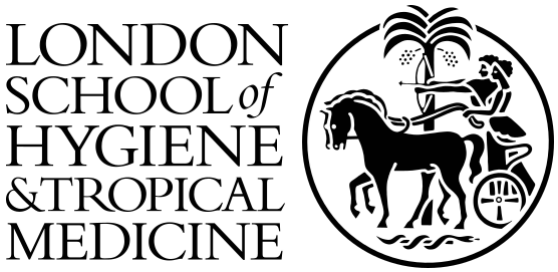

THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Bonati LH, Dobson J, Featherstone RL, et al, for the International Carotid Stenting Study investigators. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet* 2014; published online Oct 14. http://dx.doi.org/10.1016/S0140-6736(14)61184-3.

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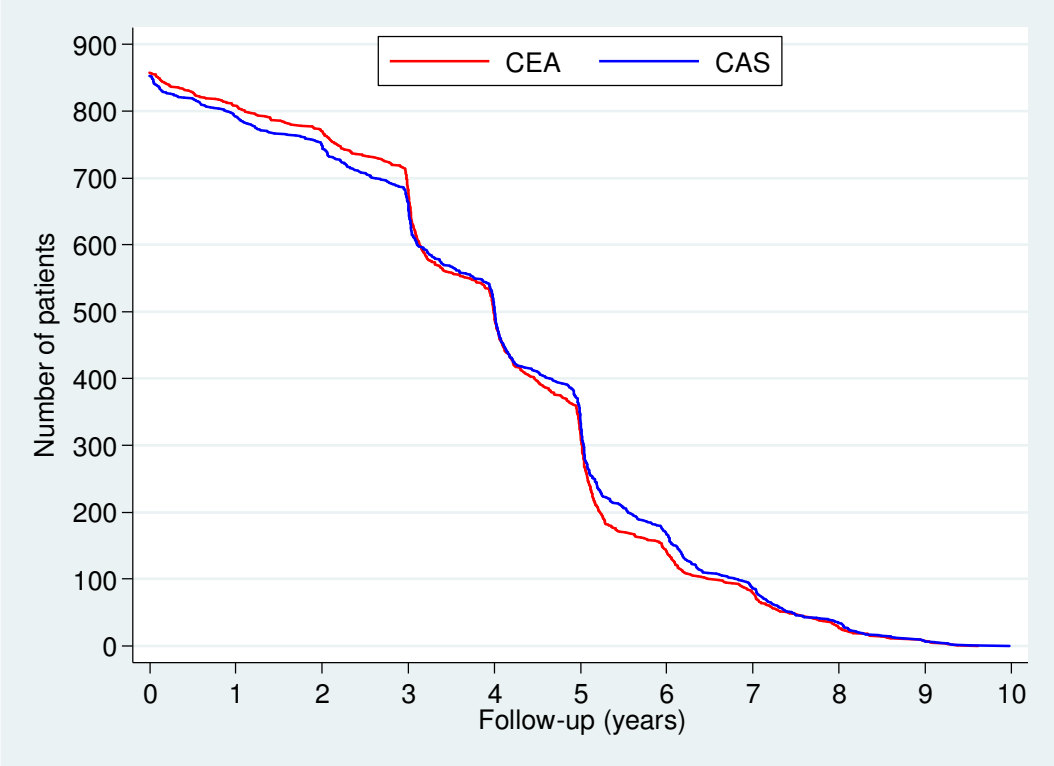
Supplementary figure 1: Duration of follow-up from randomisation by treatment group



In total there are 7354·4 patient years of follow-up (until time of last follow-up or death). CAS, carotid stenting: n=853, median follow-up = 4·2 years, interquartile range (IQR) 3·0-5·4 (max = 10·0 years, 153 deaths). CEA, carotid endarterectomy, n=857, median FU = 4·2 years, IQR 3·0-5·2 (max = 9·6 years, 129 deaths).

Supplementary table 1: technical information for stenting procedures

	Total (n=828*)
Cerebral protection device used	
Yes	585 (71%)
No	239 (29%)
Unknown	4 (0.5%)
Stent type used	
Closed stent design	371 (45%)
Open stent design	367 (44%)
No stent deployed	64 (8%)
Stent deployment or type unknown	26 (3%)
Peri-procedural antiplatelet therapy	
Any double antiplatelet therapy	674 (81%)
Aspirin and clopidogrel	594
Aspirin, dipyridamole and clopidogrel	58
Aspirin and dipyridamole	12
Aspirin and ticlopidin	6
Clopidogrel and dipyridamole	4
Single antiplatelet therapy	71 (9%)
Aspirin only	29
Clopidogrel only	42
No antiplatelet therapy	16 (2%)
Missing peri-procedural medication data	67 (8%)

*Number of patients randomly allocated stenting in whom the procedure was initiated

Supplementary table 2: technical information for endarterectomy procedures

	Total (n=821*)
Type of anaesthesia	
General anaesthesia	650 (79%)
Local anaesthesia	144 (18%)
Unknown	27 (3%)
Shunt used	
Yes	324 (39%)
No	494 (60%)
Unknown	3 (0.4%)
Type of reconstruction	
Standard with patch	459 (56%)
Standard without patch	182 (22%)
Eversion	49 (6%)
Vein interposition	3 (0.4%)
Unknown	128 (16%)

*Number of patients randomly allocated endarterectomy in whom the procedure was initiated

Supplementary table 3: Drug treatment and blood pressure levels during follow-up (intention-to-treat population)

	1 year		5 years	
	Stenting	**Endarterectomy**	**Stenting**	**Endarterectomy**
Drug treatment (n patients with data)	714	751	343	329
Any antiplatelet	668 (94%)	688 (92%)	303 (88%)	284 (86%)
Aspirin alone	401 (56%)	413 (55%)	197 (57%)	169 (51%)
Clopidogrel alone	79 (11%)	79 (11%)	40 (12%)	46 (14%)
Dipyridamole + aspirin or clopidogrel	130 (18%)	154 (21%)	48 (14%)	48 (15%)
Aspirin + clopidogrel	55 (8%)	34 (5%)	14 (4%)	17 (5%)
Anticoagulation (Vitamin K antagonists)	36 (5%)*	57 (8%)*	23 (7%)	33 (10%)
Other anticoagulation or antiplatelet	3 (0%)	10 (1%)	5 (1%)	4 (1%)
Any anticoagulation or antiplatelet	696 (97%)	731 (97%)	322 (94%)	313 (95%)
Antihypertensive	510 (71%)	566 (75%)	286 (83%)*	250 (76%)*
Lipid lowering	584 (82%)	629 (84%)	299 (87%)	282 (86%)
Blood pressure (n patients with data)	664†	685†	313†	302†
Mean systolic *mmHg*	147 (22)*	144 (22)*	142 (22)	143 (23)
Mean diastolic *mmHg*	79 (12)*	78 (11)*	77 (12)	76 (12)

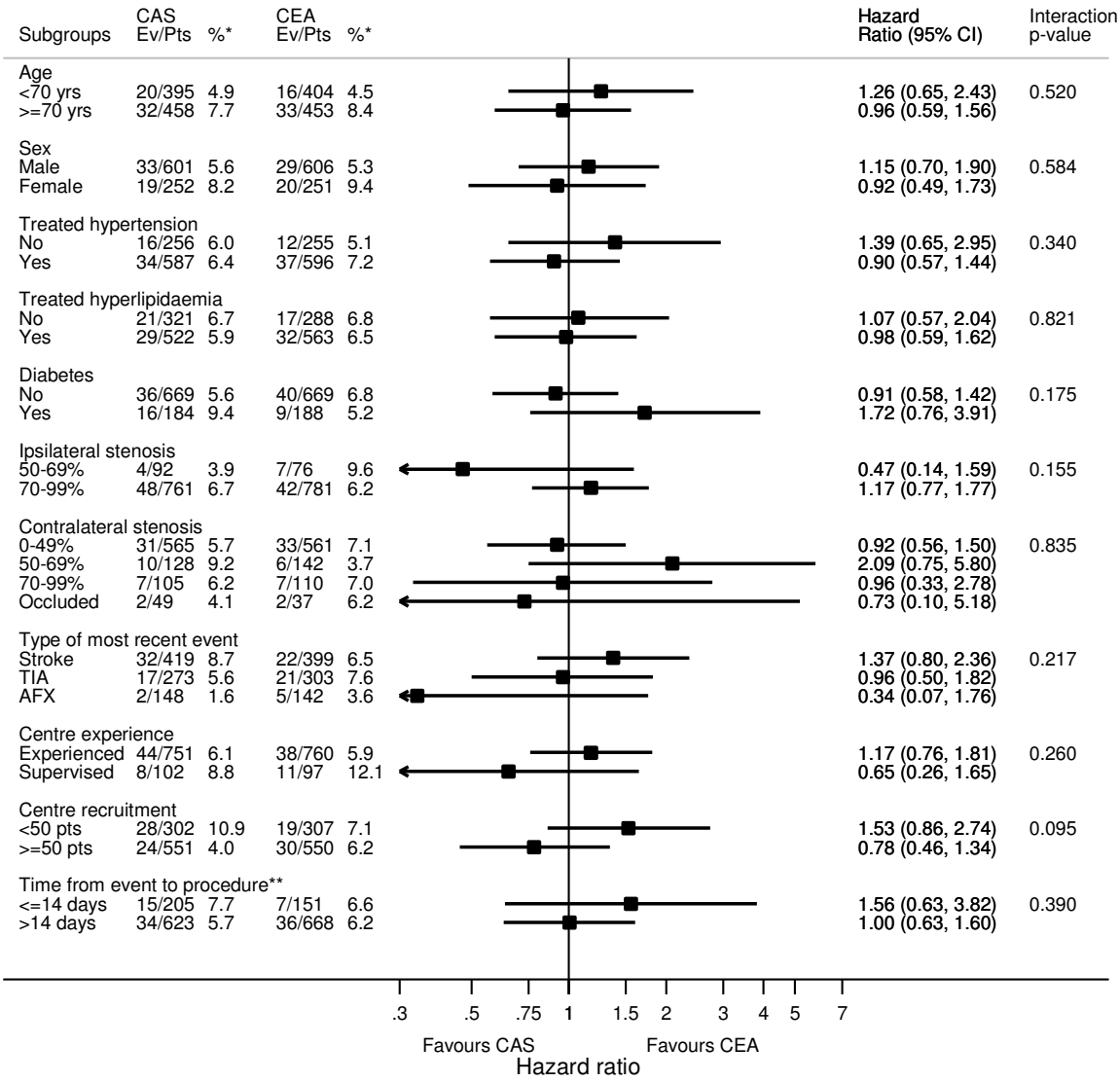
Data are number (percent) or mean (standard deviation) of patients with available information. *P-value <0.05 (statistical comparison between stenting and endarterectomy using Chi-square test for specified drug treatments and t-test for blood pressures). †Numbers of patients with data are 663 and 684 (1 year), and 312 and 301 (5 year), for diastolic blood pressure.

Supplementary table 4: Number of main outcome events between randomisation and end of follow-up (intention-to-treat population)

	Procedural period*		Follow-up period (excluding procedural period)**		Full study period (including procedural period	
	CAS (n=837)	CEA (n=836)	CAS (n=853)	CEA (n=857)	CAS (n=853)	CEA (n=857)
Any stroke	59	27	65	47	119	72
Stroke territory						
Ipsilateral carotid stroke	51	24	35	31	84	53
Contralateral carotid or vertebrobasilar stroke	7	4	32	17	39	21
Contralateral	6	2	25	9	31	11
Vertebrobasilar	2	2	8	8	10	10
Unknown territory	2	0	3	4	5	4
Stroke type						
Ischemic	57	21	53	38	107	57
Haemorrhagic	2	5	10	7	12	12
Uncertain type	0	1	4	5	4	6
Stroke severity						
Non-disabling	36	12	40	16	73	27
Disabling	15	13	16	26	31	39
Fatal	8	3	14	8	22	11
All cause death	11†	4	142†	125	153	129
Non-stroke death	4	1	127	117	131	118
Myocardial infarction‡	3	5	-	-	-	-
Non-fatal	0	5	-	-	-	-
Fatal	3	0	-	-	-	-
Cranial nerve palsy‡	1	45	-	-	-	-
Disabling cranial nerve palsy	1	1	-	-	-	-
Access site haematoma‡	30	50	-	-	-	-
Severe haematoma	8	28	-	-	-	-

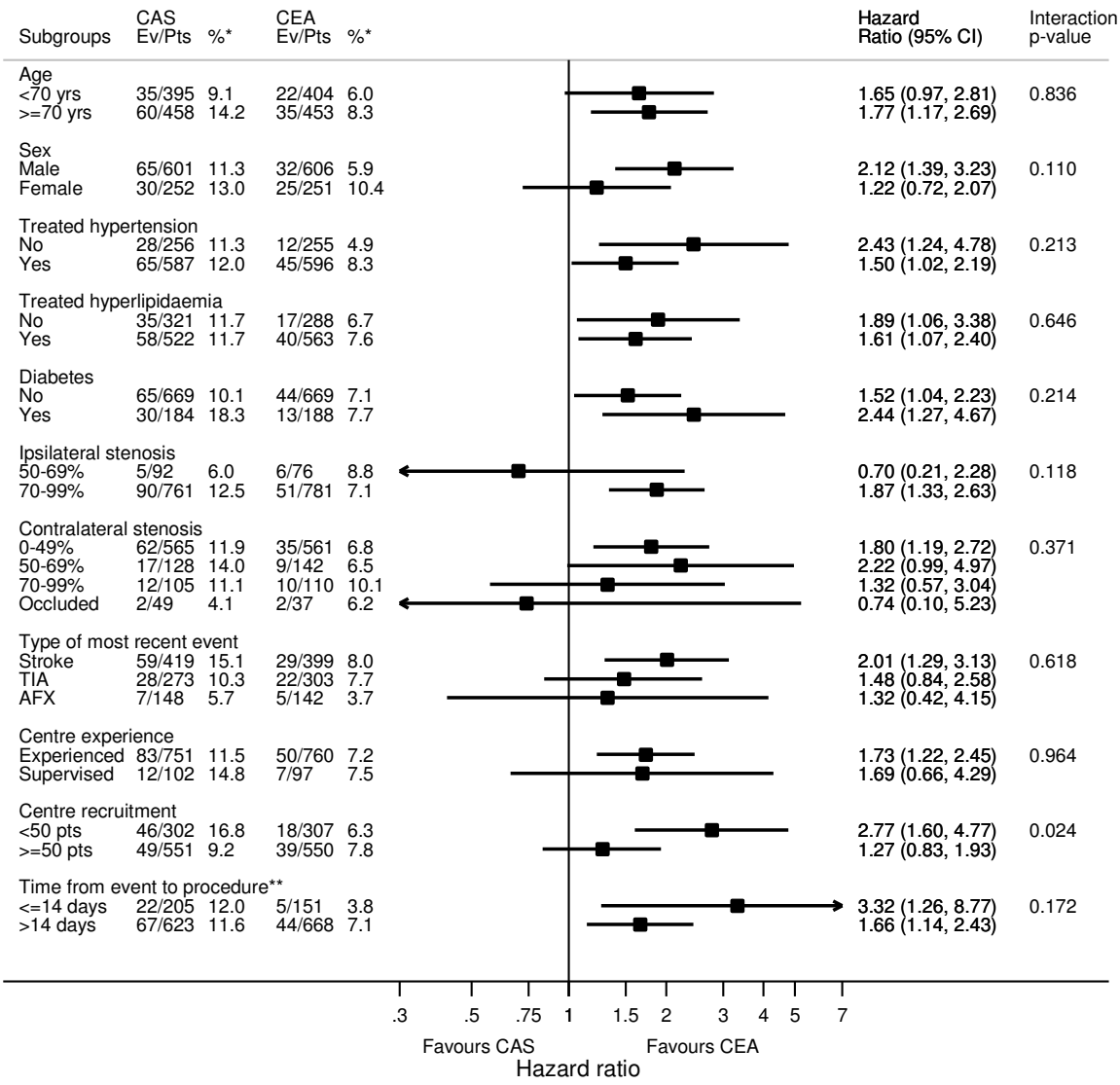
CAS, carotid stenting. CEA, carotid endarterectomy. Data are number of first outcome events of each type within each timing category. A patient may therefore contribute more than one type of outcome event within a timing category and more than one outcome event of the same type across timing categories. 53 patients (31 CAS, 22 CEA) had more than one outcome event during follow-up. *Events occurring within 30 days of first revascularisation treatment (irrespective of whether this was the randomly allocated treatment or not). **Also includes events occurring between randomisation and treatment (2 CAS, 1 CEA) and events among patients not receiving revascularisation treatment (7 CAS, 15 CEA events, in 4 CAS, 11 CEA patients). †The death of 1 patient with fatal procedural stroke (i.e. a stroke occurring within 30 days of treatment and leading to death within 30 days of stroke onset) was counted in all-cause death in the follow-up period rather than the procedural period, as the patient died more than 30 days after treatment. ‡ Outcome events only adjudicated in procedural period.

Supplementary figure 2: Hazard ratios of fatal or disabling stroke between randomisation and end of follow-up in patient subgroups.



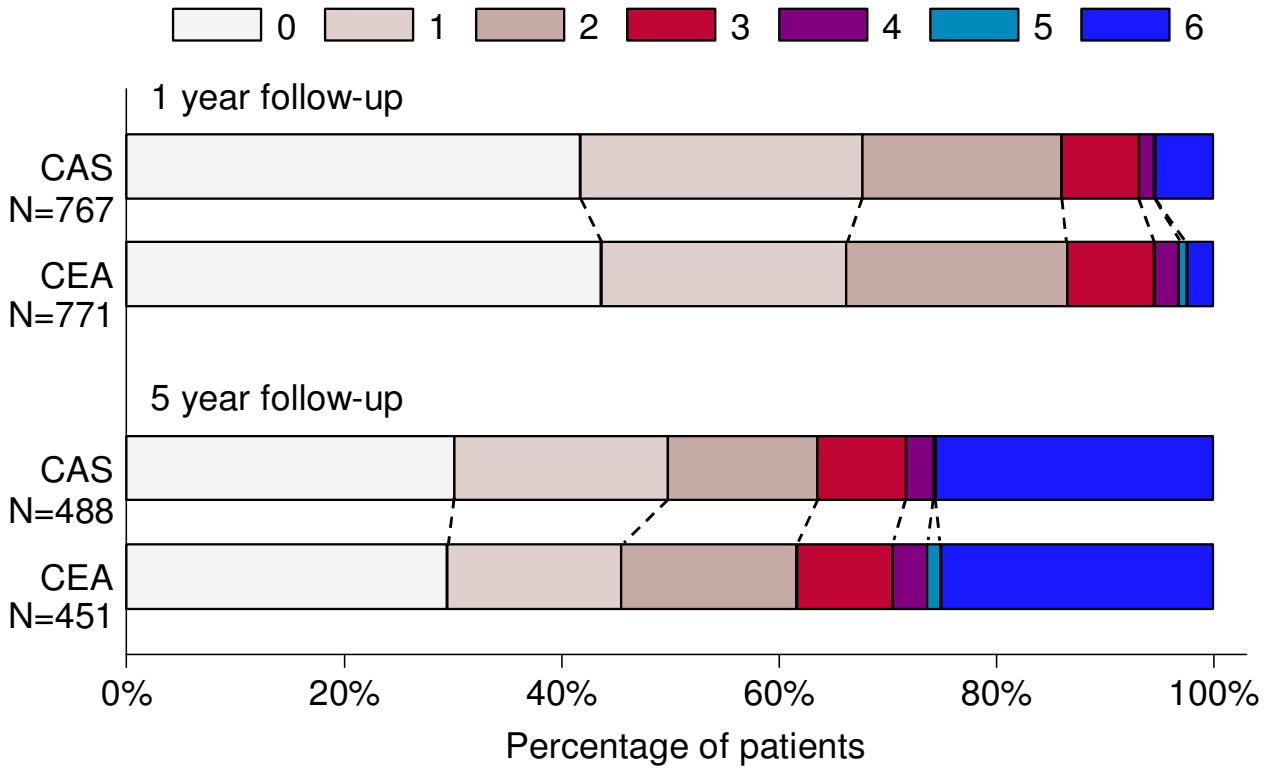
CAS, carotid stenting. CEA, carotid endarterectomy. Subgroups are defined according to baseline characteristics and analyzed by intention to treat for all available follow-up, apart from time from event to procedure, which is analyzed per protocol. Interaction P-values are calculated using likelihood ratio tests in the Cox regression models. *Data are number of events of first fatal or disabling stroke / number of patients, and Kaplan-Meier estimate of cumulative risk at 5 years. Patients with missing information were excluded from the analysis. **Time from most recent ipsilateral event before randomisation to the date of treatment, analysed per protocol from the time of procedure. All subgroups for analysis were pre-specified except for treated hyperlipidaemia which was added post-hoc.

Supplementary figure 3: Hazard ratios of procedural stroke, procedural death or ipsilateral stroke occurring during follow-up in different patient subgroups.



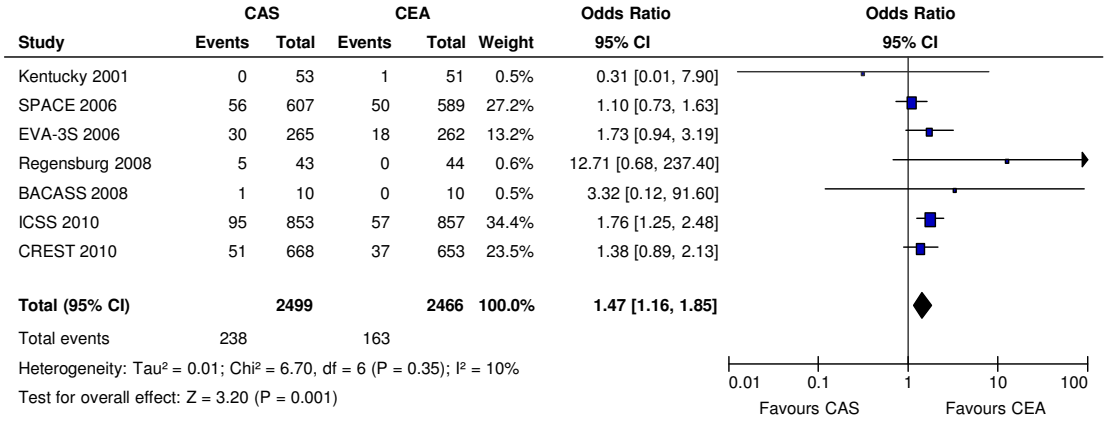
CAS, carotid stenting. CEA, carotid endarterectomy. Subgroups are defined according to baseline characteristics and analysed by intention to treat for all available follow-up, apart from time from event to procedure, which is analysed per protocol. Interaction P-values are calculated using likelihood ratio tests in the Cox regression models. *Data are number of events of first procedural stroke or procedural death or ipsilateral stroke during follow-up / number of patients, and Kaplan-Meier estimate of cumulative risk at 5 years. Patients with missing information were excluded from the analysis. **Time from most recent ipsilateral event before randomisation to the date of treatment, analysed per protocol from the time of procedure.

Supplementary figure 4: Functional ability measured by the modified Rankin Scale during follow-up



CAS, carotid stenting. CEA, carotid endarterectomy. Permutation test* comparing Rankin scores between the two groups at 1 year, unadjusted: p=0·70, adjusted for baseline mRS: p=0·11; at 5 years, unadjusted: p=0·54, adjusted for baseline mRS: p=0·98. *According to Howard et al., Stroke 2012;43(3):664-669.

Supplementary figure 5: Meta-analysis of death or any stroke occurring between randomisation and 30 days after treatment or ipsilateral stroke during follow-up



Update of the Cochrane Collaborative Group Intervention Review of randomised trials comparing endovascular treatment with endarterectomy for symptomatic carotid stenosis.[1] Only trials using primary carotid stenting in their endovascular treatment group, i.e. with routine placement of a stent, and only trials reporting outcomes in symptomatic patients were included. The combined outcome event of any stroke or death occurring between randomisation and 30 days after treatment (or 30 days after randomisation in patients receiving neither CAS nor CEA), or ipsilateral stroke occurring during follow-up is compared. Data are numbers of patients with events, total numbers of patients and Mantel-Haenszel random-effects odds ratios including 95% confidence intervals (CI) with endarterectomy as the reference treatment. Squares represent point estimates of odds ratios at trial level, with 95% CI as horizontal bars. The diamond at the bottom represents the summary OR and 95% CI. We quantified heterogeneity using the I^2 statistic.[2] Review Manager software, version 5.2.6 was used. Data from the following trials are included: Kentucky,[3] SPACE,[4] EVA-3S,[5] Regensburg,[6] BACASS,[7] ICSS,[8] CREST[9]. Studies are listed by the year of the initial publication of results. CAS, carotid artery stenting; CEA, carotid endarterectomy.

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