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Age Modifies the Relative Risk of Stenting versus Endarterectomy for Symptomatic Carotid Stenosis — A Pooled Analysis of EVA-3S, SPACE and ICSS☆

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Abstract *Background:* Recent randomised controlled trials comparing carotid artery stenting (CAS) with endarterectomy (CEA) for the treatment of symptomatic carotid stenosis were not powered to investigate differences in risks in specific patient subgroups. We therefore performed a pooled analysis of individual patient data from the Symptomatic Severe Carotid Stenosis trial (EVA-3S), the Stent-Protected Angioplasty versus Carotid Endarterectomy trial (SPACE), and the International Carotid Stenting Study (ICSS).
Methods: Individual data from all 3433 patients randomised and analysed in these trials were pooled and analysed with fixed-effect binomial regression models adjusted for source trial. The primary outcome event was any stroke or death.
Results: In the first 120 days after randomisation (ITT analysis), the primary outcome event occurred in 153/1725 patients in the CAS group (8.9%) compared with 99/1708 patients in the CEA group (5.8%, risk ratio [RR] 1.53, 95% confidence interval [CI] 1.20–1.95, $p = 0.0006$; absolute risk difference 3.2, 95% CI 1.4–4.9). Age was the only subgroup variable which significantly modified the treatment effect: in patients <70 years old (the median age), the 120-day stroke or death risk was 5.8% in CAS and 5.7% in CEA (RR 1.00, 0.68–1.47); in patients 70 years or older, there was an estimated two-fold increase in risk with CAS over CEA (12.0% vs. 5.9%, RR 2.04, 1.48–2.82, interaction $p = 0.0053$).
Interpretation: Endarterectomy was safer in the short-term than stenting, because of an increased risk of stroke associated with stenting in patients over the age of 70 years. Stenting should be avoided in older patients, but may be as safe as endarterectomy in younger patients. Determination of the efficacy and ultimate balance between the two procedures requires further data on long-term stroke recurrence.

☆ Contributors, CSTC steering committee (a full list of members appears at the end of this paper). This is a summary of the full paper "Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data" which has been published in *The Lancet* 2010; **376**(9746):1062–73.

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Introduction

In patients with recently symptomatic carotid stenosis, carotid endarterectomy reduces the risk of further stroke.[1,2] In recent years, endovascular treatment with placement of a stent has emerged as an alternative option to treat carotid stenosis. Several large trials in patients with symptomatic carotid stenosis who could undergo surgery at standard risk — the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial (EVA-3S), the Stent-Protected Angioplasty versus Carotid Endarterectomy trial (SPACE) and the International Carotid Stenting Study (ICSS) — have shown a higher peri-procedural stroke risk with stenting than with endarterectomy.[3–5] However, peri-procedural risks of stenting and endarterectomy vary with patient characteristics.[6–9] Stenting might represent a safe alternative to endarterectomy in specific groups of patients, but no single trial was large enough to compare the risks between these procedures with an acceptable degree of certainty.

With these considerations in mind, the investigators of EVA-3S, SPACE, and ICSS set up the Carotid Stenting Trialists' Collaboration (CSTC) with the purpose of conducting a prospective meta-analysis of individual patient data from these trials. The main objective was to compare the safety and efficacy of stenting and endarterectomy in pre-defined subgroups of patients. In this report, we summarise the main results of the analysis of the short-term (safety) outcome. The full results of this analysis were published in *The Lancet* in September 2010.[10]

Methods

EVA-3S (NCT 00190398), SPACE (ISRCTN 57874028), and ICSS (ISRCTN 25337470) were randomised clinical trials with blinded outcome adjudication. In all three trials, patients with recently symptomatic moderate or severe carotid stenosis (≥50% reduction of the lumen diameter according to the method used in the NASCET Trial[1]), who were considered equally suited for either procedure, were randomly allocated to undergo treatment by stenting or endarterectomy.[11–13] The pooled analysis of individual patient data was prospectively agreed at the design stage of these trials.[14]

The primary outcome event for the pooled analysis of short-term outcome was the combination of any stroke or death. Secondary major outcome events were disabling stroke or death, all-cause death, and any stroke. The intention-to-treat (ITT) analysis included all patients randomised and analysed in the contributing trials and all outcome events occurring between randomisation and 120 days thereafter. The per-protocol (PP) analysis included only those patients who received the randomly allocated treatment 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. The pooled data were analysed with fixed-effect binomial regression models including source trial terms as covariables, to obtain overall estimates of risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CI) of major outcome events.

In the ITT analysis, the interactions between the effect of treatment on the primary outcome event and 16 prospectively defined subgroup variables were examined separately in the binomial regression model. These subgroup variables were age; sex; history of diabetes, hypertension, hypercholesterolaemia, smoking, coronary heart disease, and peripheral artery disease; type of the qualifying event (retinal ischaemia including transient monocular blindness or retinal infarct, hemispheric transient ischaemic attack, or hemispheric ischaemic stroke); history of stroke before the most recent ipsilateral ischaemic event; systolic blood pressure at randomisation; degree of ipsilateral carotid stenosis (moderate, 50—69%; or severe, 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). Significant subgroup-treatment effect interactions identified in the ITT analysis were also examined in the PP analysis. In addition, the interaction with the delay between the qualifying event and treatment was assessed in the PP analysis.

Results

All 3433 patients (1725 in the stenting group and 1708 in the endarterectomy group) who were randomised and followed up in the contributing trials were included in the pooled ITT analysis. The PP analysis comprised 3324 patients who underwent stenting ($n = 1679$) or endarterectomy ($n = 1645$), as their randomly allocated revascularisation procedure. Patient baseline characteristics were similar in the two treatment groups (Table 1).

Risk ratios and numbers of major outcome events in the pooled ITT analysis are provided in Table 2. The risk of any stroke or death occurring within 120 days of randomisation was 8.9% in the stenting group and 5.8% in the endarterectomy group (RR 1.53, 95% CI 1.20—1.95, $p = 0.0006$). This effect was mainly driven by a significant difference in stroke risk (8.2% vs. 4.9%, RR 1.66, 1.28—2.15, $p = 0.0001$). Among the different subtypes of stroke severity, the largest difference was observed in the occurrence of non-disabling strokes, which were twice as frequent in the stenting group as in the endarterectomy group (4.2% vs. 2.1%, RR 1.99, 1.34—2.95, $p = 0.0004$). There were no statistically significant differences in the secondary outcome events of disabling stroke or death (4.8% vs. 3.7%, RR 1.27, 0.92—1.74) and all-cause death (1.9% vs. 1.3%, RR 1.44, 0.84—2.47).

The 30-day PP analysis produced similar results to the 120-day ITT analysis (Table 3): the risk of any stroke or death occurring between treatment and 30 days thereafter was 7.7% in the stenting group compared with 4.4% in the endarterectomy group (RR 1.74, 1.32—2.30). In the PP analysis, the difference between the procedures in disabling stroke or death, which also favoured surgery, became significant (3.9% vs. 2.6%, RR 1.48, 1.01—2.15, $p = 0.04$). There was no difference in the risk of myocardial infarction which occurred in 0.2% of patients receiving stent treatment and 0.4% of patients undergoing surgery. Cranial nerve palsy almost exclusively occurred in patients

Table 1 Baseline data of the combined trial populations.

		CAS (n = 1725)		CEA (n = 1708)	
		N, mean or median	%, SD or IQR	*N*, mean or median	%, SD or IQR
Age at randomisation, years (mean, SD)		69.3	9.0	69.7	9.2
Male (N, %)		1230	71%	1232	72%
History of diabetes (N, %)		400	23%	423	25%
History of hypertension (N, %)		1235	72%	1234	73%
Systolic blood pressure at randomisation, mm Hg (mean, SD)[a]		144.7	21.2	143.7	21.1
History of hypercholesterolaemia (N, %)[b]		676	61%	708	64%
Any smoking history (current or past) (N, %)		1106	64%	1095	64%
Current smoking (N, %)		430	25%	424	25%
History of coronary heart disease (N, %)		409	24%	420	25%
History of peripheral artery disease (N, %)[b]		179	16%	166	15%
Type of most recent ipsilateral ischaemic event before randomisation (N, %)	Retinal ischaemia	310	18%	297	18%
	TIA	589	34%	601	35%
	Hemispheric stroke	813	47%	797	47%
History of stroke before most recent event (N, %)[b]		190	17%	180	16%
Days elapsed between most recent event and randomisation (median, IQR)[c]		19	7.0—50.0	19	9.0—53.0
Randomisation within 14 days of most recent event (N, %)[c]		587	40%	577	40%
Days elapsed between most recent event and treatment (median, IQR)[c,d]		29	14—65	32	15—71
Treatment within 14 days of most recent event[c,d]		372	26%	315	22%
Score on the Modified Rankin Scale at baseline (N, %)[e]	0	826	48%	772	46%
	1	461	27%	446	26%
	2	295	17%	330	19%
	3	107	6%	126	7%
	4	19	1%	17	1%
	5	1	0%	3	0%
Degree of ipsilateral carotid stenosis (N, %)[f]	Moderate (50—69%)	332	19%	327	19%
	Severe (70—99%)	1393	81%	1381	81%
Contralateral severe carotid stenosis (≥70%) or occlusion (N, %)		235	15%	235	15%
Number of patients recruited per centre (median, IQR)		52 (29.0—108.0)			
Centre recruitment rate (average number of patients recruited per month; median, IQR)		1.1 (0.7—1.7)			

BP, blood pressure; CAS, Carotid stenting; CEA, carotid endarterectomy; IQR, interquartile range; SD, standard deviation. Percentages exclude missing data.

[a] Rounded to nearest 5 mm Hg due to digit preference.

[b] Data collected in EVA-3S and ICSS only.

[c] The date of the most recent ipsilateral ischaemic event before randomisation was not collected in the SPACE trial initially, but for the meta-analysis these dates (or if the exact date was unknown, whether or not randomisation and treatment took place within 14 days of the qualifying event), were retrieved where available.

[d] Patients receiving the randomly allocated treatment only (per-protocol-analysis).

[e] Modified Rankin Scores at baseline may reflect non-stroke impairments; protocols of contributing trials excluded patients with disabling strokes.

[f] Degree of stenosis measured by NASCET method or equivalent non-invasive method.

treated surgically (6.0%), and wound haematoma was also more common in the endarterectomy group (Table 3).

There was a statistically significant interaction between age and the effect of treatment on the primary outcome event. In the ITT analysis, the estimated 120-day risks of any stroke or death in patients <70 years old were 5.8% in the stenting group and 5.7% in endarterectomy group (RR 1.00, 0.68—1.47); in patients 70 years or older, there was an estimated two-fold increase in the risk of stroke or death with stenting over endarterectomy (12.0% vs. 5.9%, RR 2.04, 1.48—2.82, interaction $p = 0.0053$). No other subgroups showed statistically significant interactions with treatment on the primary outcome event. Age also significantly modified the effect of treatment on disabling stroke or death (<70 years: 2.5% (CAS) vs. 3.6% (CEA), RR 0.71, 0.41—1.22; ≥70 years: 7.0% vs. 3.9%, RR 1.78, 1.18—2.68; interaction $p = 0.0071$).

In an exploratory post-hoc analysis, risk ratios of the primary outcome event across six age groups were broadly

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

	CAS $n = 1725$ N events (%[a])	CEA $n = 1708$ N events (%[a])	Risk ratio[b] (95% CI)	p-Value[c]	Risk difference[b] (95% CI)
Any stroke or death	153 (8.9%)	99 (5.8%)	1.53 (1.20, 1.95)	0.0006	3.2 (1.4, 4.9)
Disabling stroke or death	82 (4.8%)	64 (3.7%)	1.27 (0.92, 1.74)	0.15	0.9 (−0.4, 2.3)
All-cause death	32 (1.9%)	22 (1.3%)	1.44 (0.84, 2.47)	0.18	0.7 (−0.2, 1.5)
Any stroke	141 (8.2%)	84 (4.9%)	1.66 (1.28, 2.15)	0.0001	3.3 (1.7, 5.0)
Stroke severity[d]					
Fatal stroke	13 (0.8%)	6 (0.4%)	2.15 (0.82, 5.65)	0.11	0.4 (−0.1, 0.9)
Disabling stroke	56 (3.2%)	43 (2.5%)	1.29 (0.87, 1.90)	0.21	0.5 (−0.5, 1.6)
Non-disabling stroke	72 (4.2%)	36 (2.1%)	1.99 (1.34, 2.95)	0.0004	2.0 (0.8, 3.2)
Stroke pathology[e]					
Ischaemic stroke	135 (7.8%)	71 (4.2%)	1.88 (1.42, 2.48)	<0.0001	3.8 (2.2, 5.4)
Haemorrhagic stroke	6 (0.3%)	11 (0.6%)	0.54 (0.20, 1.46)	0.21	−0.3(−0.8,0.1)
Unknown pathology	0	2 (0.1%)	–[f]	–[f]	–[f]
Stroke territory[e]					
Ipsilateral carotid	126 (7.3%)	75 (4.4%)	1.66 (1.26, 2.19)	0.0003	3.0 (1.4, 4.5)
Contralateral carotid or vertebrobasilar	13 (0.8%)	9 (0.5%)	1.43 (0.61, 3.34)	0.40	0.2 (−0.3, 0.8)
Unknown territory	2 (0.1%)	0	–[f]	–[f]	–[f]

CAS, carotid stenting; CEA, carotid endarterectomy; CI, confidence interval.
[a] Crude percentages (number of events divided by number of patients).
[b] Adjusted for source trial.
[c] P-values derived from binomial regression likelihood ratio test, adjusted for source trial.
[d] One patient in the endarterectomy group had two stroke events within the 120 day period after randomisation.
[e] Stroke pathology and stroke territory refer to first event.
[f] Adjusted risk ratio or risk difference and CI not estimated as model did not converge.

consistent with those obtained assuming a linear effect of age on the log risk ratios, 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 <70 years old were 5.1% in the stenting group and 4.5% in the endarterectomy group (RR 1.11, 0.73, 1.71); in the subgroup of ≥70 year olds risk estimates were 10.5% and 4.4%, respectively (RR 2.41, 1.65−3.51; interaction $p = 0.0078$).

Discussion

This prospective pooled analysis of individual patient data from the EVA-3S, SPACE and ICSS trials confirmed an increased short-term risk of any stroke or death among patients randomised to stenting compared with endarterectomy. However, the relative harm of stenting strongly depended on age: risks of stroke or death in patients younger than 70 years old were similar in the two treatment groups; by contrast, there was a two-fold increase in the risk of stenting compared with endarterectomy among patients ≥70 years old. The difference in the primary endpoint was mainly attributed to a higher risk of non-disabling strokes, which occurred twice as often in the stenting group as in the endarterectomy group (4.2 vs. 2.1%). The difference in risk of disabling stroke or death was not statistically significant in the ITT analysis (4.8 vs. 3.7%) but reached statistical significance in the PP analysis (3.9 vs. 2.6%).

In the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) there was no significant difference between these two procedures in the combined primary outcome measure of any peri-procedural stroke, MI, or death, or ipsilateral stroke during a median follow-up of 2.5 years.[15] The main difference between CREST and the trials included in the present pooled analysis was that CREST enrolled both patients with symptomatic and asymptomatic carotid stenosis. Yet among the 1321 patients with symptomatic carotid stenosis in CREST, the risk of any stroke or death between randomisation and 30 days after treatment was significantly higher in the stenting than in the surgery arm (6.0% vs. 3.2%); the corresponding hazard ratio of 1.89 (95% confidence interval 1.11−3.21) was very similar to the treatment effect observed in our pooled analysis.

The main advantage of the present meta-analysis was the availability of individual patient data. Pooling these data from three randomised trials allowed for a much higher statistical power to perform subgroup analysis. Among the prespecified list of 16 subgroup variables, age was the only one which significantly altered the relative risk of stroke or death between stenting and endarterectomy in the short term. Whereas risk estimates were similar with both treatments among patients <70 years old, a two-fold increase in risk with stenting over endarterectomy was observed in the older age group. Age also significantly modified the effect of treatment on disabling stroke or death. The exploratory analysis of relative treatment risks across six age level was consistent with the assumption of a linear increase in risk of peri-procedural stroke risk associated with stent treatment. Possible mechanisms

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

	CAS $n = 1679$ N events (%[a])	CEA $n = 1645$ N events (%[a])	Risk ratio[b] (95% CI)	p-Value[c]	Risk difference[b] (95% CI)
Any stroke or death	130 (7.7%)	73 (4.4%)	1.74 (1.32−2.30)	0.0001	3.4 (1.8, 5.0)
Disabling stroke or death	65 (3.9%)	43 (2.6%)	1.48 (1.01−2.15)	0.04	1.2 (0.0, 2.4)
All-cause death	19 (1.1%)	10 (0.6%)	1.86 (0.87−4.00)	0.10	0.6 (−0.1, 1.2)
Any stroke	125 (7.4%)	70 (4.3%)	1.74 (1.31−2.32)	0.0001	3.3 (1.7, 4.9)
Stroke severity[d]					
Fatal stroke	12 (0.7%)	6 (0.4%)	1.97 (0.74, 5.23)	0.16	0.4 (−0.1, 0.8)
Disabling stroke	47 (2.8%)	34 (2.1%)	1.35 (0.87, 2.08)	0.18	0.6 (−0.4, 1.6)
Non-disabling stroke	66 (3.9%)	31 (1.9%)	2.09 (1.37, 3.19)	0.0004	2.0 (0.8, 3.2)
Stroke pathology[e]					
Ischaemic stroke	118 (7.0%)	57 (3.5%)	2.02 (1.48, 2.75)	<0.0001	3.7 (2.2, 5.2)
Haemorrhagic stroke	7 (0.4%)	12 (0.7%)	0.57 (0.23, 1.45)	0.23	−0.3 (−0.8, 0.1)
Unknown pathology	0	1 (0.1%)	–[i]	–[i]	–[i]
Stroke territory[e]					
Ipsilateral carotid	113 (6.7%)	66 (4.0%)	1.67 (1.24, 2.25)	0.0005	2.8 (1.3, 4.3)
Contralateral carotid or vertebrobasilar	10 (0.6%)	4 (0.2%)	2.45 (0.77, 7.81)	0.11	0.4 (−0.1, 0.8)
Unknown territory	2 (0.1%)	0	–[i]	–[i]	–[i]
Myocardial infarction	4 (0.2%)	7 (0.4%)	–[i]	–[i]	–[i]
Non-fatal myocardial infarction	1 (0.1%)	7 (0.4%)	–[i]	–[i]	–[i]
Fatal myocardial infarction	3 (0.2%)	0	–[i]	–[i]	–[i]
Cranial nerve palsy[f]	7 (0.4%)	99 (6.0%)	0.07 (0.03, 0.15)	<0.0001	−5.6 (−6.7, −4.4)
Severe haematoma[g]	12 (0.7%)	32 (1.9%)	0.37 (0.19, 0.71)	0.0016	–[i]
Severe wound infection[h]	1 (0.1%)	4 (0.2%)	–[i]	–[i]	–[i]

CAS, carotid stenting; CEA, carotid endarterectomy; CI, confidence interval.
[a] Crude percentages (number of events divided by number of patients).
[b] Adjusted for source trial.
[c] p-Values derived from binomial regression likelihood ratio test, adjusted for source trial.
[d] One patient in the endarterectomy group had two stroke events within 30 days after treatment.
[e] Stroke pathology and stroke territory refer to first event.
[f] In the stenting group, cranial nerve palsy (CNP) was caused by carotid artery dissection in 2 patients; in 3 patients, CNP occurred after conversion to endarterectomy following unsuccessful initial attempts at stenting; and 2 patients had isolated dysphagia attributable to CNP following stent procedures.
[g] Defined as neck haematoma after endarterectomy or haematoma at the site of puncture after stenting, which required surgery or blood transfusion, or which prolonged hospital stay.
[h] Defined as any infection at the site of surgery or skin puncture in stenting, which required antibiotic treatment or surgery, or which prolonged hospital stay.
[i] Adjusted risk ratio or risk difference and CI not estimated as model did not converge.

underlying this relationship may include increased burden of atherosclerosis, changes in plaque characteristics, or changes in vascular anatomy with increasing age, which may each increase the risk for thromboembolism during catheterisation or stent deployment.

What are the implications of our findings for clinical practice? Results from single clinical trials and previous summary data meta-analyses have not justified any change in policy of recommending endarterectomy as the treatment of choice for symptomatic carotid stenosis. Current recommendations have therefore limited the use of stenting to patients with symptomatic carotid stenosis who had contraindications to surgery, and those with stenosis at surgically inaccessible sites, recurrent stenosis after previous endarterectomy, or post-irradiation stenosis.[16] The present results now suggest that stenting may represent a safe alternative to endarterectomy in younger patients, who could otherwise undergo surgery without increased risk. Some uncertainty remains regarding the potentially higher rate of recurrent stenosis after stenting compared with endarterectomy, and the implications this may have for long-term stroke risk in young patients treated with stents.[17,18] With these caveats in mind, an approach of offering stenting where technically feasible as an alternative option to endarterectomy to patients with symptomatic carotid stenosis below 65−70 years of age, in centres where acceptable peri-procedural outcomes have been independently verified, may 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 to test for interactions with some patient subgroups where stenting may theoretically represent a safe alternative to endarterectomy, may have been too low. The contributing trials did not specify imaging of the aortic arch prior to randomisation. The exact number of procedures performed by individual surgeons and interventionalists before joining the trials has not been consistently collected in the contributing trials, and the impact of individual experience on complication rates requires further investigation.

However, the prospectively defined meta-analysis of EVA-3S, SPACE and ICSS yielded a highly significant result of an age-dependent variation of treatment risks posed by stenting which has implications for clinical practice.

In conclusion, there is strong evidence that in the short-term, the relative harm of stenting compared with endarterectomy decreases with younger age.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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