

# 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](http://dx.doi.org/10.1016/S0140-6736(14)61184-3).

## Appendix

### International Carotid Stenting Study investigators

#### *Steering Committee:*

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.

#### *Credential committee:*

A Bradbury, M M Brown, A Clifton, P Gaines.

#### *Data Monitoring Committee:*

R Collins, A Molyneux, R Naylor, C Warlow (chair).

#### *Outcome Event Adjudication Committee:*

J M Ferro, D Thomas.

#### *Central office staff at UCL Institute of Neurology:*

L H Bonati, L Coward, J Dobson (trial statistician), D. Doig, J Ederle, R F Featherstone (trial manager), F. Kennedy, H Tindall, E Turner, D J H McCabe, A Wallis.

#### *Participating countries and centres (number of enrolled patients per centre; local investigators):*

*Australia:* Austin Health, Heidelberg (46; M Brooks, B Chambers [principal investigator], A Chan, P Chu, D Clark, H Dewey, G Donnan, G Fell, M Hoare, M Molan, A Roberts, N Roberts). Box Hill Hospital (Monash University), Melbourne (25; B Beiles, C Bladin [principal investigator], C Clifford, G Fell, M Grigg, G New). Monash Medical Centre, Clayton (26; R Bell, S Bower, W Chong, M Holt, A Saunder, P G Than [principal investigator]). Princess Alexandra Hospital, Brisbane (48; S Gett, D Leggett, T McGahan [principal investigator], J Quinn, M Ray, A Wong, P Woodruff ). Repatriation General Hospital, Daw Park, Adelaide (6; R Foreman, D Schultz [principal investigator], R Scroop, B Stanley). Royal Melbourne Hospital, Melbourne (57; B Allard, N Atkinson, W Cambell, S Davis [principal investigator], P Field, P Milne, P Mitchell, B Tress, B Yan). Royal Hobart Hospital, Hobart (18; A Beasley, D Dunbabin, D Sary, S Walker [principal investigator]).

*Belgium:* Antwerp University Hospital, Antwerp (10; P Cras, O d'Archambeau, J M H Hendriks [principal investigator], P Van Schil). A Z St Blasius, Dendermonde (5; M Bosiers [principal investigator], K Deloose, E van Buggenhout). A Z Sint Jan Brugge-Oostende, Campus Brugge, Brugges (18; J De Letter, V Devos, J Ghekiere, G Vanhooren [principal investigator]). Cliniques Universitaires St Luc, Bruxelles (1; P Astarci, F Hammer, V Lacroix, A Peeters [principal investigator], R Verhelst). Imelda Ziekenhuis, Bonheiden (3; L DeJaegher [principal investigator], A Peeters, J Verbist).

*Canada:* CHUM Notre-Dame Hospital, Montreal (30; J-F Blair, J L Caron, N Daneault, M-F Giroux, F Guilbert, S Lanthier, L-H Lebrun, V Oliva, J Raymond, D Roy [principal investigator], G Soulez, A Weill). Foothills Medical Center, Calgary (4; M Hill [principal investigator], W Hu, M Hudion, W Morrish, G Sutherland, J Wong).

*Finland:* Helsinki University Central Hospital, Helsinki (33; A Albäck, S Curtze, H Harno, P Ijäs, M Kaste (principal investigator) , K Lappalainen, M Lepäntalo, A Meretoja, S Mustanoja, T Paananen, M Porras, J Putaala, M Railo, T Sairanen, L Soenne, A Vehmas, P Vikatmaa).

*Germany:* Otto von Guericke University, Magdeburg (9; M Goertler [principal investigator], Z Halloul, M Skalej).

*Ireland:* Beaumont Hospital, Dublin (4; P Brennan, C Kelly, A Leahy, J Moroney [principal investigator], J Thornton).

*Netherlands:* Academic Medical Center, Amsterdam (56; M J W Koelemay, P J Nederkoorn [principal investigator], J A A Reekers, Y B W E M Roos). Erasmus Medical Center, Rotterdam (75; J M Hendriks, P J Koudstaal [principal investigator], P M T Pattynama, A van der Lugt, L C van Dijk, M R H M van Sambeek, H van Urk, H J M Verhagen). Haga Teaching Hospitals, The Hague (45; C M A Bruijninx, S F de Bruijn, R Keunen, B Knippenberg, A Mosch [principal investigator], F Treurniet, L van Dijk, H van Overhagen, J Wever). Isala Klinieken, Zwolle (14; F C de Beer, J S P van den Berg [principal investigator], B A A M van Hasselt, D J Zeilstra). Medical Center Haaglanden, The Hague (3; J Boiten [principal investigator], J C A de Mol van Otterloo, A C de Vries, G J Lycklama a Nijeholt, B F W van der Kallen). UMC St Radboud, Nijmegen (13; J D Blankensteijn, F E De Leeuw, L J Schultze Kool [principal investigator], J A van der Vliet). University Medical Center, Utrecht (270;

G J de Borst, G A P de Kort, L J Kapelle [principal investigator], T H Lo, W P Th M Mali, F Moll, HB van der Worp, H Verhagen).

*New Zealand:* Auckland City Hospital, Auckland (40; P A Barber, R Bouchier, A Hill, A Holden, J Stewart [principal investigator]).

*Norway:* Rikshospitalet University Hospital, Oslo (16; S J Bakke [principal investigator], K Krohg-Sørensen, M Skjelland, B Tennøe).

*Poland:* Institute of Psychiatry and Neurology (2<sup>nd</sup> Department of Neurology & Department of Neuroradiology) and Medical University of Warsaw (2<sup>nd</sup> Department of General, Vascular and Oncological Surgery), Warsaw (20; P Bialek, Z Biejat, W Czepiel, A Czlonkowska [principal investigator], A Dowzenko, J Buczek, A Kobayashi, M Lelek, J Polanski).

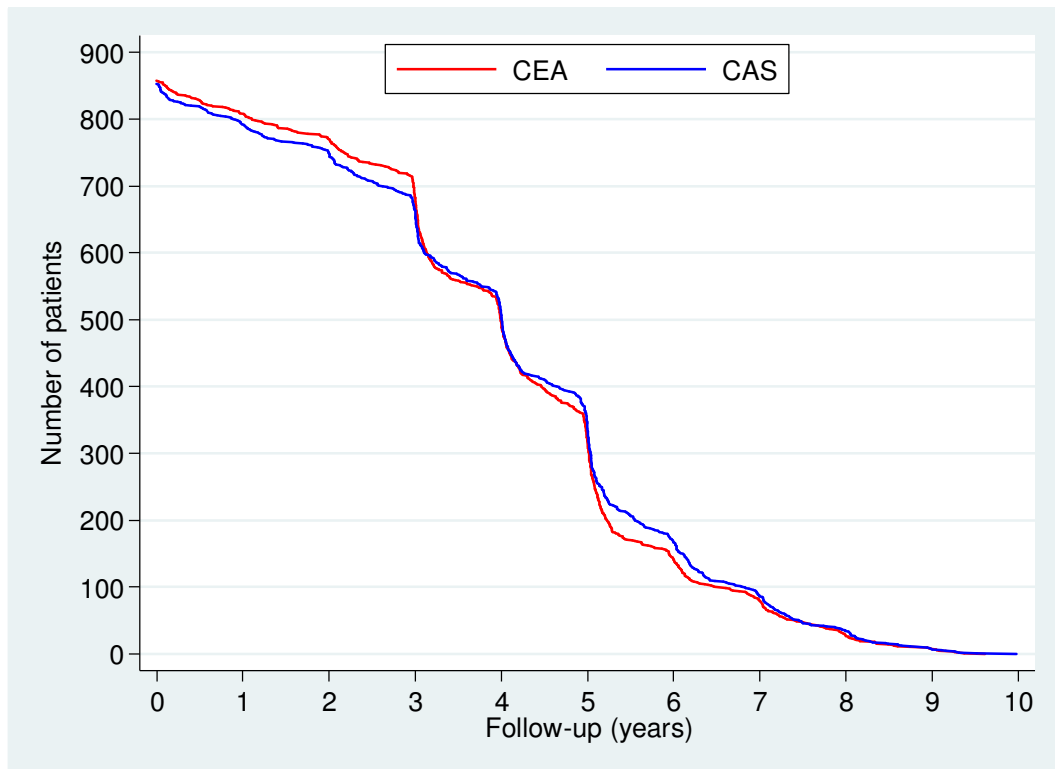
*Slovenia:* University Medical Center, Ljubljana (12; J Kirbis, Z Milosevic, B Zvan [principal investigator]).

*Spain:* Hospital Clinic, Barcelona (18; J Blasco, A Chamorro [principal investigator], J Macho, V Obach, V Rimbau, L San Roman). Parc Taulí Sabadell Hospital, Barcelona (33; J Branera, D Canovas [principal investigator], Jordi Estela, A Gimenez Gaibar, J Perendreu).

*Sweden:* Skåne University Hospital, Malmö (67; K Björse, A Gottsäter [principal investigator], K Ivancev, T Mätzsch, B Sonesson)). Sodersjukhuset, Stockholm (55; B Berg, M Delle, J Formgren, P Gillgren, T-B Kaell, P Konrad [principal investigator], N Nyman, R Takolander). The Karolinska Institute, Stockholm (5; T Andersson, J Malmstedt, M Soderman, C Wahlgren, N Wahlgren [principal investigator]).

*Switzerland:* Centre Hospitalier Universitaire Vaudois, Lausanne (12; S Binaghi, L Hirt, P Michel [principal investigator], P Ruchat). University Hospital Basel, Basel (94; L H Bonati, S T Engelter, F Fluri, L Guerke, A L Jacob, E Kirsch, P A Lyrer [principal investigator], E-W Radue, P Stierli, M Wasner, S Wetzler). University Hospital of Geneva, Geneva (16; C Bonvin, A Kalangos, K Lovblad, N Murith, D Ruefenacht, R Sztajzel [principal investigator]).

*United Kingdom:* Addenbrookes Hospital, Cambridge (5; N Higgins, P J Kirkpatrick, P Martin [principal investigator]). K Varty Birmingham Heartlands Hospital, Birmingham (11; D Adam, J Bell, A W Bradbury, P Crowe, M Gannon, M J Henderson, D Sandler, R A Shinton [principal investigator], J M Scriven, T Wilkink). Lancashire Teaching Hospitals NHS Trust, Preston (2; S D'Souza, A Egun, R Guta, S Punekar, D M Seriki [principal investigator], G Thomson). Liverpool Royal Infirmary (21) and the Walton Centre, Liverpool (7; J A Brennan, T P Enevoldson, G Gilling-Smith [principal investigator], D A Gould, P L Harris, R G McWilliams, H-C Nahser, R White). Manchester Royal Infirmary, Manchester (2; K G Prakash, F Serracino-Inglott, G Subramanian [principal investigator], J V Symth, M G Walker). Newcastle Acute Hospitals NHS Foundation Trust, Newcastle upon Tyne (108; M Clarke, M Davis, S A Dixit, P Dorman [principal investigator], A Dyker, G Ford, A Golkar, R Jackson, V Jayakrishnan, D Lambert, T Lees, S Louw, S Macdonald, A D Mendelow, H Rodgers, J Rose, G Stansby, M Wyatt). North Bristol NHS Trust, Frenchay Hospital, Bristol (13; T Baker, N Baldwin [principal investigator], L Jones, D Mitchell, E Munro, M Thornton). Royal Free Hospital, London (1; D Baker, N Davis, G Hamilton [principal investigator], D McCabe, A Platts, J Tibballs). Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield (151; J Beard, T Cleveland, D Dodd, P Gaines, R Lonsdale, R Nair, A Nassef, S Nawaz, G Venables [principal investigator]). St George's University of London and St George's NHS Healthcare Trust, London (58; A Belli, A Clifton, G Cloud, A Halliday, H Markus [principal investigator], R McFarland, R Morgan, A Pereira, A Thompson). St Mary's Hospital, Imperial College Healthcare NHS Trust, London (13; J Chataway [principal investigator], N Cheshire, R Gibbs, M Hammady, M Jenkins, I Malik, J Wolfe). University College London Hospitals NHS Foundation Trust, London (51; M Adiseshiah, C Bishop, S Brew, J Brookes, M M Brown [principal investigator], R Jäger, N Kitchen). University Hospital of South Manchester, Wythenshawe, Manchester (58; R Ashleigh, S Butterfield, G E Gamble, C McCollum [principal investigator], A Nasim, P O'Neill, J Wong). Western Infirmary, Glasgow (5; R D Edwards, K R Lees, A J MacKay, J Moss [principal investigator], P Rogers).

**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*)
<b>Cerebral protection device used</b>	
Yes	585 (71%)
No	239 (29%)
Unknown	4 (0.5%)
<b>Stent type used</b>	
Closed stent design	371 (45%)
Open stent design	367 (44%)
No stent deployed	64 (8%)
Stent deployment or type unknown	26 (3%)
<b>Peri-procedural antiplatelet therapy</b>	
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*)
<b>Type of anaesthesia</b>	
General anaesthesia	650 (79%)
Local anaesthesia	144 (18%)
Unknown	27 (3%)
<b>Shunt used</b>	
Yes	324 (39%)
No	494 (60%)
Unknown	3 (0.4%)
<b>Type of reconstruction</b>	
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
<b>Drug treatment</b> (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%)
<b>Blood pressure</b> (n patients with data)	664†	685†	313†	302†
Mean systolic <i>mmHg</i>	147 (22)*	144 (22)*	142 (22)	143 (23)
Mean diastolic <i>mmHg</i>	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.

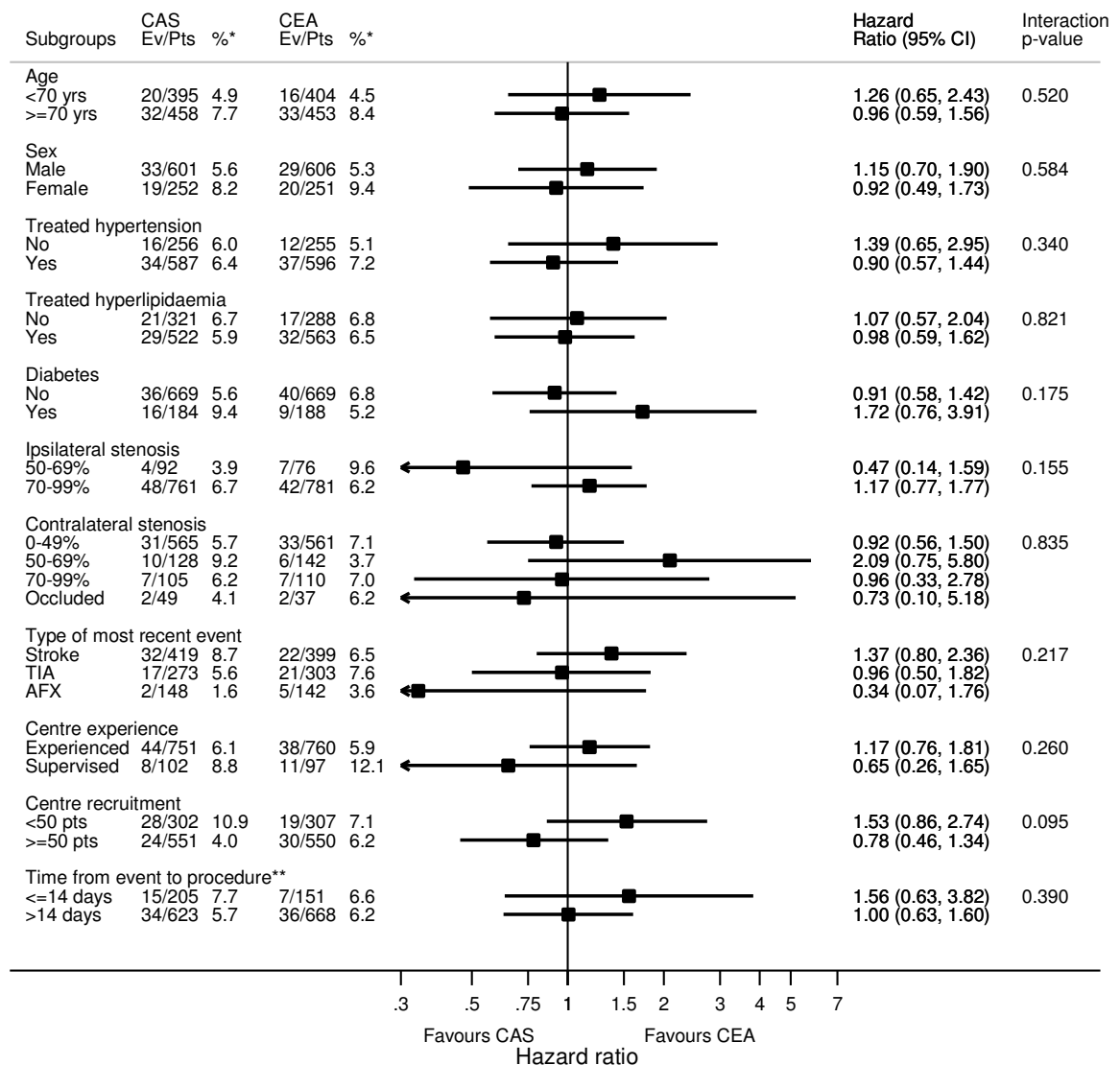
**Supplementary table 4: Number of main outcome events between randomisation and end of follow-up (intention-to-treat population)**

	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)
<b>Any stroke</b>	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
<b>All cause death</b>	11†	4	142†	125	153	129
Non-stroke death	4	1	127	117	131	118
<b>Myocardial infarction‡</b>	3	5	-	-	-	-
Non-fatal	0	5	-	-	-	-
Fatal	3	0	-	-	-	-
<b>Cranial nerve palsy‡</b>	1	45	-	-	-	-
Disabling cranial nerve palsy	1	1	-	-	-	-
<b>Access site haematoma‡</b>	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.

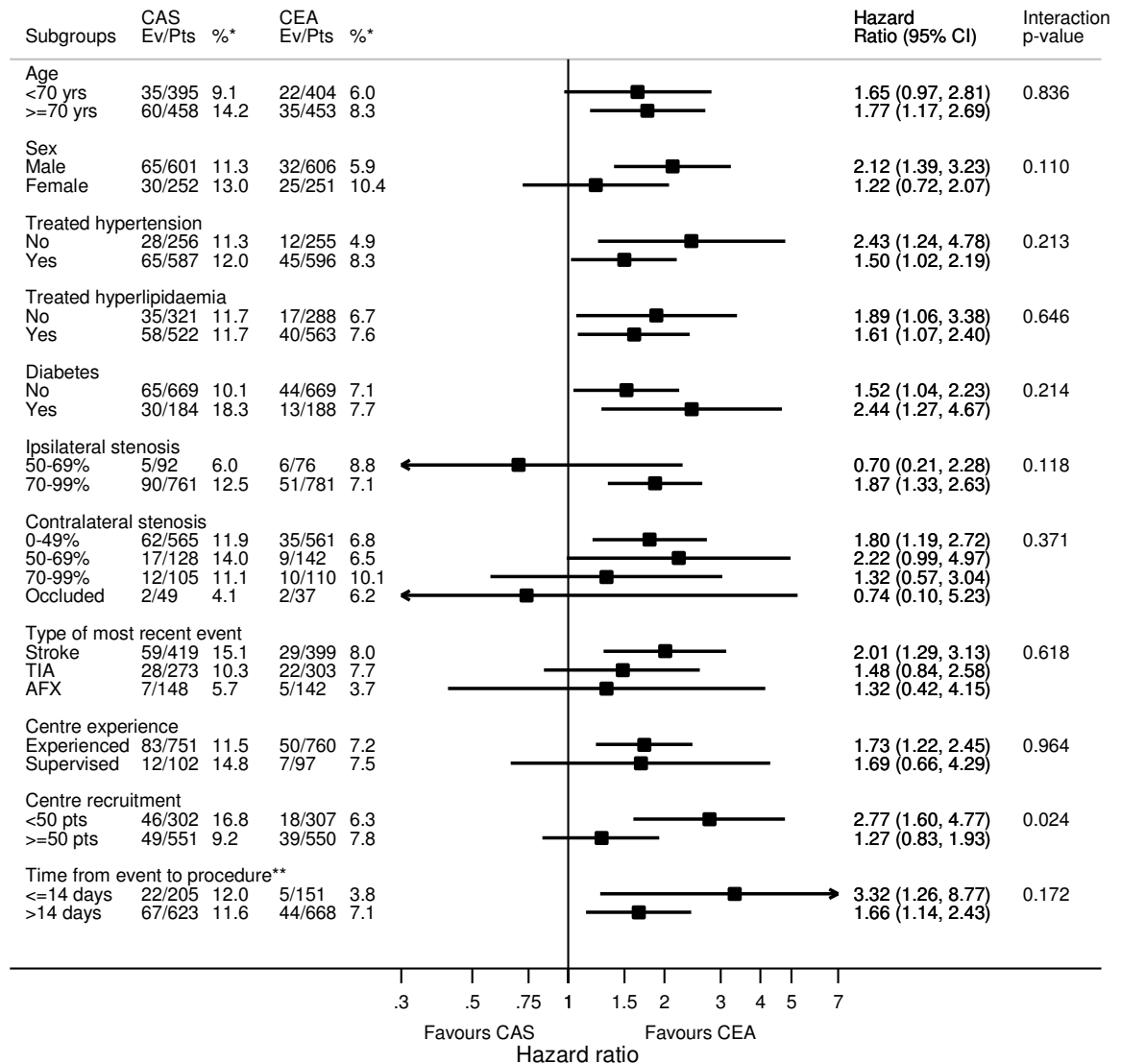


**Supplementary figure 2: Hazard ratios of fatal or disabling stroke between randomisation and end of follow-up in patient subgroups.**



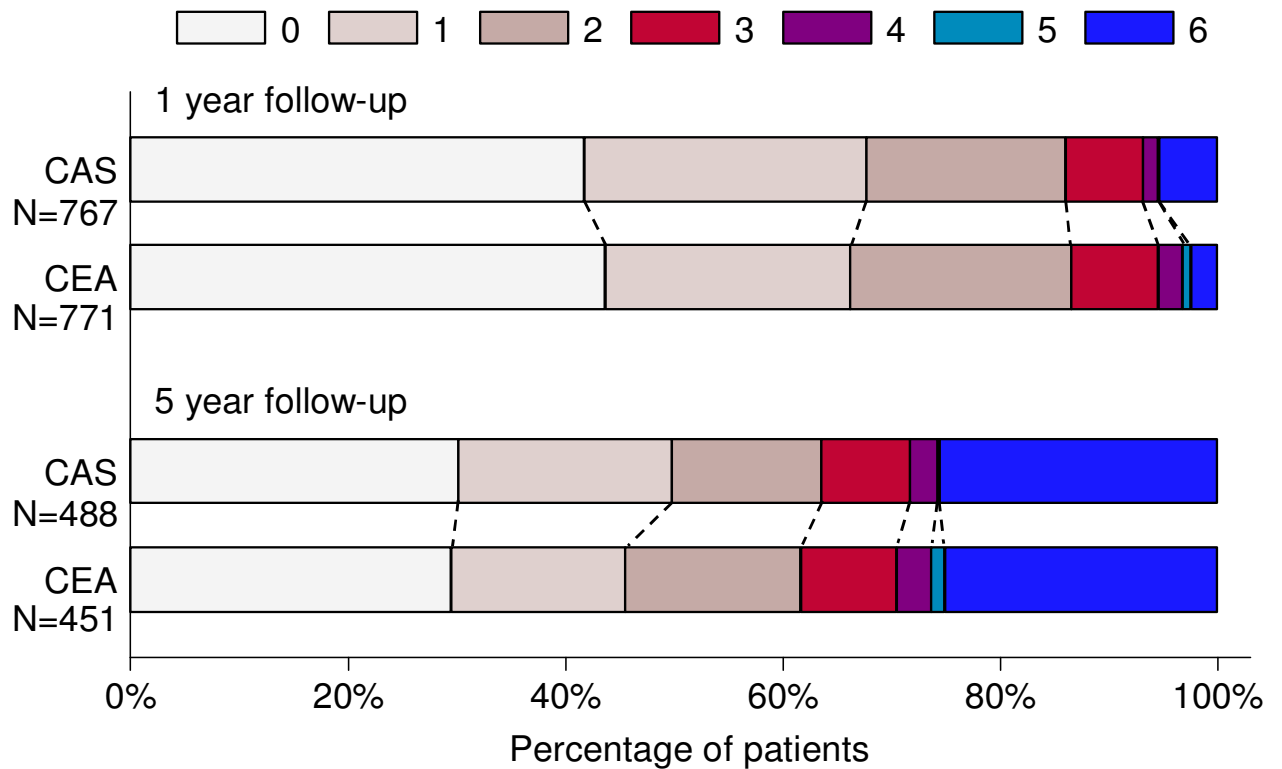
CAS, carotid stenting. CEA, carotid endarterectomy. Subgroups are defined according to baseline characteristics and analyzed by intention to treat for all available follow-up, apart from time from event to procedure, which is analyzed per protocol. Interaction P-values are calculated using likelihood 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.**



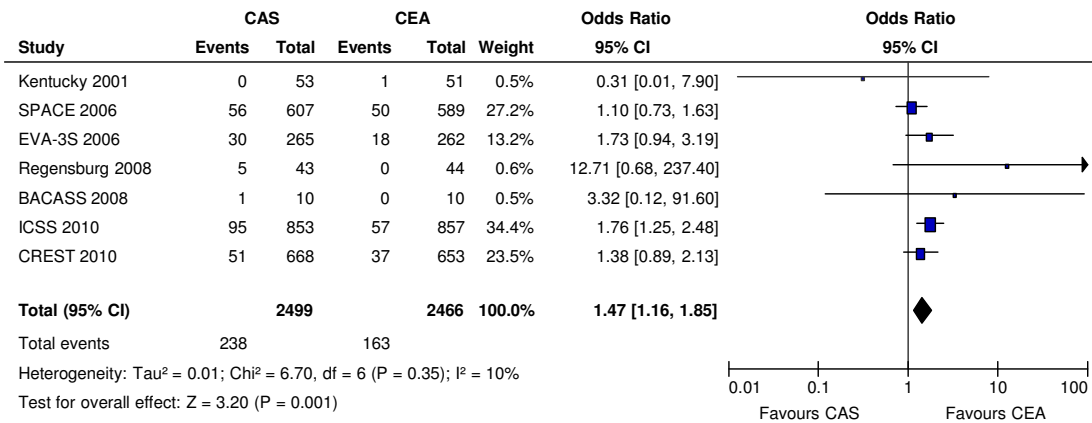
CAS, carotid stenting. CEA, carotid endarterectomy. Subgroups are defined according to baseline characteristics and analysed by intention to treat for all available follow-up, apart from time from event to procedure, which is analysed per protocol. Interaction P-values are calculated using likelihood 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.<sup>1</sup> 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<sup>2</sup> statistic.<sup>2</sup> Review Manager software, version 5.2.6 was used. Data from the following trials are included: Kentucky,<sup>3</sup> SPACE,<sup>4</sup> EVA-3S,<sup>5</sup> Regensburg,<sup>6</sup> BACASS,<sup>7</sup> ICSS,<sup>8</sup> CREST<sup>9</sup>. Studies are listed by the year of the initial publication of results. CAS, carotid artery stenting; CEA, carotid endarterectomy.

## References

- (1) Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev* 2012;9:CD000515.
- (2) Higgins JPT, Altman DG, Sterne JAC, The Cochrane Collaboration. Assessing risk of bias in included Studies. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. 2011.
- (3) Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol* 2001 Nov 15;38(6):1589-95.
- (4) Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008 Oct;7(10):893-902.
- (5) Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol* 2008 Oct;7(10):885-92.
- (6) Steinbauer MG, Pfister K, Greindl M, Schlachetzki F, Borisch I, Schuirer G, et al. Alert for increased long-term follow-up after carotid artery stenting: results of a prospective, randomized,

single-center trial of carotid artery stenting vs carotid endarterectomy. *J Vasc Surg* 2008 Jul;48(1):93-8.

- (7) Hoffmann A, Taschner C, Engelter ST, Lyrer P, Rem J, Raude EW. Carotid artery stenting versus carotid endarterectomy. A prospective, randomised trial with long term follow up (BACASS). *Schweizer Archiv für Neurologie und Psychiatrie* 2006;157:191.
- (8) Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 2010 Mar 20;375(9719):985-97.
- (9) Brott TG, Hobson RW, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010 Jul 1;363(1):11-23.