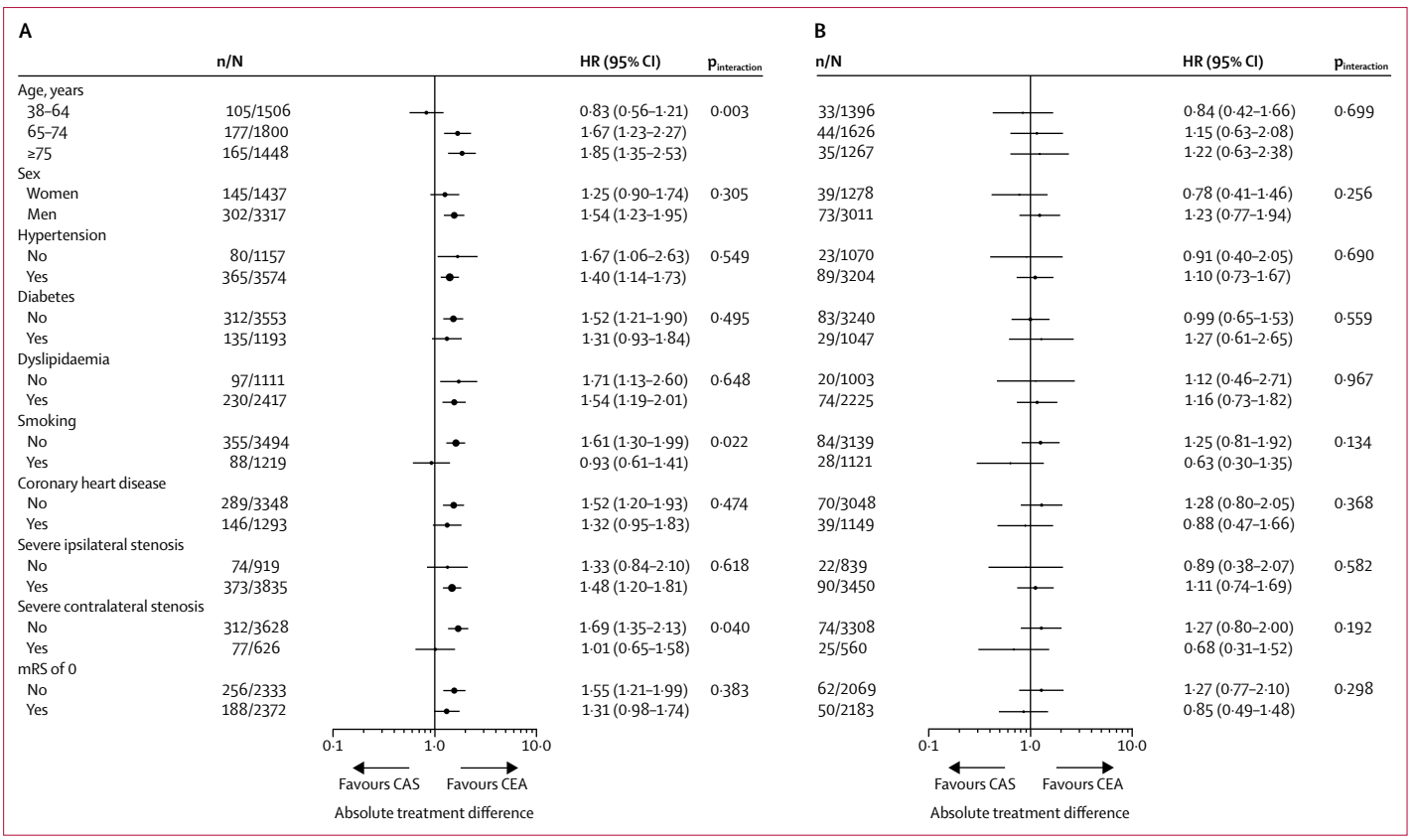


Figure 3: **Forest plots of treatment effects for the entire follow-up period**
(A) Periprocedural and postprocedural. (B) Postprocedural. Data are the CAS to CEA HR (95% CI) from proportional hazards analysis within strata defined by covariates. The size of the circle showing the treatment effect is proportional to the inverse of the standard error of the estimated difference. The p value assessing potential effect modification was estimated by the addition of an interaction term to the proportional hazards model. HR=hazard ratio. CAS=carotid artery stenting. CEA=carotid endarterectomy. HR=hazard ratio. mRS=modified Rankin Scale.

drugs. Only 9% of the patients were on lipid-lowering drugs during the first year of enrolment in ACST in 1993, and 81% were on antihypertensive drugs. By the end of enrolment in 2003, 81% were on lipid-lowering drugs and 88% were on antihypertensive drugs.[14]

The subgroup analysis in our pooled analysis of the entire follow-up period (periprocedural stroke or death or postprocedural ipsilateral stroke) supports the previously reported lower risk for stroke of CEA (relative to CAS) in older patients;[11] the analysis also identified both smoking and the presence of contralateral stenosis as treatment effect modifiers (ie, interacted with treatment). The apparent differential effect between strata defined by smoking is likely to be because of the confounding of age with smoking, in which the average age of smokers tends to be much lower than that of non-smokers. The effect modification by the presence of contralateral stenosis requires additional investigation.

Because only 112 postprocedural events occurred, the subgroup analysis of treatment differences during this period should be interpreted with caution. However, the analysis presented in figure 3 did not detect a significant treatment difference in the postprocedural period for any stratum for any covariate, and no significant evidence supported an effect modification by any covariate; hence, it appears the similar risk for CAS and CEA during the postprocedural period is consistent for these subgroups of patients.

The advantages of this pooled analysis with individual patient data include wider generalisability and improved precision. Patients, surgical interventionists, and medical teams from multiple countries and three continents participated. Combination of the four trials provided 4754 patients for analysis, allowing stable long-term estimates of the periprocedural risks and subsequent clinical durability for CAS and CEA and allowed for meaningful subgroup analyses; these results are the most precise available. Disadvantages include variability in surgical and interventionist training and experience, differences in outcome ascertainment and adjudication, and differences in intensity of patient follow-up examinations and medical treatment. A limitation of any long-term postprocedural outcome analysis is that, by definition, the procedures had to be performed long ago, in this case more than a decade ago. Another limitation is that we limited our analyses to first strokes, hence our

report does not inform on the risk of recurrent strokes. However, 112 ipsilateral first strokes occurred during the postprocedural period; if those patients had the high 5-year recurrence risk for any stroke noted in NASCET (4·5%),[12] only an additional six recurrent strokes would have been detected.

In summary, this pooled analysis of the four major randomised controlled trials comparing CEA and CAS shows that if these procedures are performed safely, most patients who are revascularised can anticipate freedom from stroke for up to 10 years after either CEA or CAS. Nonetheless, the net long-term superiority of CEA over CAS shown in the past decade warrants the improvements in the procedural safety of CAS, which are ongoing. Accordingly, although the combined periprocedural and postprocedural outcome results continued to favour CEA, the similarity of the postprocedural rates suggest that improvements in the periprocedural safety of CAS could provide similar outcomes of the two procedures. The mechanisms of the postprocedural strokes that occurred over the long term remain to be established.

Contributors

TGB and DC wrote the first drafts of the paper. GH and JG undertook the statistical analysis. J-LM, PAR, LHB, and JHV extracted individual patient data from the contributing trials. All authors made substantial contributions to the conception and design of the study, acquisition of data or analysis, data interpretation, and critical revision of the Article. TGB and MMB had the final responsibility for the analyses and manuscript content.

Declaration of interests

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