Eur J Vasc Endovasc Surg (2019) 58, 479–493

REVIEW

Editor's Choice – Overview of Primary and Secondary Analyses From 20 Randomised Controlled Trials Comparing Carotid Artery Stenting With Carotid Endarterectomy

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WHAT THIS PAPER ADDS

This paper provides an overview of primary/secondary outcome data from 20 randomised controlled trials comparing carotid endarterectomy (CEA) with carotid artery stenting (CAS) in symptomatic and asymptomatic patients, including meta-analyses for peri-operative risks and late ipsilateral stroke. Secondary analyses include (i) risk factors for stroke after CEA/CAS; (ii) the effect of peri-operative stroke or myocardial infarction on long term survival; (iii) non-stroke complications; (iv) the significance of new white matter lesions on late stroke and cognitive impairment; and (v) whether asymptomatic 70%–99% restenoses increase the risk of ipsilateral stroke after CEA and CAS.

Objectives: The aim of this review was to carry out primary and secondary analyses of 20 randomised controlled trials (RCTs) comparing carotid endarterectomy (CEA) with carotid artery stenting (CAS).

Methods: A systematic review and meta-analysis of data from 20 RCTs (126 publications) was carried out.

Results: Compared with CEA, the 30 day death/stroke rate was significantly higher after CAS in seven RCTs involving 3467 asymptomatic patients (odds ratio [OR] 1.64, 95% confidence interval [CI] 1.02–2.64) and in 10 RCTs involving 5797 symptomatic patients (OR 1.71, 95% CI 1.38–2.11). Excluding procedural risks, late ipsilateral stroke was about 4% at 9 years for both CEA and CAS, i.e., CAS was durable. Reducing procedural death/stroke after CAS may be achieved through better case selection, e.g., performing CEA in (i) symptomatic patients aged $>$ 70 years; (ii) interventions within 14 days of symptom onset; and (iii) situations where stroke risk after CAS is predicted to be higher (segmental/remote plaques, plaque length $>$ 13 mm, heavy burden of white matter lesions [WMLs], where two or more stents might be needed). New WMLs were significantly more common after CAS (52% *vs.* 17%) and were associated with higher rates of late stroke/transient ischaemic attack (23% *vs.* 9%), but there was no evidence that new WMLs predisposed towards late cognitive impairment. Restenoses were more common after CAS (10%) but did not increase late ipsilateral stroke. Restenoses (70%–99%) after CEA were associated with a small but significant increase in late ipsilateral stroke (OR 3.87, 95% CI 1.96–7.67; $p < .001$).

Conclusions: CAS confers higher rates of 30 day death/stroke than CEA. After 30 days, ipsilateral stroke is virtually identical for CEA and CAS. Key issues to be resolved include the following: (i) Will newer stent technologies and improved cerebral protection allow CAS to be performed $<$ 14 days after symptom onset with risks similar to CEA? (ii) What is the optimal volume of CAS procedures to maintain competency? (iii) How to deliver better risk factor control and best medical treatment? (iv) Is there a role for CEA/CAS in preventing/reversing cognitive impairment?

Keywords: Carotid artery stenting, Carotid endarterectomy, Credentialing, Randomised trials, Secondary outcomes, Stroke

Article history: Received 14 June 2018, Accepted 5 June 2019, Available online 4 September 2019

INTRODUCTION

Twenty randomised controlled trials (RCTs) have compared carotid endarterectomy (CEA) with carotid angioplasty (CA) or carotid artery stenting (CAS), resulting in 126 publications in 36 medical/surgical journals between 1998 and 2019.[1–40,41–80,81–126] Even for those interested in the

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1078-5884/

https://doi.org/10.1016/j.ejvs.2019.06.003

management of carotid disease, it remains a daunting task to keep abreast of the literature. The aim was to provide an overview of clinically important primary/secondary analyses, from the 20 RCTs.

MATERIALS AND METHODS

A systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[126] The PubMed/MEDLINE, Embase, and Cochrane databases were searched by two investigators (A.R.N, A.J.B.) from 1 January 1998 to 20 March 2019 to identify RCTs comparing early and late outcomes after CEA *vs.* CA/CAS. Data extraction was performed independently and results were compared between investigators. Any disagreement was resolved by consensus. Using medical subject heading terms ("carotid endarterectomy", "carotid artery stenting", and "randomised trials"), along with manual searching of references derived from constituent RCTs, previous meta-analyses and manual searches of journals, 620 reports were identified (Fig. 1). Abstracts were read to identify RCTs comparing CEA and CA/CAS. Of the 620 reports, 480 were excluded as they were not carotid RCTs and 14 were excluded (RCT methodology), leaving 126 publications for the systematic review.[1–85]

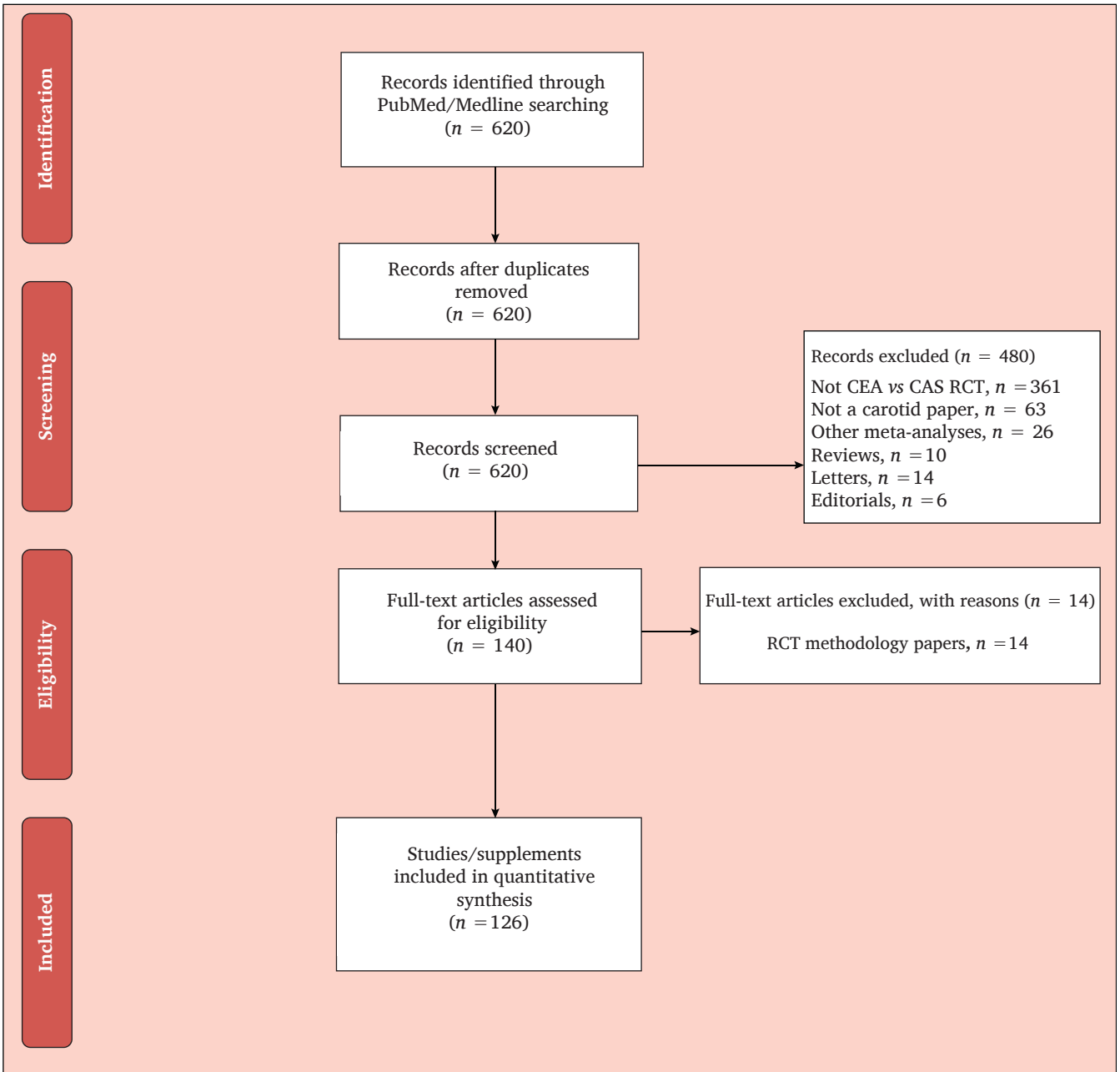

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA) flow diagram of randomised controlled trials comparing carotid artery stenting with carotid endarterectomy. CEA = carotid endarterectomy; CAS = carotid artery stenting; RCT = randomised controlled trial.

The project comprised three sections. Firstly, 30 day risks, including death, stroke, death/stroke, disabling stroke, death/disabling stroke, myocardial infarction (MI), death/stroke/MI, and cranial nerve injury (CNI) were examined. These were meta-analysed for (i) CEA *vs.* CAS in all asymptomatic patients; (ii) CEA *vs.* CAS in all symptomatic patients; (iii) CEA *vs.* CAS in asymptomatic patients where RCTs recruited >500 patients (excluding CA); and (iv) CEA *vs.* CAS in symptomatic patients where RCTs recruited >500 patients (excluding CA). The second section provides an overview of clinically useful secondary analyses. Where possible, data from meta-analyses by the Carotid Stent Trialists Collaboration (CSTC) were used, rather than individual RCTs. Unless stated, most were pre-planned analyses. The third section reports meta-analyses for late stroke. Several RCTs recruited symptomatic and asymptomatic patients (Table S1, supplementary material), but did not always provide separate outcome data. Data from a meta-analysis by Kakkos *et al*. were used,[127] where the authors contacted the Principle Investigator (PI) of the RCT by Kuliha *et al*.[105] to provide information about missing data in asymptomatic patients (Stavros Kakkos, personal communication).

The Jadad score was used to assess the quality of RCTs (Table S1).[128] To score a point, the RCT had to report withdrawals/dropouts in each study and their reasons. Additional points were given if the randomisation method was described and deemed appropriate, and if the method of blinding was described and considered appropriate. Points were deducted if the randomisation method was described, but deemed inappropriate, and where blinding was described, but considered inappropriate. The Jadad score ranges from 0 (lowest quality) to 5 (highest quality).

Five and nine year data for late ipsilateral stroke, any stroke, and major stroke were taken from a 2019 CSTC meta-analysis of the four largest RCTs: the Endarterectomy Versus Angioplasty in patients with symptomatic severe carotid stenosis trial (EVA-3S), the Stent Protected percutaneous Angioplasty of the Carotid artery versus Endarterectomy trial (SPACE); the International Carotid Stenting Study (ICSS) and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).[126]

Statistical analyses

Statistical analyses were carried out with the R package for Microsoft Windows (version 3.1). Random and fixed effect meta-analyses were performed using proportions of patients experiencing the outcome of interest. Odds ratios (OR) or hazard ratios (HR), with 95% confidence intervals (CIs) were calculated for each RCT. In RCTs where one arm reported no post-operative events, but another arm reported at least one event, a fixed factor of 0.5 was added to cells of the study results with zero events to calculate an appropriate OR and allow synthesis. This type of continuity correction is an established approach to incorporate zero event studies and 0.5 is the most common choice of correction factor.[130] Studies with zero outcome events in both limbs were excluded from the meta-analysis. ORs were combined using meta-analysis, involving fixed/random effects models, as appropriate. Interstudy heterogeneity was analysed using the I^2 statistic, which describes the percentage total variation across studies because of heterogeneity and is a recognised method of quantifying heterogeneity in literature syntheses.[130] An I^2 value $\geq$ 50% reflects significant heterogeneity due to real differences in study populations, protocols, and interventions. Based on the I^2 statistic, a fixed effects model was used if I^2 was <50% and a random effects model if I^2 was >50%. A p value $<$ .05 was considered statistically significant. Meta-analyses of proportions were used to calculate weighted proportions for the events of interest, using a fixed or random effects model based on the I^2 statistic. Additional statistical analyses were undertaken, as necessary (A.S.), usually involving 2 $\times$ 2 contingency tables using a Fisher's exact test (FET), with a two tailed p value.

RESULTS

Credentialing of transfemoral CAS practitioners

In CREST, 427 practitioners applied to perform CAS;[62] 238 (56%) entered the 'lead in' phase; 73 (17%) were exempted and allowed to randomise, while 116 (27%) were rejected (inexperience, event rates too high). CREST maintained strict oversight. After one outcome event, a centre was put "on watch". After two, the centre was placed "on audit". Upon completion of the "lead in" phase, 21 centres were "on watch", while 14 were being "audited". In EVA-3S, CAS practitioners had performed >12 CAS procedures and/or 35 stents in supra-aortic vessels.[17] SPACE required interventionists to have performed 25 CA/CAS procedures.[22] ICSS required 50 stent procedures, including 10 CAS interventions.[32] The latter three RCTs allowed less experienced practitioners to be proctored by more experienced colleagues, until they reached competency.

Risk factor control and antiplatelet therapy

In CEA patients, there was no mention of antiplatelet strategies in four RCTs.[8,17,31,108] Antiplatelet monotherapy was used in 11 RCTs,[1,2,12,22,28,65,101,104,106,109,111] while aspirin and clopidogrel was recommended in four.[9,10,105,107] In CAS patients, antiplatelet monotherapy was used in two RCTs,[1,2] while dual antiplatelet therapy (DAPT) was used in the rest. DAPT duration varied from two to four weeks,[12] four weeks,[17,22,65,101,104,107] six weeks,[28,106] and 12 weeks.[109] In four RCTs, the duration of DAPT was not specified.[9,10,31,105] ICSS evaluated serial blood pressure (BP) changes in 766 CAS patients and 819 CEA patients.[34] Preoperatively, there was no difference in BP between CEA and CAS patients. At discharge, both CAS and CEA were associated with BP decreases, which were greater after CAS. At one and 12 months, systolic/diastolic BP differences no

longer persisted, but significantly fewer CAS patients took antihypertensive medications at 12 months compared with CEA patients.

CREST evaluated how well risk factor control was being implemented,[83] requiring four domains to be maintained: (i) low density lipoprotein cholesterol < 100 mg/dL (59% baseline, 74% after 48 months); (ii) systolic BP < 140 mmHg (52% baseline, 65% at 48 months); (iii) fasting blood glucose < 126 mg/dL (75% baseline, 81% at 48 months); and (iv) smoking cessation (74% baseline, 81% at 48 months). Only 17% achieved all four domain targets at baseline, increasing to 36% by 48 months.

Peri-operative morbidity and mortality

Peri-operative stroke/death

Asymptomatic patients. Fig. 2 details procedural risks in seven RCTs (n = 3467) comparing CEA with CAS (i.e., excluding CA). CAS patients incurred significantly higher rates of "any stroke" and "death/any stroke" compared with CEA patients. Regarding the other end points, there was no significant difference. In Fig. 3, 30 day data are detailed for 3034 patients in the three largest RCTs that randomised >500 patients. CAS was associated with significantly higher rates of "any stroke" compared with CEA

Symptomatic patients. Fig. 4 details peri-operative risks in 10 RCTs (n = 5797) comparing CEA with CAS (i.e., excluding CA). CAS was associated with significantly higher rates of "any stroke", "death/any stroke", "death/disabling stroke", and "death/stroke/MI". In Fig. 5, outcome data are presented for 4754 patients in the largest four RCTs that randomised >500 patients. CAS was associated with significantly higher rates of "any stroke", "death/stroke", and "death/stroke/MI".

Aetiology of peri-operative stroke. Seven RCTs published data on 309 patients who suffered a peri-operative stroke.[2,20,22,48,78,104,106] Overall, 86% of strokes after CEA were ischaemic, with intracerebral haemorrhage (ICH) accounting for 14%. After CAS, 94% of strokes were ischaemic, with 6% being due to ICH. Strokes after CEA were significantly more likely to be due to ICH (FET p = .036).

CREST reported patterns of computed tomographic infarction after peri-operative stroke.[78] The most common was "scattered embolic infarction" (38% of CAS strokes) *vs.* 38% after CEA. "Cortical infarction" occurred in 31% of CAS patients suffering a stroke and in 21% of CEA patients, while "subcortical infarction" was present in 17% of CAS patients and 31% of CEA patients. Bilateral or multiple territory infarctions were present in 14% of CAS related strokes *vs.* 0% after CEA.

ICSS was unable to determine the likeliest cause of ischaemic stroke in 14/58 (24%) CAS patients and 5/27 (19%) CEA patients.[48] Ipsilateral embolism was considered responsible for 10/58 (17%) post-CAS strokes *vs.* 4/27 (15%) after CEA. Haemodynamic stroke was attributed to 15/58 (26%) strokes after CAS *vs.* 5/27 (19%) after CEA. Post-operative thrombosis was responsible for 11/58 (19%) of strokes after CAS *vs.* 4/27 (15%) after CEA. Cardiac embolism caused 2/58 (3%) of strokes after CAS *vs.* 3/27 (11%) after CEA. Multiple aetiologies were attributed in 3/58 (5%) strokes after CAS *vs.* 0% after CEA.

Vascular territory and timing of peri-operative stroke. Eight RCTs reported the vascular territory in 330 strokes.[2,12,22,48,78,101,104,106,123] After CEA, 93% were ipsilateral, with 7% contralateral or vertebrobasilar. After CAS, 91% were ipsilateral, with 9% contralateral/vertebrobasilar (FET p = .537). CSTC reported the timing of peri-operative stroke in 4797 patients.[123] The risk of "immediate" stroke (day of procedure) was 4.7% after CAS *vs.* 1.9% after CEA (OR 2.6, 95% CI 1.9—3.8). Delayed stroke (days 1—30) was 2.5% after CAS *vs.* 2% after CEA (OR 1.3, 95% CI 0.9—1.9).

Temporal trends in peri-operative death/stroke/MI. CREST hypothesised that increasing experience would reduce peri-operative complications after CAS.[87] After adjusting for symptom status and patient characteristics,

	Death	Stroke	Death/ Stroke	Disabling Stroke	Death/ Disabling stroke	MI	Death/ Stroke/MI
	7 RCTs n = 2286	8 RCTs n = 3467	8 RCTs n = 3467	5 RCTs n = 2918	Insufficient data	5 RCTs n = 2948	5 RCTs n = 2948
CEA	0.7% (0.3–1.8)	1.9% (1.3–2.9)	2.1% (1.5–3.1)	0.5% (0.2–1.2)	Insufficient data	1.8% (1.1–2.8)	3.1% (2.2–4.3)
CAS	0.7% (0.3–1.7)	3.0% (2.3–3.8)	3.1% (2.4–4.0)	0.5% (0.3–1.0)	Insufficient data	0.8% (0.5–1.4)	3.3% (2.5–4.2)
OR (95% CI)	1.02 (0.18–5.90)	1.73 (1.06–2.84)	1.64 (1.02–2.64)	1.57 (0.40–6.19)	Insufficient data	0.53 (0.24–1.16)	1.14 (0.72–1.81)

Significant benefit favouring CEA No significant difference between CAS and CEA

Figure 2. Thirty day outcomes after carotid artery stenting (CAS) *vs.* carotid endarterectomy (CEA) in 3467 asymptomatic patients randomised within seven randomised controlled trials (RCTs).[10,12,28,65,101,105,106] OR = odds ratio; CI = confidence interval; MI = myocardial infarction.

	Death	Stroke	Death/ Stroke	Disabling Stroke	Death/ Disabling stroke	MI	Death/ Stroke/MI
		3 RCTs n = 3034	3 RCTs n = 3034	2 RCTs n = 2634		2 RCTs n = 2634	2 RCTs n = 2634
CEA	Insufficient data	1.5% (0.9–2.4)	1.6% (1.0–2.5)	0.3% (0.1–1.0)	Insufficient data	1.5% (0.6–3.9)	3.2% (2.3–4.5)
CAS	Insufficient data	2.7% (2.2–3.5)	2.7% (2.1–3.6)	0.5% (0.2–1.0)	Insufficient data	0.8% (0.3–1.9)	3.3% (2.6–4.3)
OR (95% CI)		1.82 (1.02–3.23)	1.71 (0.98–3.00)	1.57 (0.40–6.19)		0.53 (0.24–1.16)	1.11 (0.70–1.78)

Significant benefit favouring CEA No significant difference between CAS and CEA

Figure 3. Thirty day outcomes following carotid artery stenting (CAS) *vs.* carotid endarterectomy (CEA) in three randomised controlled trials (RCTs) that randomised > 500 asymptomatic patients.[28,65,101] OR = odds ratio; CI = confidence interval; MI = myocardial infarction.

there was no significant decline in death/stroke/MI across three successive time periods (6%, 5.9%, and 5.6%, respectively) or in death/stroke (5.1%, 5.1%, and 4.7%, respectively). There was a non-significant decrease in death/stroke after CAS in asymptomatic patients (2.7%, 1.9%, and 1.7%, respectively).

Factors associated with increased 30 day death/stroke

Clinical predictors

Age. A CSTC meta-analysis (Table 1) on the effect of age on 30 day death/stroke in 4754 symptomatic patients[117] observed that age had no effect on death/stroke after CEA, but there was an increase in death/stroke with increasing age after CAS. When compared with CEA (column 3, Table 1), a threshold of 70 years was statistically significant. Above 70 years, CAS incurred significantly higher rates of death/stroke.[56] Below 70 years, CAS had similar death/stroke rates to CEA.

Sex. In CREST, 30 day death/stroke/MI was significantly higher after CAS in women (6.8%) *vs.* 3.8% in women undergoing CEA (HR 1.84, 95% CI 1.02—3.37).[75] Female sex had no influence on MI after CEA/CAS, but stroke was significantly higher in women undergoing CAS (5.5%) *vs.* 2.2% after CEA (HR 2.63, 95% CI 1.23—5.65). Sex effects were most marked in symptomatic women, possibly because of smaller calibre arteries and higher baseline BP.[75]

Baseline BP. Increased diastolic BP was an independent risk factor for stroke after CEA but not after CAS.[47,53] The relative risk of stroke increased by a factor of 1.3 per 10 mmHg (95% CI 1.02—1.66).[53]

Side of lesion. There were inconsistent data in the RCTs. SPACE reported that the side of the symptomatic lesion had no impact on 30 day death/stroke after CAS (left 6% *vs.* right 7.7% [p = .51]) or CEA (left 6.1% *vs.* right 4.9% [p = .58]).[25] ICSS reported no effect in CEA patients (left 4.4% *vs.* right 3.6% [p = .52]), while death/stroke was significantly higher after left sided CAS (left 9.4% *vs.* right 5.1% [p = .019]).[53]

Effect of body mass index. In EVA-3S/SPACE, body mass index (BMI) did not influence death/stroke after CAS (BMI < 20 = 7%; BMI 20—25 = 9%; BMI 25—30 = 10%; BMI > 30 = 8% [p_{trend} = .39]) or CEA (BMI < 20 = 3%; BMI 20—25 = 7%; BMI 25—30 = 8%; BMI > 30 = 6% [p_{trend} = .77]).[120]

Operating in the first 14 days after symptom onset. A CSTC meta-analysis (n = 2839)[114] observed that 30 day death/stroke was significantly higher when CAS was performed less than seven days after symptom onset (9.4%) *vs.* 2.8% after CEA (OR 3.4, 95% CI 1.01—13.1; p = .03). Thirty day death/stroke remained significantly higher when CAS was performed 8—14 days after symptom onset (8.1%) *vs.* 3.4% after CEA (OR 2.42, 95% CI 1.0—5.7; p = .04).[114] A second meta-analysis (n = 138) included symptomatic CREST patients.[119] Thirty day death/stroke after CAS less than seven days after symptom onset was 8.4% *vs.* 1.3% after CEA (OR 6.51, 95% CI 2.0—21.21; p = .002). Thirty day fatal/disabling stroke was also significantly more common when CAS was performed less than seven days after symptom onset (3.1%) *vs.* 0.4% after CEA (OR 8.38, 95% CI 1.09—64.76; p = .04).

Effect of pre-existing coronary heart disease death/stroke. CSTC evaluated 30 day death/stroke in 4641 symptomatic patients stratified for the presence of coronary heart disease (CHD) and age.[124] CHD was present in 1293 patients (28%). In patients with CHD, 30 day death/stroke was significantly higher after CAS compared with CEA in patients aged ≥75 years (HR 2.78, 95% CI 1.32—5.85) but not in patients aged 70—74 years (HR 1.09, 95% CI 0.45—2.65) or those aged < 70 years (HR 1.71, 95% CI 0.79—3.71). In patients with no history of CHD, 30 day death/stroke after CAS was significantly higher in patients aged 70—74

	Death	Stroke	Death/ Stroke	Disabling Stroke	Death/ Disabling stroke	MI	Death/ Stroke/MI
	9 RCTs n = 4257	9 RCTs n = 5535	10 RCTs n = 5754	6 RCTs n = 4855	5 RCTs n = 3534	6 RCTs n = 3980	6 RCTs n = 3719
CEA	1.4% (0.9–2.0)	4.6% (3.26–6.37)	5.08% (3.7–6.9)	1.8% (1.1–3.1)	3.2% (2.5–4.1)	1.6% (1.0–2.3)	5.1% (4.13–6.30)
CAS	1.9%	8.5% (5.87–12.14)	9.3% (6.8–12.6)	3.28% (1.6–6.7)	5.21% (3.0–8.9)	0.8% (0.5–1.4)	8.4% (5.0–13.8)
OR (95% CI)	1.38 (0.81–2.34)	1.73 (1.38–2.18)	1.71 (1.38–2.11)	1.35 (0.91–1.99)	1.42 (1.00–2.02)	0.50 (0.24–1.02)	1.61 (1.21–2.14)

Significant benefit favouring CEA No significant difference between CAS and CEA

Figure 4. 30 day outcomes following carotid artery stenting (CAS) *vs.* carotid endarterectomy (CEA) in ten randomised controlled trials (RCTs) which included 5797 symptomatic patients.[1,8,9,12,17,22,31,65,105,107] OR = odds ratio; CI = confidence interval; MI = myocardial infarction.

years (HR 3.62, 95% CI 1.80—7.29) and ≥75 years (HR 2.64, 95% CI 1.52—4.59); however, it was equal in patients aged < 70 years (HR 1.05, 95% CI 0.63—1.73). CSTC concluded that CEA should not be withheld in patients with CHD and that CAS was as safe as CEA in patients with CHD aged <75 years. In patients without CHD, CAS outcomes were only equivalent to CEA in patients aged <70 years.[124]

"Previously" asymptomatic vs. "totally" asymptomatic. An unplanned CREST analysis reported that early and late CEA/CAS outcomes were unaffected when stratified for whether asymptomatic patients had never reported any clinical events in the past *vs.* patients who had reported symptoms more than six months in the past.[100]

Imaging predictors for peri-operative stroke

Stenosis severity and bilateral severe disease. In CAVATAS, ICSS, SPACE, and CREST, stenosis severity and/or the presence of contralateral occlusion/severe stenosis had no effect on death/stroke after CEA/CAS.[7,25,47,53,95]

Plaque features. CREST analysed plaque features on pre-randomisation angiograms in 438 CEA and 1240 CAS patients. Sequential lesions and remote lesions extending beyond the bulb were associated with significantly higher death/stroke rates after CAS (5.8%) *vs.* 0.7% after CEA (OR 9.01, 95% CI 1.2—6.78).[95] Plaque length > 13 mm was associated with a 6.1% death/stroke after CAS *vs.* 1.9% after CEA (OR 3.42, 95% CI 1.19—9.78).[95] CREST undertook a separate analysis in 1123 CAS patients to see if increasing age was associated with plaque length. CREST concluded that plaque length accounted for only 8% of the increased risk in elderly CAS patients, suggesting other mechanisms were responsible for the age effect.[91]

Pre-existing white matter lesions on magnetic resonance imaging. ICSS scored pre-operative white matter lesions (WMLs) using the Age Related White Matter Changes (ARWMC) score. The median pre-operative score was 7.[37] An ICSS subgroup (CAS = 536; CEA = 500) was stratified for whether the ARWMC score was <7 or ≥ 7. With CEA,

	Death	Stroke	Death/ Stroke	Disabling Stroke	Death/ Disabling stroke	MI	Death/ Stroke/MI
	3 RCTs n = 3413	4 RCTs n = 4754	4 RCTs n = 4754	4 RCTs n = 4754	3 RCTs n = 3413	3 RCTs n = 3551	2 RCTs n = 3031
CEA	0.9% (0.5–1.47)	4.8% (4.0–5.7)	5.5% (4.7–6.5)	2.4% (1.8–3.1)	3.2% (2.5–4.2)	1.0% (0.3–3.1)	5.2% (4.2–6.5)
CAS	1.2% (0.48–2.92)	7.8% (6.8–9.0)	8.7% (7.6–9.9)	3.3% (2.6–4.1)	4.3% (3.4–5.4)	0.7% (0.4–1.3)	8.0% (5.9–10.7)
OR (95% CI)	1.67 (0.88–3.17)	1.66 (1.32–2.10)	1.61 (1.29–2.01)	1.39 (0.98–1.97)	1.38 (0.96–1.98)	0.51 (0.25–1.07)	1.60 (1.19–2.14)

Significant benefit favouring CEA No significant difference between CAS and CEA

Figure 5. Thirty day outcomes following carotid endarterectomy (CEA) *vs.* carotid artery stenting (CAS) in four randomised controlled trials (RCTs) that randomised > 500 symptomatic patients.[17,22,31,65] OR = odds ratio; CI = confidence interval; MI = myocardial infarction.

Table 1. Effect of age on 30 day death/stroke in symptomatic patients randomised within EVA-3S, SPACE-1, ICSS, and CREST[a]

Age group, y	CAS HR (95% CI)	CEA HR (95% CI)	CAS *vs.* CEA HR (95% CI)
<60	1.0[b]	1.0[b]	0.62 (0.31–1.23)
60–64	1.79 (0.89–3.60)	1.01 (0.34–1.9)	1.07 (0.56–2.01)
65–69	2.16 (1.13–4.13)	0.81 (0.43–1.52)	1.61 (0.90–2.88)
70–74	4.01 (2.19–7.32)	1.20 (0.68–2.13)	2.09 (1.32–2.32)
75–79	3.94 (2.14–7.28)	1.29 (0.74–2.25)	1.91 (1.21–3.01)
≥80	4.15 (2.20–7.84)	1.09 (0.57–2.10)	2.43 (1.35–4.38)

Age based hazard ratio (HR) calculation for carotid artery stenting (CAS) *vs.* carotid endarterectomy (CEA). If HR is < 1.0, CAS is associated with lower peri-operative death/stroke. If HR is > 1.0, CAS is associated with higher rates of peri-operative stroke/death. All HR age based calculations compared against age <60 years; CI = confidence interval.

[a] Based on individual patient meta-analysis by the Carotid Stent Trialists Collaboration. Table reproduced with permission from Naylor AR *et al.*[136]

[b] All HR age based calculations were compared against patients aged <60 years.

there was no relationship between ARWMC score and peri-operative stroke. With CAS, peri-operative stroke was significantly increased with an ARWMC score ≥7 compared with when the score was <7 (HR 2.76, 95% CI 1.17–6.51).[73] Higher rates of disabling stroke were also observed in CAS patients whose ARWMC score was ≥7 (HR 3, 95% CI 1.1–8.36). When comparing CEA with CAS in patients with an ARWMC score ≥7, CAS was associated with significantly higher stroke rates (HR 2.98, 95% CI 1.29–6.93; $p = .011$). There was no difference in procedural stroke in either CEA or CAS patients with an ARWMC <7. ICSS concluded that CAS should be avoided in patients with extensive WMLs on pre-operative MRI.[37]

CAS techniques and peri-operative stroke. CSTC performed a meta-analysis on the influence of cerebral protection devices (CPD), stent design, pre-dilatation, post-dilatation, and DAPT on 30 day death/stroke in 1557 CAS patients in ICSS, EVA-3S, and SPACE.[122] Open cell stents were associated with significantly higher rates of death/stroke (10.3% in 595 patients) compared with closed cell stents (6% in 962 patients [RR 1.76, 95% CI 1.23–2.52; $p = .002$]). Filter CPDs were not associated with a significant reduction in death/stroke (8.0% in 950 patients) *vs.* 7.1% in 607 CAS procedures where no CPD was used (RR 1.1, 95% CI 0.71–1.70; $p = .67$). Pre-dilatation was not associated with increased death/stroke (7.4% in 760 patients) *vs.* 7.9% in 796 CAS procedures without pre-dilatation (RR 0.98, 95% CI 0.69–1.44; $p = .919$). Post-dilatation was associated with a 7.2% death/stroke rate in 1177 patients *vs.* 8.2% in 134 CAS patients without post-dilatation (RR 0.87, 95% CI 0.47–1.62; $p = .67$). CAS using DAPT did not confer a significant reduction in 30 day death/stroke (7.5% in 1357 patients) *vs.* 9.4% in 171 CAS patients on aspirin monotherapy (RR 0.84, 95% CI 0.5–1.4; $p = .52$).[12]

Number of stents inserted. CREST analysed 1531 "lead in" and 1121 trial patients undergoing CAS and showed that when one stent was deployed, the peri-operative stroke rate was 4% in 2545 patients *vs.* 15% where two or more stents were deployed (OR 2.9, 95% CI 1.49–5.64). Patients with two or more stents were significantly more likely to have ulcerated plaques ($p = .006$), be older ($p = .01$), and have longer lesion lengths ($p = .02$).[99]

Volume: outcome relationship and specialty performing CAS

In a CSTC meta-analysis of interventionist experience in 1546 symptomatic CAS patients,[116] 30 day death/stroke did not vary with lifetime operator experience ($p = .8$) or lifetime operator stenting experience ($p = .7$). Annual CAS volume did influence 30 day death/stroke, where three or fewer CAS procedures per year were associated with a 10.1% rate of death/stroke *vs.* 5.1% in interventionists performing more than six procedures per annum (OR 2.30, 95% CI 1.36–3.87). CREST found that the specialty of the interventionist did not influence procedural risks.[68,80]

Predicting stroke/death after CEA/CAS. CSTC tested 23 models for predicting 30 day death/stroke in 2184 CAS patients and 2261 CEA patients.[121] None could reliably predict 30 day risks in symptomatic patients undergoing CEA or CAS.

Non-stroke complications after CEA or CAS

Peri-operative MI and type of anaesthesia used during CEA. In CREST, the incidence of MI after CAS was 19/1123 (1.7%); 35/1038 (3.4%) with CEA under general anaesthesia; and 2/111 (1.8%) with CEA under locoregional anaesthesia.[94]

Local complications

Cranial nerve injury. In a meta-analysis of 7535 patients in 13 RCTs,[1,2,9,10,12,17,46,88,101,104,106,107,109] cranial nerve injury (CNI) after CAS was 0.5% (95% CI 0.3–0.9) *vs.* 5.4% (95% CI 4.7–6.2) after CEA (OR 0.07, 95% CI 0.04–0.1). In ICSS, 45/821 CEA patients (5.5%) developed 50 CNIs, of which 11

(22%) persisted at 30 days, but only one was disabling.[46] Affected nerves included mandibular branch facial (2.8%); hypoglossal (1.6%); vagus (0.7%); glossopharyngeal (0.5%); and accessory (0.1%). Health related quality of life studies showed no evidence that CNIs had an adverse impact at 12 months.[88,72]

Neck haematoma. In six RCTs (2988 CEA patients), 2.2% (95% CI 1.2—3.9) developed a haematoma, requiring re-exploration.[2,9,17,46,65,101] Risk factors included female sex, anticoagulation, and atrial fibrillation.[46] In CREST, arteriotomy closure (patch/primary) had no influence on haematoma formation.[89]

Post-operative arrhythmias and blood pressure instability. CAS patients were significantly less likely to require treatment for hypertension (1.4%) compared with CEA patients (6.1%; OR 0.21, 95% CI 0.14—0.33),[31,65] but CAS patients were significantly more likely to require treatment for hypotension (10.5%) than CEA patients (4.2%; OR 2.06, 95% CI 1.57—2.73).[9,17,31,65] CAS patients were also significantly more likely to require treatment for bradycardia (4.2%) compared with CEA patients (1.0%; OR 3.56, 95% CI 1.30—9.77).[8,9,17,31,65]

New ischaemic WMLs after CEA/CAS

Incidence. Seven ICSS centres performed pre- and post-operative magnetic resonance imaging (MRI) in 231 patients (CAS = 124; CEA = 107) to establish the incidence of new WMLs and permanent tissue injury at one month (Table 2).[32] CAS patients had significantly more acute new WMLs on day one (52%) compared with CEA patients (17%; OR 5.21, 95% CI 2.78—9.79). Using MRI fluid attenuated inversion recovery imaging, 33% of CAS patients had persisting WMLs at one month *vs.* 8% after CEA (OR 3.28, 95% CI 1.50—7.2). Overall, 15% of CAS patients had a single new WML *vs.* 8% after CEA; 19% of CAS patients had two to five WMLs *vs.* 5% after CEA, while 16% of CAS patients had more than five new WMLs *vs.* 4% after CEA ($p_{trend} < .001$).[38] Individual WMLs after CAS were of a significantly smaller volume (0.02 mL) compared with after CEA (0.08 mL; $p < .001$). However, the 0.17 mL (interquartile range [IQR] 0.06—0.58) median total volume of WMLs after CAS, was similar to the 0.19 mL (IQR 0.06—0.58) observed after CEA ($p = .8$).

Conversion from acute to persisting WMLs was lower after CAS, possibly owing to smaller lesion volumes after CAS.[41] New WMLs were more likely to affect cortical areas and white matter supplied by leptomeningeal arteries after CAS than new WMLs after CEA (OR 4.2, 95% CI 1.7—10.2; $p = .002$).[74] The proportion of CAS patients with new WMLs at one month (not seen on day 1) was 7% *vs.* 1% after CEA (OR 5.55, 95% CI 0.65—47.19).[32] The incidence of new WMLs in CAS patients using a filter CPD was significantly higher ($n = 38/56$ [68%]) compared with in unprotected CAS patients (n = 24/68 [35%]; OR 3.28, 95% CI 1.5—7.2 [$p = .003$]).[32]

Factors associated with new WMLs. Factors associated with new WMLs included (i) lower systolic BP;[32] (ii) diabetes;[32] (iii) hemispheric stroke at presentation;[32] (iv) left sided stenoses;[32] (v) plaque echolucency;[45] (vi) increasing age;[52] (vii) male sex;[52] (viii) type II/III aortic arch *vs.* type I arch;[56] (ix) $> 60°$ angle between the common carotid artery (CCA) and internal carotid artery;[56] (x) CPDs;[32] and (xi) intraprocedural haemodynamic depression (HD).[43] Altinbas *et al*. evaluated HD in 229 ICSS patients,[43] observing that HD (one or more of hypotension requiring treatment, bradycardia, or asystole) affected 12% ($n = 15/122$) of CAS patients *vs.* nine of 107 CEA patients (8%). After CAS, patients with HD had a mean of 13 new WMLs *vs.* four in CAS patients without HD (OR 3.36, 95% CI 1.73—6.5).[43] By contrast, the number of new WMLs after CEA was too small for analysis.

Clinical relevance of new WMLs. Late stroke/transient ischaemic attack. In ICSS, CAS patients with new WMLs had significantly higher rates of late stroke/transient ischaemic attack (TIA; 23%) compared with CAS patients who had no new WMLs (9%; HR 3.52, 95% CI 1.21—10.22 [$p = .021$]. There was no association between new WMLs and late stroke/TIA after CEA.[49]

Cognitive function. In the RCT by Kuliha *et al*. (CEA = 73; CAS = 77),[105] patients with new WMLs had significantly greater decreases in cognitive scores at 24 h. However, by 30 days, there was only a non-significant trend.

Silent intracerebral haemorrhage on MRI. The ICSS MRI substudy also analysed new haemorrhagic brain lesions (NHBL) after CEA ($n = 78$) and CAS ($n = 84$).[59] Five CAS patients (6%) developed a NHBL at 30 days *vs.* five (6.4%) after CEA. None were symptomatic and most occurred in the territory supplied by the treated carotid artery. New NHBLs were not associated with any baseline clinical or MRI variables.[59]

Long term observations

Late stroke. Table 3 details five year ipsilateral stroke, any stroke, and disabling stroke (excluding peri-operative stroke/death) in a CSTC meta-analysis of 4754 symptomatic patients.[125] Five year ipsilateral stroke was 3.1% (95% CI 2.3—4.1) after CEA and 3.2% after CAS (95% CI 2.3—4.2) (HR 1.06, 95% CI 0.73—1.54), equating to an average annual ipsilateral stroke rate of 0.6% (95% CI 0.46—0.79) after CEA and 0.64% (95% CI 0.49—0.83) after CAS. The nine year rate of ipsilateral stroke was 3.9% (95% CI 2.7—5.8) after CEA and 4.5% (95% CI 3.2—6.2) after CAS (absolute risk reduction [ARR] at nine years 0.5%, 95% CI −1.6 to 2.7).

Five year ipsilateral stroke in asymptomatic patients in ACT-1 (excluding peri-operative risks) was 2.2% after CAS *vs.* 2.7% after CEA, giving an average annual ipsilateral stroke rate of 0.44% after CAS and 0.54% after CEA.[101] In SPACE-2, the one year risk of ipsilateral stroke (including

Table 2. Incidence of new acute and persisting white matter lesions after carotid endarterectomy (CEA) and carotid artery stenting (CAS) in symptomatic patients: an International Carotid Stenting Study substudy[a]

Timepoint	CAS *n/m* (%)	CEA *n/m* (%)	OR (95% CI)	*p* value
Day 1 post-operatively	62/124 (50)	18/107 (17)	5.21 (2.78–9.79)	<.001
1 month post operative FLAIR MRI	28/86 (33)	6/75 (8)	5.93 (2.25–15.62)	<.001

Data are given as *n*/m (%), where m is total number of patients per study group. OR = odds ratio; CI = confidence interval; MRI = magnetic resonance imaging; FLAIR = fluid attenuated inversion recovery.
[a] Based on data from Bonati *et al.*[32].

peri-operative stroke/death) was 2.5% for CEA, 3.0% for CAS, and 0.9% with best medical treatment (BMT).[30] The one year risk of "any stroke" (including peri-operative risk) was 3.9% after CEA, 4.1% after CAS, and 0.9% after BMT.

Cognitive function after carotid interventions. In 120 ICSS patients, Altinbas *et al*. observed a significant decrease in cognitive sum score post-operatively after CAS but not after CEA.[33] However, the overall change in cognitive sum score after CAS at six months (0.19) was not significantly different to that seen after CEA (0.02).[33] Seventy-eight ICSS patients underwent pre-operative MRI and serial assessment of cognitive function.[36] The hypothesis was that patients with an increasingly severe WML burden (pre-operatively) would have greater post-operative cognitive decline, because of hypoperfusion of cerebral white matter. Patients were stratified according to their pre-operative ARWMC score. At six months, cognitive function was significantly impaired (compared with pre-operatively) after CEA and CAS, but there was no association between WML severity and late cognitive deterioration.[36] In the RCT by Kuliha *et al*. ($n = 150$), there was a significant decline in cognitive function after CEA and CAS at one and 30 days, but no significant difference in cognitive decline between CEA and CAS.[105] Patients with new WMLs after CEA/CAS had a significantly greater decline in cognitive function at 24 h but not at 30 days.[105]

Cost effectiveness. Two thirds of costs involve the index procedure, while one third covers surveillance.[55] Across the larger RCTs, CAS was associated with a small but significant increase in total costs: $662 in hospital costs;[9] $1368 at one year;[15] $808 at five years;[55] and $524 at 10 years.[79]

Quality of life analyses. In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, CAS patients reported better Short Form 36 (SF-36) scores and disease specific scales at two weeks (*vs.* CEA) but no significant differences at one month.[14] In CREST,[72] CAS patients had better outcomes across multiple components of the SF-36 at one month, especially physical function, pain, and physical component summary scale (all $p < .01$). Using disease specific scales, CAS patients had less difficulty with driving, swallowing, neck pain, and headaches, while having more difficulty with walking and leg pain (all $p < .05$). By one year, there were no differences in any health related quality of life (HRQoL) variable between CEA and CAS. Peri-operative stroke was associated with significantly poorer one year HRQoL outcomes across all SF-36 domains, while peri-operative MIs/CNIs were not associated with poorer outcomes at one year.[72] ICSS observed no difference in quality adjusted life years (3.247 for CAS, 3.228 for CEA),[55] while CREST reported that reduction in quality adjusted life expectancy was only 0.008 years for CAS *vs.* CEA.[79]

Peri-operative MI/stroke and reduced survival

In CREST, peri-operative MI was associated with increased mortality at four years (HR 3.4, 95% CI 1.67–6.92),[74] as was peri-operative stroke, where four year mortality was 21.1% *vs.* 11.6% in patients not suffering a stroke (HR 2.78, 95% CI 1.63–4.76).[78] CREST undertook 10 year analyses on the impact of peri-operative stroke/MI on survival in 2272 patients.[98] Patients suffering a peri-operative stroke were significantly more likely to die within 10 years (HR 1.74, 95% CI 1.21–2.5; $p < .003$). Reduced survival was mainly due to

Table 3. Meta-analysis: five year rates of stroke after carotid endarterectomy (CEA) and carotid artery stenting (CAS) in 4289 symptomatic patients (excluding peri-operative risk)[a]

Stroke type	CEA ($n = 2168$)	CAS ($n = 2121$)	CAS *vs.* CEA HR (95% CI)
Ipsilateral stroke – %	3.1 (2.3–4.1)	3.2 (2.3–4.2)	1.06 (0.73–1.54)
Major stroke – %	1.4 (0.9–2.2)	1.2 (0.7–1.9)	0.86 (0.48–1.56)
Any stroke – %	6.9 (5.7–8.3)	7.3 (6.0–8.8)	1.08 (0.84–1.38)

Data are given as mean (95% CI) unless stated otherwise. CI = confidence interval; HR = hazard ratio; CEA = carotid endarterectomy; CAS = carotid artery stenting.
[a] Based on a meta-analysis of individual patient data from Endarterectomy Versus Angioplasty in patients with symptomatic severe carotid stenosis trial (EVA-3S), SPACE (Stent Protected percutaneous Angioplasty of the Carotid artery versus Endarterectomy trial), International Carotid Stenting Study (ICSS), and Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Adapted from Brott *et al.*[125]

deaths in the first 90 days after CEA/CAS (HR 14.41, 95% CI 5.33—38.94; $p < .001$). Thereafter, there was a trend, but no significant increase, in late mortality between 91 days and 10 years (HR 1.40, 95% CI 0.93—2.10). Patients suffering a peri-operative MI were also significantly more likely to die within 10 years (HR 3.61, 95% CI 2.28—5.73; $p = .006$). However, increased mortality continued through the first 90 days after CEA/CAS (HR 8.2, 95% CI 1.86—36.2; $p < .001$) and from 91 days to 10 years (HR 3.4, 95% CI 2.09—5.53; $p < .001$).[98]

Restenosis after CEA/CAS

Prevalence of restenosis >70%. A meta-analysis of 11 RCTs observed that over a mean four year follow up, the prevalence of restenosis >70% in 1078 CEA patients was 5.8% (95% CI 4.1—8.2). Over a mean five year follow up, the prevalence of restenosis >70% in 2716 CAS patients was 10.0% (95% CI 6.0—16.3).[131]

Risk factors for restenosis. In CAVATAS, restenosis was associated with current (previous) smoking (HR 2.32, 95% CI 1.19—4.54) and a 50%—69% lesion detected within 60 days of treatment (HR 3.76, 95% CI 1.88—7.52).[5] Plaque length > 0.65 times the distal CCA diameter was associated with restenosis after CAS (HR 1.68, 95% CI 1.12—2.53) but not CEA.[5] However, comparing CAVATAS with other RCTs is confounded because the majority underwent CA, rather than CAS. CAVATAS reported that the incidence of 70%—99% restenoses was significantly lower after CAS compared with CA (HR 0.43, 95% CI 0.19—0.97).[5] EVA-3S found no association between restenosis and smoking, sex, hypertension, and antiplatelet/lipid therapy, but increasing age at baseline was a significant predictor. There was no association between open/closed stents and restenoses.[19] In CREST, patched CEA was associated with significant reductions in restenosis (*vs.* primary closure), but patching did not reduce late ipsilateral stroke.[89] In ICSS, restenosis was associated with older age, female sex, smoking, non-insulin dependent diabetes, angina, increased BP at randomisation, and increased cholesterol levels at randomisation.[58] Stent fractures were not associated with increased restenosis rates.[103]

Late ipsilateral stroke. Meta-analyses evaluated stroke rates ipsilateral to 70%—99% restenoses after CAS (five RCTs;

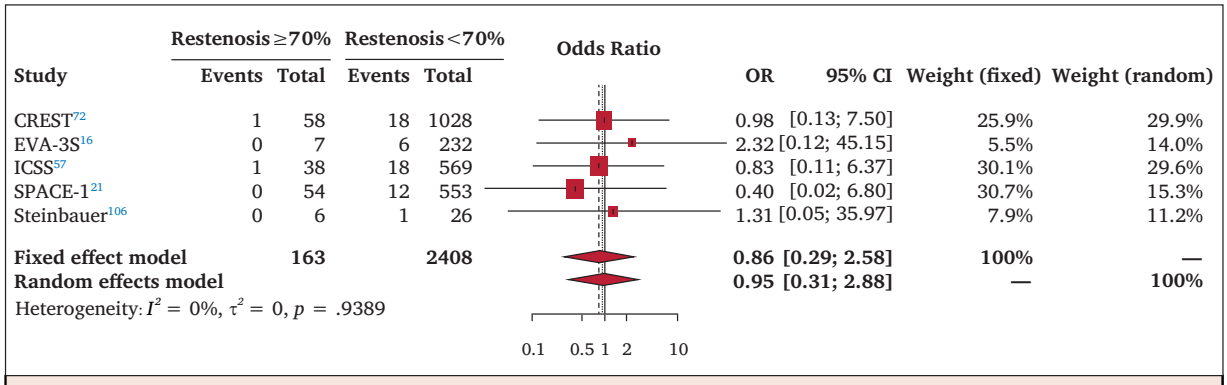

Figure 6. Forest plot depicting the relationship between asymptomatic restenosis ≥70% or no restenosis >70% after carotid artery stenting and the risk of late ipsilateral stroke in five randomised controlled trials. OR = odds ratio; CI = confidence interval.

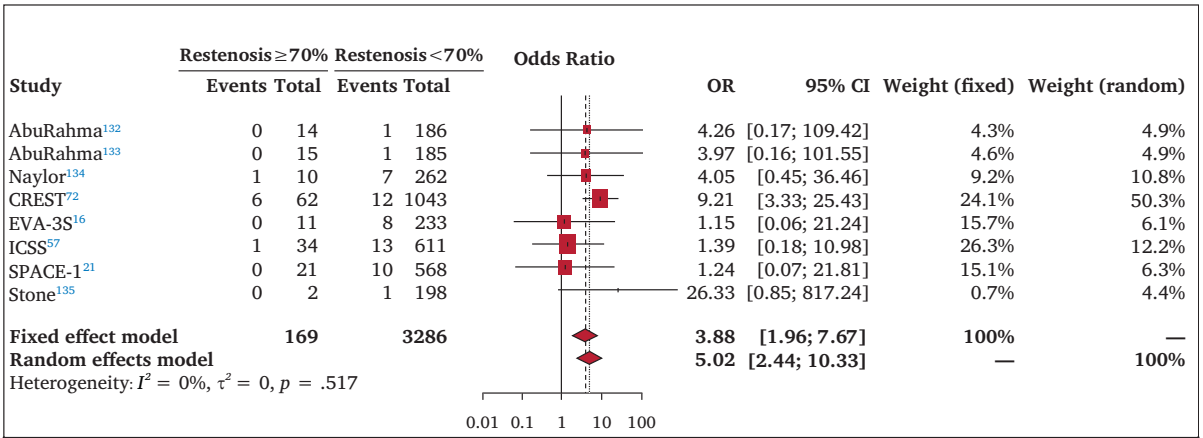

Figure 7. Forest plot depicting the relationship between asymptomatic restenosis ≥70% or no restenosis >70% after carotid endarterectomy and the risk of late ipsilateral stroke in eight randomised controlled trials. OR = odds ratio; CI = confidence interval.

$n = 2571$)[21,23,58,76,107] and CEA (eight RCTs; $n = 3455$).[21,23,58,76,132–135] PIs provided data regarding restenosis severity at the surveillance scan *before* stroke onset, rather than after stroke onset. The crude risk of ipsilateral stroke in CAS patients with 70%–99% restenoses (Fig. 6) was 1.22% *vs.* 2.28% in patients with 0%–69% restenoses (HR 0.86, 95% CI 0.29–2.58). The weighted absolute risk difference (ARD) was 0.23% (95% CI −0.90 to 4.11). Fig. 7 provides a similar meta-analysis for stroke ipsilateral to 70%–99% restenoses in 3455 CEA patients. The crude risk of ipsilateral stroke in CEA patients with 70%–99% restenoses was 4.7% *vs.* 1.6% in patients with 0%–69% restenoses (OR 3.87, 95% CI 1.96–7.67; $p < .001$). The weighted ARD was 5.26% (95% CI 2.37–10.80).

SUMMARY

The 20 RCTs have provided important primary and secondary data that have been (and will be) used to influence national and international guidelines of practice.[136,137] Peri-operative death/stroke was significantly higher after CAS, especially in symptomatic patients. Excluding procedural risks, late ipsilateral stroke rates were about 4% at nine years for both CEA and CAS, i.e. CAS was durable. In order to improve 10 year survival, peri-operative stroke/MI must be prevented. This requires greater emphasis on delivering better risk factor control and BMT. Reducing procedural death/stroke after CAS (which will improve the overall long term benefit of CAS) might be achieved through emerging CAS technologies, but improved case selection is essential, e.g., preferentially performing CEA in (i) symptomatic patients aged > 70 years; (ii) interventions less than 14 days from symptom onset; and (iii) situations where stroke risk after CAS is higher (segmental/remote plaques, plaque length > 13 mm, heavy burden of WMLs, avoiding situations where two or more stents need to be deployed). New WMLs were significantly more common after CAS and may be associated with higher rates of late stroke/TIA, mandating better risk factor control and BMT in these patients. There is no current evidence that new WMLs predispose to cognitive impairment. Restenoses were more common after CAS, but did not increase late ipsilateral stroke. CEA was associated with a small, but significant increase in stroke ipsilateral to 70%–99% restenoses.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.06.003.

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