# Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data

*Carotid Stenting Trialists' Collaboration**

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*Members listed at end of paper
Correspondence to: Prof Martin M Brown, Institute of Neurology, University College London, Box 6, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK
m.brown@ion.ucl.ac.uk

## Summary

**Background** Results from randomised controlled trials have shown a higher short-term risk of stroke associated with carotid stenting than with carotid endarterectomy for the treatment of symptomatic carotid stenosis. However, these trials were underpowered for investigation of whether carotid artery stenting might be a safe alternative to endarterectomy in specific patient subgroups. We therefore did a preplanned meta-analysis of individual patient data from three randomised controlled trials.

**Methods** Data from all 3433 patients with symptomatic carotid stenosis who were randomly assigned and analysed in the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the International Carotid Stenting Study (ICSS) were pooled and analysed with fixed-effect binomial regression models adjusted for source trial. The primary outcome event was any stroke or death. The intention-to-treat (ITT) analysis included all patients and outcome events occurring between randomisation and 120 days thereafter. The per-protocol (PP) analysis was restricted to patients receiving the allocated treatment and events occurring within 30 days after treatment.

**Findings** In the first 120 days after randomisation (ITT analysis), any stroke or death occurred significantly more often in the carotid stenting group (153 [8·9%] of 1725) than in the carotid endarterectomy group (99 [5·8%] of 1708, risk ratio [RR] 1·53, [95% CI 1·20–1·95], p=0·0006; absolute risk difference 3·2 [1·4–4·9]). Of all subgroup variables assessed, only age significantly modified the treatment effect: in patients younger than 70 years (median age), the estimated 120-day risk of stroke or death was 50 (5·8%) of 869 patients in the carotid stenting group and 48 (5·7%) of 843 in the carotid endarterectomy group (RR 1·00 [0·68–1·47]); in patients 70 years or older, the estimated risk with carotid stenting was twice that with carotid endarterectomy (103 [12·0%] of 856 *vs* 51 [5·9%] of 865, 2·04 [1·48–2·82], interaction p=0·0053, p=0·0014 for trend). In the PP analysis, risk estimates of stroke or death within 30 days of treatment among patients younger than 70 years were 43 (5·1%) of 851 patients in the stenting group and 37 (4·5%) of 821 in the endarterectomy group (1·11 [0·73–1·71]); in patients 70 years or older, the estimates were 87 (10·5%) of 828 patients and 36 (4·4%) of 824, respectively (2·41 [1·65–3·51]; categorical interaction p=0·0078, trend interaction p=0·0013].

**Interpretation** Stenting for symptomatic carotid stenosis should be avoided in older patients (age ≥70 years), but might be as safe as endarterectomy in younger patients.

**Funding** The Stroke Association.

## Introduction

In patients with recently symptomatic carotid stenosis, carotid endarterectomy reduces the risk of further stroke.[1,2] In the past few years, endovascular treatment with placement of a stent has emerged as an alternative to carotid endarterectomy. Outcomes after stenting were not worse than those after endarterectomy in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial,[3] in which the two procedures were compared in patients with increased surgical risk, who also mostly had asymptomatic carotid stenosis. By contrast, results from several large trials in patients with symptomatic carotid stenosis who were judged to be at standard surgical risk—the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the International Carotid Stenting Study (ICSS)—have shown a higher periprocedural risk of stroke with stenting than with endarterectomy.[4–6] Nevertheless, important questions have remained unanswered: differences between definitions of primary short-term outcome measures and wide confidence intervals for the treatment effects in some trials render accurate assessment of the excess risk posed by stenting difficult. More importantly, periprocedural risks of stenting and endarterectomy vary with patient characteristics.[7–10] Outcomes might therefore be similar between the two procedures in specific groups of patients, but no trial was large enough to establish the balance of stenting and endarterectomy in any patient subgroup with an acceptable degree of certainty.

The investigators of the EVA-3S, SPACE, and ICSS studies set up the Carotid Stenting Trialists' Collaboration (CSTC) with the purpose of doing a preplanned meta-analysis of individual patient data from these trials. The main objectives were, first, to provide an accurate estimate of the risk ratio of major outcome events with stenting and endarterectomy in patients with symptomatic carotid stenosis; and second, to compare the safety and efficacy of these two procedures in predefined subgroups of patients. Here, we report the main results of the pooled analysis of the short-term outcome.

## Methods

### Trials

The meta-analysis of patients' data from EVA-3S (ClinicalTrials.gov, number NCT00190398), SPACE (International Standard Randomised Controlled Trial, number ISRCTN57874028), and ICSS (ISRCTN25337470) was agreed at the design stage of the three trials.[11] All three trials were randomised clinical trials with blinded outcome adjudication, in which patients with symptomatic moderate or severe carotid stenosis (≥50% reduction of lumen diameter according to the method used in the North American Symptomatic Carotid Endarterectomy Trial [NASCET],[1] or its non-invasive equivalent), who were thought to be equally suited for either procedure, were randomly allocated in equal proportions to treatment by stenting or endarterectomy.[12–14] The plan for this pooled analysis excluded non-randomised comparisons, randomised trials in which mainly balloon angioplasty without stenting was investigated,[15] small trials done early in the development of carotid stenting,[16–19] and trials that included mainly patients with asymptomatic carotid stenosis or those at increased risk of surgery.[3,20] Data from the subset of patients with symptomatic carotid stenosis who were enrolled in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) will be included in future analyses.[21]

### Outcome events

Definitions of outcome events, subgroup variables, and the statistical method for the meta-analysis were specified and documented in a protocol before the data were analysed (webappendix pp 9–17). The primary outcome event for the analysis of short-term outcome was the combination of any stroke or death. Secondary outcome events were disabling stroke or death, all cause death, any stroke, myocardial infarction, severe local haematoma, and severe wound infection. Stroke was defined as an acute deficit of focal neurological function with symptoms lasting for longer than 24 h, resulting from intracranial vascular disturbance (ischaemia or haemorrhage). Visual loss, resulting from retinal ischaemia that lasted for longer than 24 h, was included within the category of stroke. Disabling stroke was defined as any stroke resulting in new or increased disability with a score on the modified Rankin scale of 3 or greater, 30 days or more after stroke onset; all other non-fatal strokes were classified as non-disabling. Fatal stroke was defined as any stroke resulting in death within 30 days of stroke onset. Diagnosis of myocardial infarction was made clinically and required confirmation by use of two of three criteria—ie, a history of longlasting chest discomfort, the development of specific abnormalities on a standard 12-lead electrocardiogram (ECG), and increase in the activity of specific cardiac enzymes of more than twice the upper limit of normal. Routine postprocedural screening for asymptomatic myocardial infarction was not required in any of the three trials. Myocardial infarction was not included among the prespecified endpoints in the SPACE trial;[14] for this reason we did not include myocardial infarction in the primary outcome event cluster of the pooled analysis. Nevertheless, we adjudicated reports of adverse events from this trial using the criteria for myocardial infarction described above.

### Statistical analysis

The intention-to-treat (ITT) analysis included all patients randomly assigned and analysed in the three trials. Outcome events occurring between randomisation and 120 days thereafter were then compared according to the randomly allocated treatment. The per-protocol (PP) analysis included only those patients who received the randomly allocated treatment (stenting or endarterectomy) as the first initiated revascularisation procedure after randomisation. Only outcome events occurring between the first treatment and 30 days thereafter were included in the PP analysis, and patients crossing over to the other treatment, those who did not receive either treatment, and those who died before treatment were excluded.

See Online for webappendix

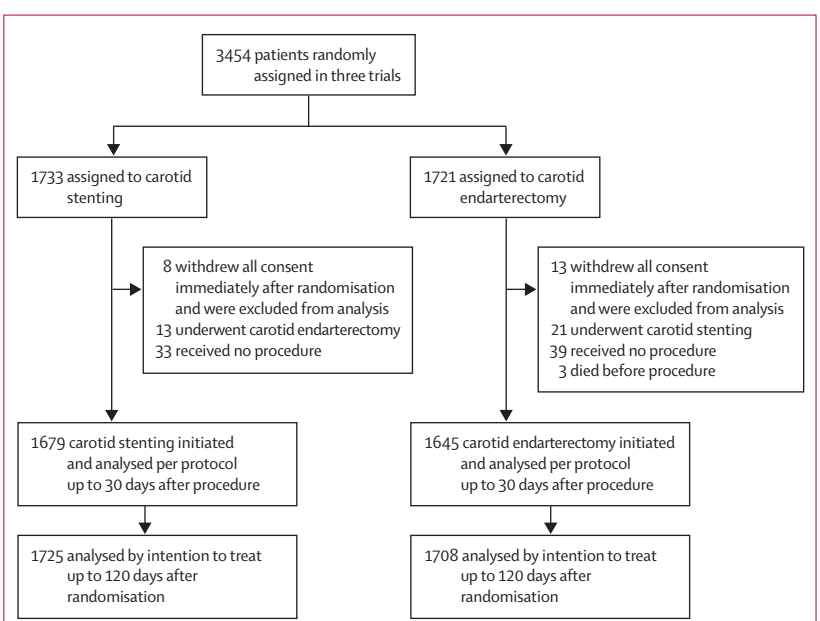



*Figure 1:* **Flow diagram of patients in trials included in meta-analysis**

The combined data were analysed with fixed-effect binomial regression models, including source trial terms as covariables, to obtain overall estimates of risk ratios (RRs) and 95% CIs of the main outcome events as the primary aggregate measures of treatment effect. Potential heterogeneity of the treatment effects of each trial was examined by testing for interactions between source trial and treatment effect and estimation of $I^2$.[22] RRs were also adjusted for baseline variables for which most data were gathered in all three trials. Additionally, estimated risk differences with 95% CIs were calculated with fixed-effect binomial regression. Very few patients were expected to be censored without an event within the 120 days of the ITT analysis. Nevertheless, a sensitivity time-to-event analysis was done with Cox regression by use of the Breslow method to handle tied failures,[23] censoring patients at 120 days after randomisation or at the time of last follow-up if shorter than 120 days.

In the ITT analysis, the interaction between the effect of treatment on the primary outcome event and each of the following prospectively defined subgroup variables was examined separately in the binomial regression model: age at randomisation in years (calculated as the difference between date of birth and date of randomisation); sex; history of diabetes, hypertension, hypercholesterolaemia, smoking (current or past), coronary heart disease, and peripheral artery disease; type of the most recent ischaemic event (retinal ischaemia including transient monocular blindness or retinal infarct, hemispheric transient ischaemic attack, or hemispheric ischaemic stroke) in the region supplied by the ipsilateral carotid artery before randomisation; history of stroke before the most recent ipsilateral ischaemic event; systolic blood pressure at randomisation; degree of ipsilateral carotid stenosis (moderate, defined as a reduction in luminal diameter of 50–69% according to NASCET criteria, or severe, defined as 70–99%), and contralateral severe carotid stenosis or occlusion; centre contribution (total number of patients recruited into a trial at the centre), and centre recruitment rate (average number of patients recruited per month, starting with the first patient and ending with the last patient randomly assigned at the centre). The interaction with the time between the last ipsilateral ischaemic event and the date of treatment was assessed in the PP analysis only. Continuous subgroup variables were categorised before analysis with empirically relevant cutoff values. When cutoff values were not defined empirically, variables were dichotomised at rounded values similar to the median. For the categorical interaction, age was dichotomised into less than and greater than 70 years (near the median age of the combined trial populations); for the trend interaction, age was used a continuous variable. Interactions between treatment effect and a predefined subset of variables (age at randomisation, sex, type of most recent ipsilateral ischaemic event before randomisation, degree of ipsilateral carotid stenosis, and presence of contralateral severe carotid stenosis or occlusion) were also assessed for the secondary outcome event of disabling stroke or death. Significant interactions that were identified in the ITT analysis were also assessed in the PP analysis. Additionally, significant interactions were assessed after adjustment for baseline variables for which most of the data were gathered in all three trials, and checked at trial level for consistency.[24]

A post-hoc analysis was done to investigate the linearity of the potential age-treatment interaction on the primary outcome event. The specific RRs and 95% CIs for six age groups, obtained from a binomial regression model with

| | CAS (n=1725) | CEA (n=1708) |
|---|---|---|
| Age at randomisation (years; mean, SD) | 69·3 (9·0) | 69·7 (9·2) |
| Men | 1230/1725 (71%) | 1232/1708 (72%) |
| History of diabetes | 400/1715 (23%) | 423/1701 (25%) |
| History of hypertension | 1235/1715 (72%) | 1234/1701 (73%) |
| Systolic blood pressure at randomisation (mm Hg; mean, SD)* | 144·7 (21·2) | 143·7 (21·1) |
| History of hypercholesterolaemia† | 676/1108 (61%) | 708/1112 (64%) |
| Any smoking history (current or past) | 1106/1715 (64%) | 1095/1701 (64%) |
| Current smoking | 430/1715 (25%) | 424/1701 (25%) |
| History of coronary heart disease | 409/1715 (24%) | 420/1701 (25%) |
| History of peripheral artery disease† | 179/1108 (16%) | 166/1112 (15%) |
| Type of most recent ipsilateral ischaemic event before randomisation | | |
| Retinal ischaemia | 310/1712 (18%) | 297/1695 (18%) |
| Transient ischaemic attack | 589/1712 (34%) | 601/1695 (35%) |
| Hemispheric stroke | 813/1712 (47%) | 797/1695 (47%) |
| History of stroke before most recent event† | 190/1118 (17%) | 180/1119 (16%) |
| Days elapsed between most recent event and randomisation (median, IQR)‡ | 19 (7–50) | 19 (9–53) |
| Randomisation within 14 days of most recent event‡ | 587/1470 (40%) | 577/1457 (40%) |
| Days elapsed between most recent event and treatment (median, IQR)‡§ | 29 (14–65) | 32 (15–71) |
| Treatment within 14 days of most recent event‡§ | 372/1434 (26%) | 315/1404 (22%) |
| Score on the modified Rankin scale at baseline¶ | | |
| 0 | 826/1709 (48%) | 772/1694 (46%) |
| 1 | 461/1709 (27%) | 446/1694 (26%) |
| 2 | 295/1709 (17%) | 330/1694 (19%) |
| 3 | 107/1709 (6%) | 126/1694 (7%) |
| 4 | 19/1709 (1%) | 17/1694 (1%) |
| 5 | 1/1709 (<1%) | 3/1694 (<1%) |
| Degree of ipsilateral carotid stenosis | | |
| Moderate (50–69%) | 332/1725 (19%) | 327/1708 (19%) |
| Severe (70–99%) | 1393/1725 (81%) | 1381/1708 (81%) |
| Contralateral severe carotid stenosis (≥70%) or occlusion | 235/1575 (15%) | 235/1576 (15%) |

Data are n/N (%), unless otherwise indicated. Percentages exclude missing data (N=number of patients for whom data were available). CAS=carotid stenting. CEA=carotid endarterectomy. *Rounded to nearest 5 mm Hg because of digit preference. †Data were not gathered in the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial. ‡Date of the most recent ipsilateral ischaemic event before randomisation was not gathered in the SPACE trial initially, but for the meta-analysis these dates (or if the exact date was not known, whether or not treatment and randomisation took place within 14 days of the qualifying event) were gathered where available (see webappendix p 3 for numbers of patients with available timing of randomisation and treatment in the SPACE trial). §Patients receiving the randomly allocated treatment only (per-protocol analysis). ¶Modified Rankin scores at baseline might indicate non-stroke impairments; protocols of contributing trials excluded patients with disabling strokes.

***Table 1:*** **Baseline data of combined trial populations**

an interaction between treatment and categorised age, were compared graphically with RRs and 95% CIs across a range of ages, obtained from a model containing an interaction between treatment and continuous age, in which a linear effect of age on the log RR was assumed. Both models were additionally adjusted for the main interaction effects and source trial.

### Role of the funding source

The sponsors of the contributing trials, and of the meta-analysis, 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

All 3433 patients who were randomly assigned to treatment and followed up in the contributing trials were included in the pooled ITT analysis (figure 1). The PP analysis, which included only patients who underwent the procedure they were randomly allocated to, included 3324 patients (figure 1). 101 (39%) of 260 stent procedures were done with a supervisor in EVA-3S, 51 (9%) of 591 in SPACE, and 99 (12%) of 828 in ICSS.

Baseline characteristics of patients were similar in the stenting and endarterectomy groups of the pooled study populations (table 1; webappendix pp 2–4 for separate data from contributing trials). Median times between the most recent ipsilateral event and treatment were similar in both treatment groups in EVA-3S (stent 32 days [IQR 15–54], endarterectomy 33 days [17–58]) and SPACE (17 days [10–32] and 17 days [11–27], respectively) but were shorter in the stent group than in the endarterectomy group in ICSS (35 days [15–82] and 40 days [18–87], respectively). Among patients receiving the randomly allocated treatment with known timing of treatment, the proportion treated within 14 days of the last ipsilateral ischaemic event was greater in the SPACE trial (224 [33%] of 674) than in EVA-3S (107 [21%] of 517) or ICSS (356 [22%] of 1647). The proportion of patients with moderate (50–69%) carotid stenosis at baseline was greater in SPACE (455 [38%] of 1196) than in EVA-3S (36 [7%] of 527) and ICSS (168 [10%] of 1710). Otherwise, patients' baseline characteristics were similar in the three trials (webappendix pp 2–4).

In all three trials combined, a median of 52 patients (IQR 29–108) were recruited per centre, and the recruitment rate per centre was 1·1 patients per month (0·7–1·7). In EVA-3S, which was stopped early, centre contribution (median 28 patients recruited per centre [IQR 15–47]) and centre recruitment rate (0·7 patients per month [0·4–0·9]), were lower than in the other two trials (SPACE, 52 patients per centre [42–108] and 1·2 patients per month [0·9–1·9], respectively; ICSS, 58 patients per centre [33–108], and 1·2 patients per month [0·7–1·7], respectively).

Table 2 and figure 2 show the risk ratios and numbers of major outcome events in the pooled ITT analysis. The risk of any stroke or death (the primary outcome event) occurring within 120 days of randomisation in the combined analysis was higher in the stenting group than in the endarterectomy group (table 2). This effect was mainly attributed to a significant difference in stroke risk (table 2). The two treatment groups differed most in the occurrence of non-disabling strokes, which

| | CAS (n=1725) | CEA (n=1708) | Risk ratio* (95% CI) | p value† | Risk difference* (95% CI) |
|---|---|---|---|---|---|
| Any stroke or death | 153 (8·9%) | 99 (5·8%) | 1·53 (1·20 to 1·95) | 0·0006 | 3·2 (1·4 to 4·9) |
| Disabling stroke or death | 82 (4·8%) | 64 (3·7%) | 1·27 (0·92 to 1·74) | 0·15 | 0·9 (–0·4 to 2·3) |
| All-cause death | 32 (1·9%) | 22 (1·3%) | 1·44 (0·84 to 2·47) | 0·18 | 0·7 (–0·2 to 1·5) |
| Any stroke | 141 (8·2%) | 84 (4·9%) | 1·66 (1·28 to 2·15) | 0·0001 | 3·3 (1·7 to 5·0) |
| Stroke severity‡ | | | | | |
| Fatal | 13 (0·8%) | 6 (0·4%) | 2·15 (0·82 to 5·65) | 0·11 | 0·4 (–0·1 to 0·9) |
| Disabling | 56 (3·2%) | 43 (2·5%) | 1·29 (0·87 to 1·90) | 0·21 | 0·5 (–0·5 to 1·6) |
| Non-disabling | 72 (4·2%) | 36 (2·1%) | 1·99 (1·34 to 2·95) | 0·0004 | 2·0 (0·8 to 3·2) |
| Stroke type§ | | | | | |
| Ischaemic | 135 (7·8%) | 71 (4·2%) | 1·88 (1·42 to 2·48) | <0·0001 | 3·8 (2·2 to 5·4) |
| Haemorrhagic | 6 (0·3%) | 11 (0·6%) | 0·54 (0·20 to 1·46) | 0·21 | –0·3 (–0·8 to 0·1) |
| Unknown | 0 | 2 (0·1%) | .. | .. | .. |
| Stroke region§ | | | | | |
| Ipsilateral carotid | 126 (7·3%) | 75 (4·4%) | 1·66 (1·26 to 2·19) | 0·0003 | 3·0 (1·4 to 4·5) |
| Contralateral carotid or vertebrobasilar | 13 (0·8%) | 9 (0·5%) | 1·43 (0·61 to 3·34) | 0·40 | 0·2 (–0·3 to 0·8) |
| Unknown | 2 (0·1%) | 0 | .. | .. | .. |

Data are number (%), unless otherwise indicated. Percentages are number of events divided by number of patients. ..=Adjusted risk ratio or risk difference and 95% CI were not estimated because model did not converge. CAS=carotid stenting. CEA=carotid endarterectomy. *Adjusted for source trial. †Derived by use of binomial regression likelihood ratio test, adjusted for source trial. ‡One patient in the endarterectomy group had two stroke events within 120 days after randomisation. §Refers to first event.

*Table 2:* **Outcome events occurring within 120 days of randomisation (intention-to-treat analysis)**

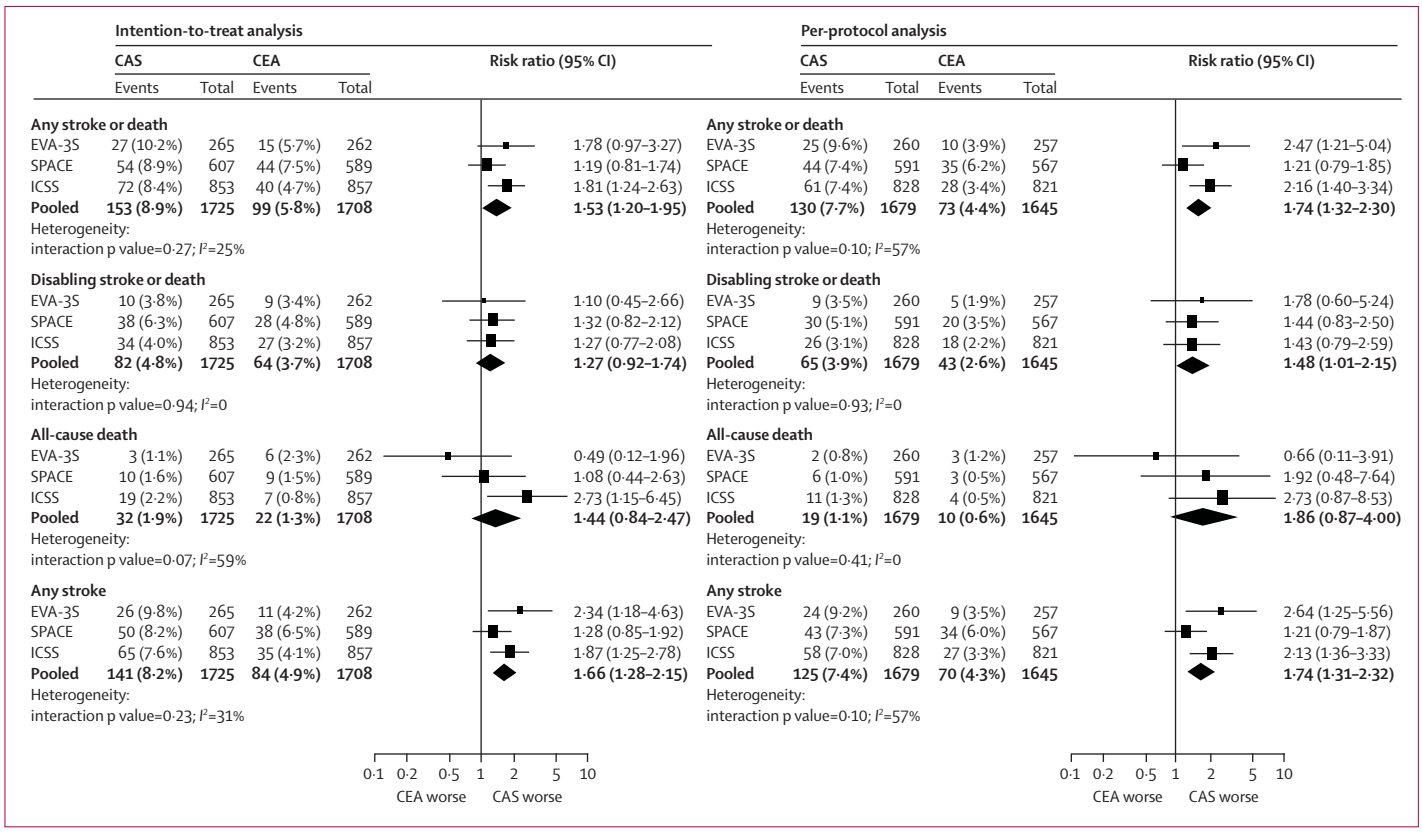



***Figure 2:*** **Forest plot of risk ratios of major outcome events in trials and in pooled analysis**

Data are number or number (%), unless otherwise indicated. Percentages are number of events divided by number of patients. Squares and horizontal bars represent within-trial treatment risk ratios and 95% CIs, respectively, with carotid endarterectomy (CEA) as the reference group, on a log scale. The size of squares represents study weight. Diamonds represent pooled risk ratios and 95% CIs, adjusted for source trial. In the investigation of heterogeneity, the interaction p value represents the significance of the interaction between source trial and treatment effect in the regression model (likelihood ratio test); a significant p value suggests heterogeneity. The estimate of $I^2$ was based on summary statistics from each trial and represents the percentage of the total variation in estimated treatment effects across trials better accounted for by heterogeneity rather than by chance. CAS=carotid stenting. EVA-3S=Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis. SPACE=Stent-Protected Angioplasty versus Carotid Endarterectomy. ICSS=International Carotid Stenting Study.

arose twice as frequently in the stenting group as in the endarterectomy group (table 2). There were no significant differences in the secondary outcome events of disabling stroke or death, and all-cause death (table 2).

The time-to-event sensitivity analysis of hazard ratios up to 120 days after randomisation produced a very similar result for the primary outcome event and the secondary outcome events (figure 3).

The results of the 30-day PP analysis were similar to the 120-day ITT analysis (table 3, figure 2). Absolute risk estimates in the PP analysis were lower than in the ITT analysis, but risk ratios were consistently higher: the risk of any stroke or death occurring between treatment and 30 days thereafter was higher in the stenting group than in the endarterectomy group (table 3). There was a significant difference in disabling stroke or death in favour of surgery (table 3). Myocardial infarction within 30 days of treatment was rare, occurring in fewer patients treated with stenting than in those undergoing endarterectomy (table 3). Cranial nerve palsy occurred almost exclusively in the endarterectomy group (table 3). Severe neck haematoma after surgery was more common than was haematoma at the site of skin puncture following stent treatment (table 3).

There was little evidence of statistical heterogeneity between the trials in the primary outcome event of any stroke or death, or in the secondary major outcome events of disabling stroke or death, and any stroke, both in the ITT and in the PP analyses (figure 2).

A significant interaction was noted between age and the effect of treatment on the primary outcome event (figure 4). In the ITT analysis, the estimated 120-day risk of any stroke or death in patients younger than 70 years was similar in the stenting and endarterectomy groups (figure 4); in patients 70 years or older, the estimated risk of stroke or death with stenting was twice that with endarterectomy (figure 4 shows p value for categorical interaction; p=0·0014 for trend interaction with age on a continuous scale). No other subgroups showed significant interactions with treatment for the primary outcome event. Age also significantly modified the effect of treatment on disabling stroke or death (figure 5; p=0·0007 for trend interaction).

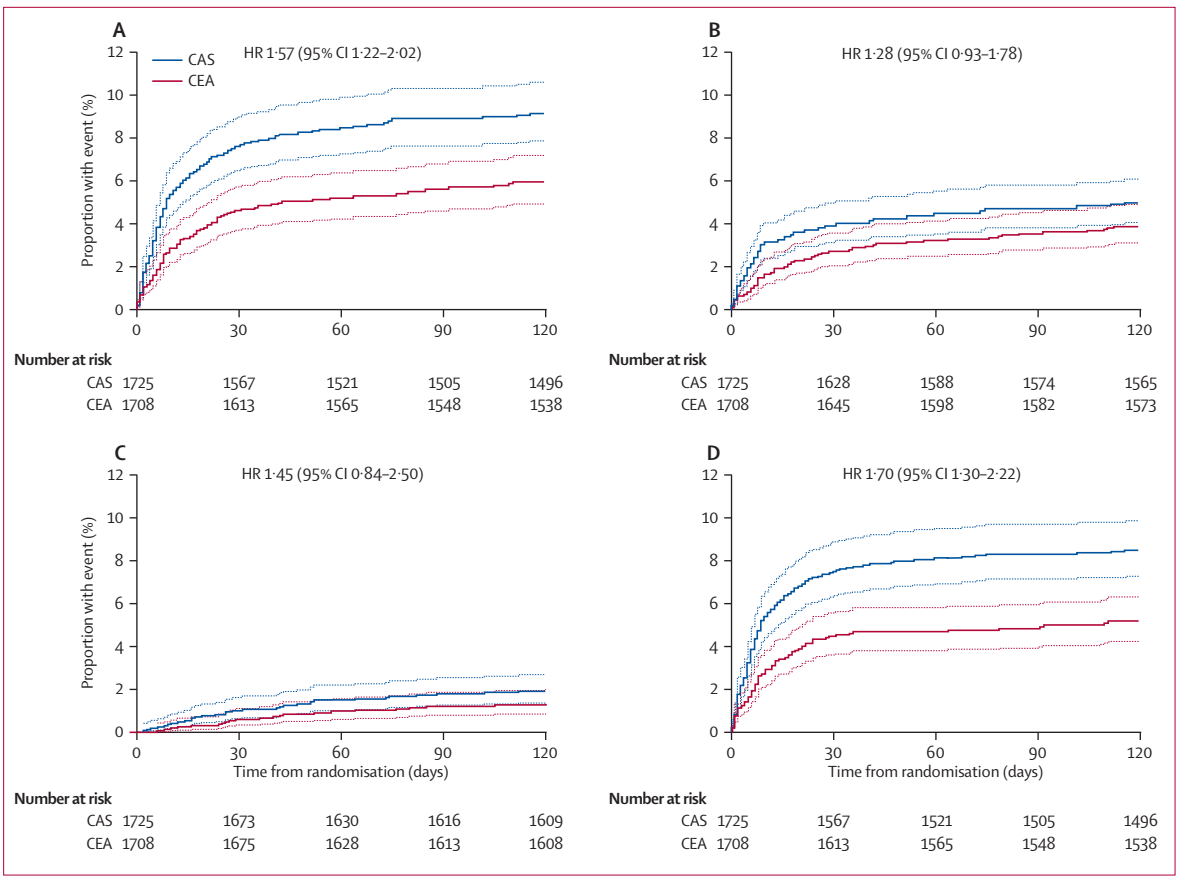



***Figure 3:*** **Kaplan-Meier plots of major outcome events occurring between randomisation and 120 days thereafter by treatment group in the pooled intention-to-treat analysis**

(A) Any stroke or death. (B) Disabling stroke or death. (C) All-cause death. (D) Any stroke. The graphs show the unadjusted Kaplan-Meier estimates (continuous lines) and 95% CIs (dashed lines) of the cumulative proportions of patients with an outcome event in the two treatment groups. HR=hazard ratio from Cox regression analysis with carotid endarterectomy (CEA) as the reference group, adjusted for source trial. CAS=carotid stenting.

The same qualitative effect of age was noted in all three trials with higher risk ratios in patients 70 years or older than in those younger than 70 years (figure 6), although the interaction was only significant in SPACE. In the pooled data, risk ratios of the primary outcome event across six age groups were generally consistent with those obtained assuming a linear effect of age on the log RRs (figure 7), with treatment effects favouring endarterectomy more strongly with increasing age (p=0·0015 for trend interaction across age groups).

The interaction between age and the effect of treatment on the primary outcome event was also significant in the PP analysis: risk estimates of stroke or death within 30 days of treatment among patients younger than 70 years were 43 (5·1%) of 851 patients in the stenting group and 37 (4·5%) of 821 in the endarterectomy group (RR 1·11 [0·73–1·71]); in the subgroup that was 70 years or older, the risk estimates were 87 (10·5%) of 828 patients and 36 (4·4%) of 824, respectively (2·41 [1·65–3·51]; categorical interaction p=0·0078, trend interaction p=0·0013). The risks of disabling stroke or death in the PP analysis of stenting versus endarterectomy were 18 (2·1%) of 851 versus 22 (2·7%) of 821 (0·79 [0·43–1·45]) in the younger age group, and 47 (5·7%) of 828 versus 21 (2·5%) of 824 (2·22 [1·34–3·68]) in the older age group (categorical interaction p=0·0098, trend interaction p=0·0002).

Analyses were additionally adjusted for the following baseline variables, for which most of the data were gathered for all trials: age at randomisation, and sex; history of diabetes, hypertension, smoking, and coronary heart disease; type of most recent event before randomisation; systolic blood pressure, modified Rankin scale, degree of ipsilateral carotid stenosis, centre contribution, and centre recruitment rate. After adjustment, the comparison of the main outcome events for stenting and endarterectomy, and the interactions between age and effect of treatment on any stroke or death, and disabling stroke or death remained essentially the same, both in the ITT and in the PP analyses (webappendix pp 5–6).

## Discussion

This prospective meta-analysis of patients' data from EVA-3S, SPACE, and ICSS shows that in patients with

| | CAS (n=1679) | CEA (n=1645) | Risk ratio* (95% CI) | p value† | Risk difference* (95% CI) |
|---|---|---|---|---|---|
| Any stroke or death | 130 (7·7%) | 73 (4·4%) | 1·74 (1·32 to 2·30) | 0·0001 | 3·4 (1·8 to 5·0) |
| Disabling stroke or death | 65 (3·9%) | 43 (2·6%) | 1·48 (1·01 to 2·15) | 0·04 | 1·2 (0 to 2·4) |
| All-cause death | 19 (1·1%) | 10 (0·6%) | 1·86 (0·87 to 4·00) | 0·10 | 0·6 (–0·1 to 1·2) |
| Any stroke | 125 (7·4%) | 70 (4·3%) | 1·74 (1·31 to 2·32) | 0·0001 | 3·3 (1·7 to 4·9) |
| Stroke severity‡ | | | | | |
| Fatal | 12 (0·7%) | 6 (0·4%) | 1·97 (0·74 to 5·23) | 0·16 | 0·4 (–0·1 to 0·8) |
| Disabling | 47 (2·8%) | 34 (2·1%) | 1·35 (0·87 to 2·08) | 0·18 | 0·6 (–0·4 to 1·6) |
| Non-disabling | 66 (3·9%) | 31 (1·9%) | 2·09 (1·37 to 3·19) | 0·0004 | 2·0 (0·8 to 3·2) |
| Stroke type§ | | | | | |
| Ischaemic | 118 (7·0%) | 57 (3·5%) | 2·02 (1·48 to 2·75) | <0·0001 | 3·7 (2·2 to 5·2) |
| Haemorrhagic | 7 (0·4%) | 12 (0·7%) | 0·57 (0·23 to 1·45) | 0·23 | –0·3 (–0·8 to 0·1) |
| Unknown | 0 | 1 (0·1%) | .. | .. | .. |
| Stroke region§ | | | | | |
| Ipsilateral carotid | 113 (6·7%) | 66 (4·0%) | 1·67 (1·24 to 2·25) | 0·0005 | 2·8 (1·3 to 4·3) |
| Contralateral carotid or vertebrobasilar | 10 (0·6%) | 4 (0·2%) | 2·45 (0·77 to 7·81) | 0·11 | 0·4 (–0·1 to 0·8) |
| Unknown | 2 (0·1%) | 0 | .. | .. | .. |
| Myocardial infarction | 4 (0·2%) | 7 (0·4%) | .. | .. | .. |
| Non-fatal | 1 (0·1%) | 7 (0·4%) | .. | .. | .. |
| Fatal | 3 (0·2%) | 0 | .. | .. | .. |
| Cranial nerve palsy¶ | 7 (0·4%) | 99 (6·0%) | 0·07 (0·03 to 0·15) | <0·0001 | –5·6 (–6·7 to –4·4) |
| Severe haematoma‖ | 12 (0·7%) | 32 (1·9%) | 0·37 (0·19 to 0·71) | 0·0016 | .. |
| Severe wound infection** | 1 (0·1%) | 4 (0·2%) | .. | .. | .. |

Data are number (%), unless otherwise indicated. Percentages are number of events divided by number of patients. CAS=carotid stenting. CEA=carotid endarterectomy. ..=Adjusted risk ratio or risk difference and 95% CIs were not estimated because model did not converge. *Adjusted for source trial. †Derived by use of binomial regression likelihood ratio test, adjusted for source trial. ‡One patient in the endarterectomy group had two stroke events within 30 days after treatment. §Refers to first event. ¶In the stenting group, cranial nerve palsy was caused by carotid artery dissection in two patients; in three patients, cranial nerve palsy occurred after conversion to endarterectomy following unsuccessful initial attempts at stenting; and two patients had isolated dysphagia attributable to cranial nerve palsy after stent procedures. ‖Defined as neck haematoma after endarterectomy or haematoma at the site of puncture after stenting, which required surgery, blood transfusion, or prolonged hospital stay. **Defined as any infection at the site of surgery or skin puncture in stenting, which required antibiotic treatment, surgery, or prolonged hospital stay.

*Table 3:* **Outcome events occurring within 30 days of treatment (per-protocol analysis)**

symptomatic carotid stenosis, the short-term risk of any stroke or death was significantly higher after stenting than after endarterectomy, with an estimated increase in RR of about 50% and an estimated absolute risk difference of 3% at 120 days after randomisation. However, the harm of stenting strongly depended on age; whereas estimated risks of stroke or death in patients younger than 70 years were similar in the two treatment groups, we noted that the risk of stenting doubled among patients 70 years or older compared with the younger age group. By contrast, the risk of stroke or death associated with endarterectomy was similar in old and young patients.

The major strengths of the present meta-analysis, which resulted from the prospective agreement at an early stage in the planning of the trials to do the pooled analysis, were that the study designs and patient populations were very similar between the contributing trials, and there was no strong evidence of heterogeneity in within-trial treatment effects.

Non-disabling strokes contributed the largest part of the combined primary outcome event and occurred twice as often in the stenting group as in the endarterectomy group. In comparison, the risk of disabling stroke or death was low in both treatment groups; the difference was not significant in the ITT analysis (table 2) but was in the PP analysis (table 3). Cranial nerve palsies occurred almost exclusively as a result of endarterectomy, and severe wound haematoma was also more common in the surgery group (table 3).

The investigators of the CREST study,[21] which included patients with symptomatic and asymptomatic carotid stenosis, reported similar rates of their combined primary outcome measure of any periprocedural stroke, myocardial infarction, death, or ipsilateral stroke during a median follow-up of 2·5 years, in both groups. However, among 1321 patients with symptomatic carotid stenosis, the risk of any stroke or death between randomisation and 30 days after treatment was significantly higher in the stenting group than in the surgery group (6·0% *vs* 3·2%), resulting in an estimated hazard ratio of 1·89 (95% CI 1·11–3·21; p=0·02), which was similar to the treatment effect noted in our pooled analysis. We have updated an earlier systematic summary-data meta-analysis of randomised trials in which endovascular treatment was compared with endarterectomy for symptomatic carotid stenosis,[25] which also included trials

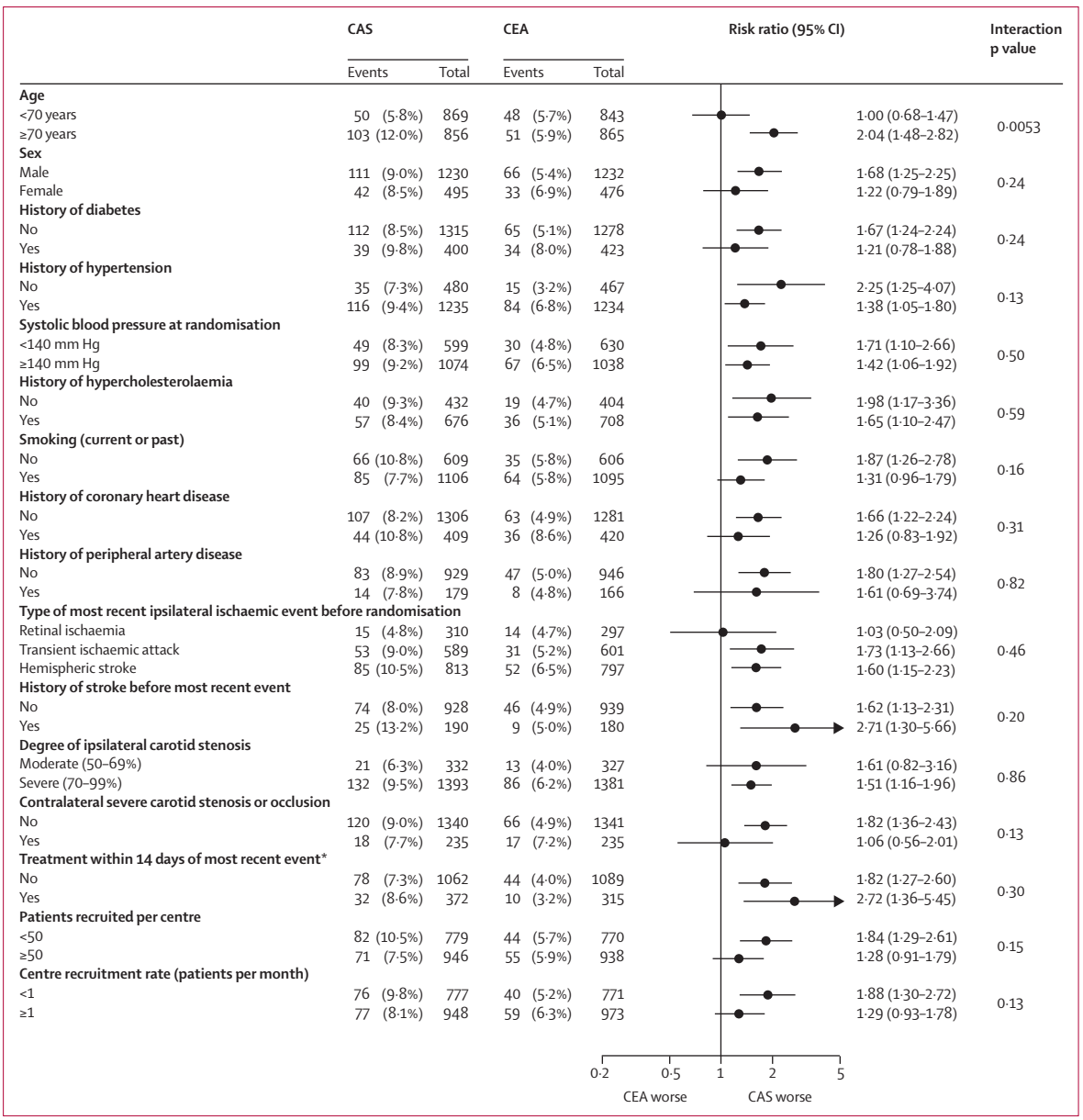



***Figure 4*: Treatment risk ratios of any stroke or death within 120 days of randomisation in patient subgroups**

Data are number or number (%), unless otherwise indicated. Percentages are number of events divided by number of patients. Analysis was by intention to treat. Dots and horizontal bars represent treatment risk ratios and 95% CIs within subgroups, respectively, with carotid endarterectomy (CEA) as the reference group, on a log scale. Risk ratios and interaction p values (categorical interaction) were adjusted for source trial. Patients with missing subgroup data were excluded from subgroup analysis (for details of missing data see webappendix pp 2–4). *Risk ratio of any stroke or death within 30 days of treatment in patients receiving the randomly allocated treatment (per-protocol analysis). CAS=carotid stenting.

that were not part of the present pooled analysis,[16–19,26] with the results of ICSS and CREST. This update included a total of 5617 patients enrolled in nine trials, of which the population of the present analysis represents 61%, and resulted in a very similar short-term risk ratio of any stroke or death (ITT, fixed-effect RR 1·61 [1·32–1·97]), indicating that our findings were not biased by exclusion of previous trials and CREST (webappendix pp 7–8).

One potential advantage of stenting as an alternative to endarterectomy was the avoidance of general complications of surgery or anaesthesia, most importantly myocardial infarction. Indeed, a reduction of the risk of myocardial infarction with stenting compared with endarterectomy was shown in the SAPPHIRE trial,[3] which included patients at increased risk of surgery. However, only a rise in creatinine kinase was needed for the definition of myocardial infarction in this trial, and there was no difference in the occurrence of Q-wave infarction. In CREST, in which patients were screened for myocardial infarction with routine postprocedural

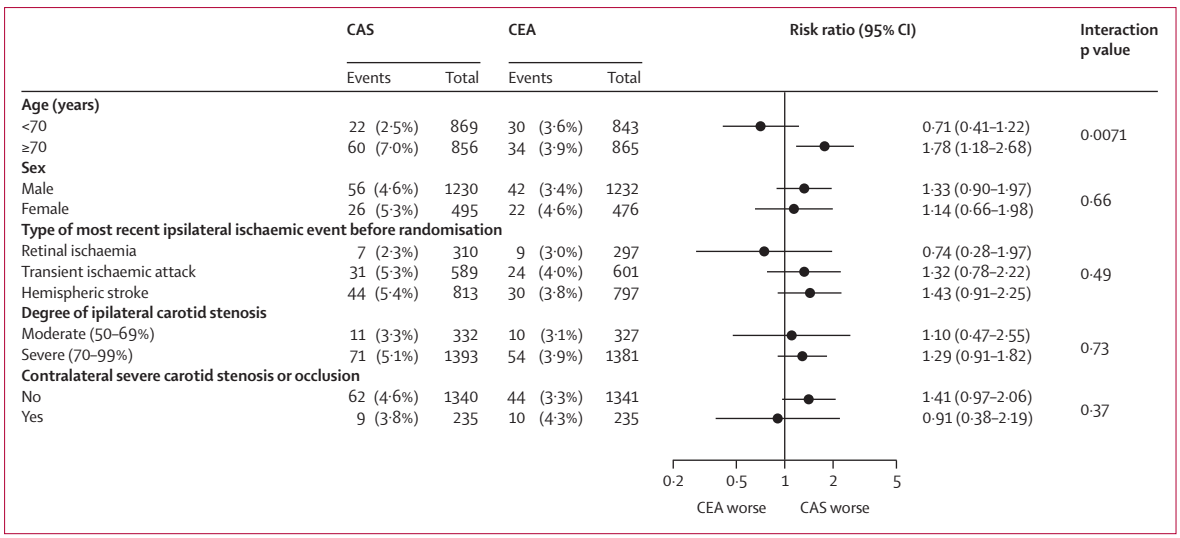



***Figure 5:*** **Treatment risk ratios of disabling stroke or death within 120 days of randomisation in selected patient subgroups**
Data are number or number (%), unless otherwise indicated. Percentages are number of events divided by number of patients. Analysis was by intention to treat. Dots and horizontal bars represent treatment risk ratios and 95% CIs, respectively, within subgroups, with carotid endarterectomy (CEA) as the reference group, on a log scale. Risk ratios and interaction p values (categorical interaction) were adjusted for source trial. Patients with missing subgroup data were excluded from subgroup analysis (for details of missing data see webappendix pp 2–4). CAS=carotid stenting.

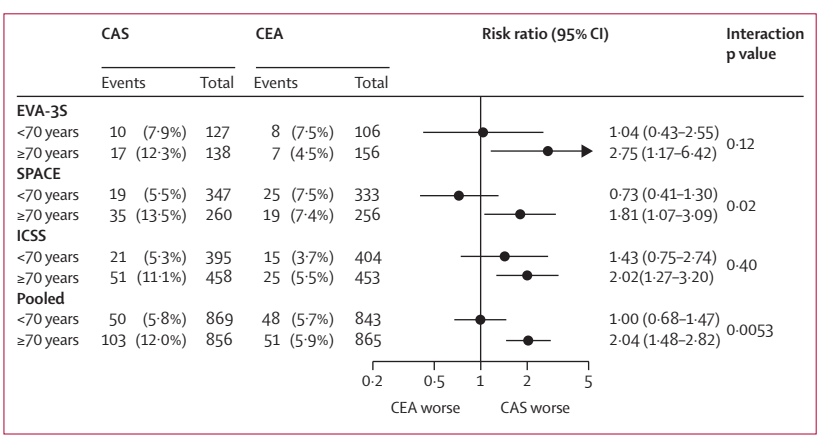



***Figure 6:*** **Interaction between age and treatment risk ratios of any stroke or death within 120 days of randomisation in contributing trials**
Data are number or number (%), unless otherwise indicated. Percentages are number of events divided by number of patients. Analysis was by intention to treat. Dots and horizontal bars represent treatment risk ratios and 95% CIs, respectively, within subgroups, with carotid endarterectomy (CEA) as the reference group, on a log scale. Within-trial risk ratios and interaction p values (categorical interaction) were unadjusted; pooled risk ratios and interaction p values were adjusted for source trial. CAS=carotid stenting. EVA-3S=Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis. SPACE=Stent-Protected Angioplasty versus Carotid Endarterectomy. ICSS=International Carotid Stenting Study.

ECG and testing of cardiac enzymes, the risk of myocardial infarction in symptomatic patients was 2·3% with endarterectomy and 1·0% with stenting. By contrast, in the trials included in the present analysis, only patients with chest pain or other cardiac symptoms tended to be screened for myocardial infarction, and the pooled risk of myocardial infarction was less than 0·5% in both treatment groups. Another reason for the differences in rates of myocardial infarction between the European and the American trials might be the substantially higher baseline prevalence of cardiovascular disease in CREST (38% among symptomatic patients). Importantly, in an MRI substudy of ICSS, the risk of silent cerebral ischaemia was three times greater with stenting than with endarterectomy, which counterbalances the increase in the risk of silent myocardial infarction associated with endarterectomy in CREST.[27]

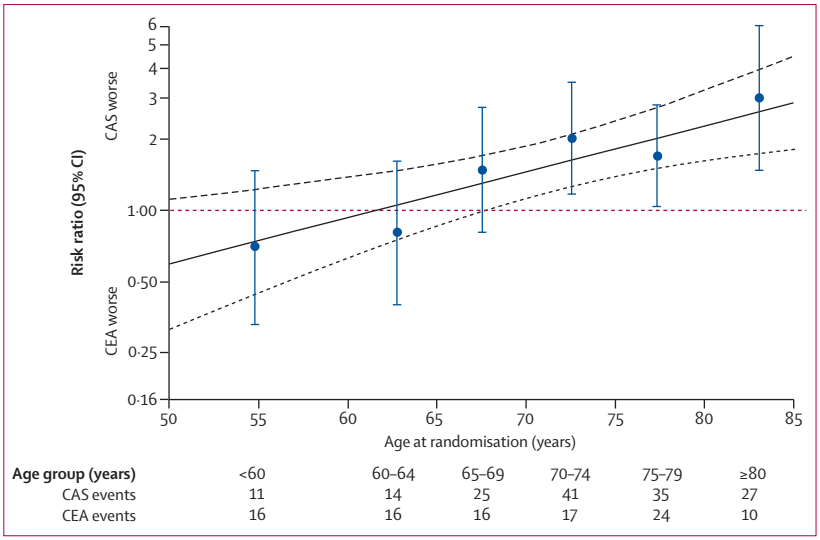
Pooling of data from individual patients allowed for much higher statistical power for subgroup analysis than had previously been the case at the level of trials. To reduce the danger of false-positive subgroup effects, we prespecified a list of subgroup variables before the trial data were pooled and analysed. Among all examined variables, age was the only one that significantly modified the effect of treatment on the primary outcome event. Whereas risk estimates of any stroke or death within the first 120 days after randomisation were similar with both treatments among patients younger than 70 years, the risk was two times greater with stenting than with endarterectomy in the older age group (figure 4). Age also significantly modified the effect of treatment on disabling stroke or death. Thus, the age-related increase in complication rates with stenting was not restricted to non-disabling strokes. Both interactions were also significant in the PP analysis.

Several ancillary analyses were done to validate and further explore the relation between age and the relative risk of the two procedures. First, we noted a consistent effect of age at the level of all three trials included in the meta-analysis, with higher risk ratios (favouring surgery) in the older age groups than in the younger patients. Second, the age interaction remained significant after adjustment for other baseline variables. Third, the exploratory analysis of treatment effects in six age strata

was consistent with a linear increase of the risk ratio between stenting and endarterectomy with age. This notion lends support to a biological mechanism mediating the association between age and stroke risk in stenting; age might represent a marker of the general burden of atherosclerosis of the aortic arch, or might be associated with increased plaque instability, altered configuration of the aortic arch, or vessel tortuosity. Hence, elderly patients might be at increased risk of dislodgment of plaque debris or thrombi during the stent procedure. Our results are consistent with previous studies showing increased stroke rates with increasing age in carotid stenting,[10] but little effect of age on risk associated with endarterectomy.[8,9] A similar age interaction was also reported in CREST with respect to the primary outcome event in the total study population, but this interaction was not reported separately for the subgroup of symptomatic patients.

Consistent with published work, surgical risk was higher in women than in men, whereas risk of stenting was virtually unaffected by sex.[8–10] Although the confidence interval of the risk ratio in women crossed 1, there was no significant difference in treatment effects between men and women, hence the overall estimate of relative risk applies to both sexes (figure 4). Findings of previous research have also identified systolic hypertension, peripheral vascular disease, and contralateral carotid occlusion as risk factors for stroke associated with endarterectomy.[7,8] Whereas the relative harm of stenting in comparison with endarterectomy seemed to be reduced in all of these patient groups in the present meta-analysis (with the exception of peripheral artery disease), confidence intervals of risk ratios in subgroups overlapped broadly, and none of the interactions was significant. Patients in whom the carotid stenosis caused a cerebral transient ischaemic attack or a stroke are known to be at higher risk of complications than are those presenting with ocular ischaemia, both with endarterectomy and stenting.[8,10] However, even in the combined analysis, only 607 patients had retinal qualifying events, and few outcome events occurred in this subgroup. Therefore, we cannot draw any conclusions about the safety of stenting in relation to endarterectomy in any of those subgroups.

There has been concern that the unfavourable short-term outcome after stenting in some of the trials suggested insufficient experience with the procedure.[28–30] The number of interventions and endarterectomies undertaken by collaborating radiologists and surgeons before joining the trials and outside the trials during recruitment was not available for the present analysis. Instead we used total numbers of patients recruited and recruitment rates at the treating centres as an estimation of the experience of staff who undertake the procedures. Although risk ratios were lower in centres contributing larger numbers of patients and with higher recruitment rates than in smaller centres, they were still in favour of endarterectomy, and interactions were not significant. Our findings therefore do not lend support to the assumption that the difference in short-term outcome between stenting and endarterectomy in some trials is mainly attributed to inclusion of inexperienced centres.




| Age group (years) | <60 | 60–64 | 65–69 | 70–74 | 75–79 | ≥80 |
|---|---|---|---|---|---|---|
| CAS events | 11 | 14 | 25 | 41 | 35 | 27 |
| CEA events | 16 | 16 | 16 | 17 | 24 | 10 |

***Figure 7:*** **Treatment risk ratios of any stroke or death within 120 days of randomisation by age (both continuous and by age groups)**
Analysis was by intention to treat. Blue dots and vertical bars represent treatment risk ratios and 95% CIs, respectively, adjusted for source trial for each age group, with carotid endarterectomy (CEA) as the reference group, plotted on a log scale at the mean age in each group. The continuous risk ratios by age (line) and 95% CI (dashed lines) were calculated by use of a binomial regression model containing treatment, continuous age, and their interaction, adjusted for source trial. CAS=carotid stenting.

What are the implications of the results of our meta-analysis for clinical practice? Results from clinical trials and previous meta-analyses of summary data have not justified any shift away from endarterectomy as the treatment of choice for symptomatic carotid stenosis. Current recommendations have restricted the use of stenting to symptomatic patients with contraindications to endarterectomy, carotid stenosis at surgically inaccessible sites, recurrent stenosis after previous endarterectomy, and stenosis after irradiation.[31] Our findings suggest that stenting might also be a viable alternative to endarterectomy in younger patients, in whom surgery could otherwise be undertaken without increased risk. Some uncertainty remains about the potentially higher rate of recurrent stenosis after stenting than with endarterectomy, and the implications this might have for long-term stroke risk in young patients treated with stents.[32,33] With these caveats in mind, an approach of offering stenting when technically feasible as an alternative option to endarterectomy to patients younger than 65–70 years with symptomatic carotid stenosis, in centres in which acceptable periprocedural outcomes have been independently verified, might seem justified, as long as patients are made aware of a possible increase in the risk of restenosis.

Our study has some limitations. Even with the pooled analysis of three randomised trials, statistical power was insufficient to provide a reliable comparison of treatment

risks in some patient subgroups in which stenting might theoretically represent a safe alternative to endarterectomy—eg, women, patients presenting with ocular ischaemia, and those with severe contralateral carotid disease. The recommendation, on the basis of findings of clinical trials in which endarterectomy was compared with medical treatment, is that carotid stenosis should be treated within 2 weeks of symptoms.[8] In our pooled analysis, only about one in four patients was treated within this timeframe. However, no significant difference in treatment effect was noted between patients treated within 2 weeks and those treated later. Imaging of the aortic arch before randomisation was not specified in the trials included in the meta-analysis; additional research is needed to clarify whether the age-related increase in stroke associated with stenting is mediated through atherosclerosis and configuration of the aortic arch. The exact number of procedures undertaken by each surgeon and interventionalist before joining the trials has not been consistently gathered in the contributing trials, and the effect of individual experience on complication rates needs further investigation. Data from the subgroup of 1321 patients with symptomatic carotid stenosis who were randomly assigned in CREST were not available for the present analysis. However, the prospectively defined meta-analysis of EVA-3S, SPACE, and ICSS showed a highly significant age-dependent variation of risks posed by stenting that has implications for clinical practice, and which is unlikely to be substantially changed by inclusion of data from CREST. In conclusion, there is strong evidence that, in the short term, the harm of stenting compared with endarterectomy decreases with younger age.

#### Contributors

LHB wrote the first draft of the report and was supervised by MMB. JD and AA designed the statistical analysis plan and JD undertook the statistical analyses. JLM, PAR, JD, and LHB extracted patients' data from contributing trials. All the authors listed in the writing committee made substantial contributions to conception and design of the study, acquisition of data, or analysis and interpretation of data; and also contributed to drafting the report or revising it critically for important intellectual content. MMB, JLM, and PAR contributed equally to the report. LHB and MMB had the final responsibility for the analyses and the content of the report.

#### Carotid Stenting Trialists' Collaboration (CSTC)

*Writing Committee:* Leo H Bonati (Department of Neurology and Stroke Unit, University Hospital Basel, Switzerland; Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, UK), Joanna Dobson (Medical Statistics Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK), Ale Algra (Department of Neurology and Julius Centre for Health Sciences and Patient Care, University Medical Centre Utrecht, Netherlands), Alain Branchereau (Department of Vascular Surgery, Hôpital Timone Adultes, Marseille, France), Gilles Chatellier (Clinical Research Unit, Hôpital Européen Georges Pompidou, Université René Descartes, Paris, France), Gustav Fraedrich (Department of Vascular Surgery, Medical University, Innsbruck, Austria), Willem P Mali (Department of Radiology, University Medical Centre Utrecht, Netherlands), Hermann Zeumer (Department of Diagnostic and Interventional Neuroradiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany), Martin M Brown* (Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, UK), Jean-Louis Mas* (Department of Neurology, Hôpital Sainte-Anne, Université Paris Descartes, INSERM UMR894, Paris, France), Peter A Ringleb* (Department of Neurology, University Hospital Heidelberg, Germany). *Contributed equally to the report.

*Steering Committee:* A Algra (independent chair); *EVA-3S* A Branchereau, G Chatellier, J-L Mas; *SPACE* G Fraedrich, P A Ringleb, H Zeumer; *ICSS* L H Bonati, M M Brown, W P Mali; J Dobson (meta-analysis statistician).

*Steering Committees of trials included in CSTC: EVA-3S* J-L Mas (chair), G Chatellier (co-chair), J-P Becquemin, J-F Bonneville, A Branchereau, D Crochet, J C Gaux, V Larrue, D Leys, J Watelet; *SPACE* W Hacke (chair), M Hennerici, J R Allenberg, P C Maurer, H-H Eckstein, H Zeumer, O Jansen; *ICSS* A Algra, J Bamford (chair), J Beard, M Bland, A W Bradbury, M M Brown (chief investigator), A Clifton, P Gaines, W Hacke, A Halliday, I Malik, J-L Mas, A J McGuire, P Sidhu, G Venables.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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