SUPPLEMENTAL MATERIAL

Early endarterectomy carries a lower procedural risk than early stenting in patients with symptomatic stenosis of the internal carotid artery – results from four randomized controlled trials

Barbara Rantner MD, PhD;[1] Barbara Kollerits PhD;[2] GS Roubin, MD;[3] PA Ringleb, MD;[4] O Jansen, MD;[5] G Howard, DrPH;[6] J Hendrikse, MD;[7] A Halliday, MD;[8] J Gregson;[9] H-H Eckstein, MD;[10] D Calvet, MD;[11] R Bulbulia, MD;[12] LH Bonati, MD;[13,14] JP Becquemin, MD;[15] A Algra, MD;[16,17] MM Brown, MD;[14]* J-L Mas, MD;[18]* TG Brott, MD;[19]* G Fraedrich, MD;[1]*#

On behalf of the Carotid Stenosis Trialists' Collaboration.

**Contributed equally*

1. Department of Vascular Surgery, Medical University of Innsbruck, Innsbruck, Austria
2. Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria
3. Cardiovascular Associates of the Southeast, Birmingham, AL
4. Department of Neurology, University of Heidelberg Medical School, Heidelberg, Germany
5. Clinic for Radiology and Neuroradiology, UKSH Campus Kiel, Kiel, Germany
6. Department of Biostatistics, UAB School of Public Health, Birmingham, AL
7. Department of Radiology, University Medical Centre Utrecht, Utrecht, the Netherlands
8. Nuffield Department of Surgical Sciences, John Radcliffe Hospital, Oxford, United Kingdom

9. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom
10. Department of Vascular and Endovascular Surgery/Vascular Centre, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany
11. Department of Neurology, Hôpital Sainte-Anne, Université Paris-Descartes, DHU Neurovasc Sorbonne Paris Cité, INSERM U894, Paris, France
12. Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Oxford University, Oxford, United Kingdom
13. Department of Neurology and Stroke Centre, University Hospital Basel, Basel, Switzerland
14. Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, University College London, United Kingdom
15. University of Paris, XII, Vascular Surgery, Hôpital Henri Mondor, Créteil, France
16. Department of Neurology and Neurosurgery, Brain Centre Rudolf Magnus, University Medical Centre Utrecht, Utrecht, the Netherlands
17. Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands
18. Department of Neurology, Hôpital Sainte-Anne, Université Paris-Descartes, DHU Neurovasc Sorbonne Paris Cité, INSERM U894, Paris, France
19. Department of Neurology, Mayo Clinic, Jacksonville, FL

[#] **Corresponding author:**

Gustav Fraedrich MD

Department of Vascular Surgery

Medical University Innsbruck

Anichstrasse 35

6020 Innsbruck

Email: gustav.fraedrich@i-med.ac.at

Tel: +43-50504-22587

Fax:+43-50504-2559

Carotid Stenosis Trialists' Collaboration (CSTC)

Writing Committee: Barbara Rantner (Department of Vascular Surgery, Innsbruck Medical University, Innsbruck, Austria), Barbara Kollerits (Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria), Gary S Roubin (Cardiovascular Associates of the Southeast, Birmingham, AL), Peter A Ringleb (Department of Neurology, University Hospital Heidelberg, Germany), Olaf Jansen (Clinic for Radiology and Neuroradiology, UKSH Campus Kiel, Kiel, Germany), George Howard (Department of Biostatistics, UAB School of Public Health, Birmingham, AL), Jeroen Hendrikse (Department of Radiology, University Medical Centre Utrecht, Utrecht, the Netherlands), Alison Halliday (Nuffield Department of Surgical Sciences, John Radcliffe Hospital, Oxford, United Kingdom), John Gregson (Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom), Hans-Henning Eckstein (Department of Vascular and Endovascular Surgery/Vascular Centre, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany), David Calvet (Department of Neurology, Hôpital Sainte-Anne, Université Paris-Descartes, DHU Neurovasc Sorbonne Paris Cité, INSERM U894, Paris, France), Richard Bulbulia (Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Oxford University, Oxford, United Kingdom), Leo H Bonati (Department of Neurology and Stroke Unit, University Hospital Basel, Switzerland; Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, UK), Jean-Pierre Becquemin (Department of Vascular Surgery, University Hospital Henri Mondor, 94010 Creteil, France), Ale Algra (Department of Neurology and Julius Centre for Health Sciences and Patient Care, University Medical Centre Utrecht, Netherlands), Martin M Brown* (Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, UK), Jean-Louis Mas* (Department of Neurology, Hôpital Sainte-Anne, Université Paris Descartes, INSERM UMR894, Paris, France), Thomas G Brott (Department of Neurology, Mayo Clinic, Jacksonville, FL), Gustav Fraedrich* (Department of Vascular Surgery, Medical University, Innsbruck, Austria). *Contributed equally to the report

Steering Committee: A. Algra (independent chair); EVA-3S: J.P. Becquemin, D. Calvet, J-L. Mas; ICSS: L.H. Bonati (coordinator), M.M. Brown, J. Hendrikse; SPACE and SPACE-2: H-H. Eckstein, G. Fraedrich, O. Jansen, P.A. Ringleb; CREST and CREST-2: T.G. Brott, G. Howard, G.S. Roubin; ACST-1 and ACST-2: R. Bulbulia, A. Halliday; trial statistician: J. Gregson. The members of the Steering Committees and a list of Investigators contributing data to the trials including those in this pooled analysis can be found in earlier publications[1-3].

Acknowledgments:

The prospective individual patient-data meta-analysis by the Carotid Stenting Trialists' Collaboration was funded by a grant from The Stroke Association. The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial was funded by a grant from the Programme Hospitalier de Recherche Clinique of the French Ministry of Health, Assistance Publique–Hôpitaux de Paris. The Stent-Protected Angioplasty versus Carotid Endarterectomy in symptomatic patients trial was funded by grants from the Federal Ministry of Education and Research, Germany, the German Research Foundation, the German Society of Neurology, the German Society of Neuroradiology (German Radiological Society), Boston Scientific, Guidant, and Sanofi-Aventis. The International Carotid Stenting Study was funded by grants from the Medical Research Council, the Stroke Association, Sanofi-Synthélabo, and the European Union. The Carotid Revascularization Endarterectomy vs. Stenting Trial was supported by the National Institute of Neurological Disorders and Stroke

(NINDS) and the NIH (R01 NS 038384) and received supplemental funding from Abbott Vascular Solutions (formerly Guidant), including donations of Accunet and Acculink systems, equivalent to approximately 15% of the total study cost, to CREST centers in Canada and to CREST centers in the United States that were at Veterans Affairs sites.

Supplementary Table I: Logistic mixed models of two treatment groups (CAS vs. CEA) depending on timing of treatment in three groups (0-7 days, 8-14 days and >14 days) on three different outcomes within 30 days after treatment (any stroke or death, any stroke and fatal or disabling stroke).

	CEA n event/ n total (%)	**CAS** n event/ n total (%)	**Crude RR (95% CI)** *	**p-value**
Any stroke or death				
0-7 days	3/226 (1.3)	24/287 (8.4)	6.51 (2.00-21.21)	0.002
8-14 days	13/320 (4.1)	25/352 (7.1)	1.75 (0.91-3.36)	0.09
>14 days	52/1495 (3.5)	104/1446 (7.2)	2.07 (1.49-2.86)	<0.0001
Any stroke				
0-7 days	3/226 (1.3)	23/287 (8.0)	6.27 (1.93-20.44)	0.002
8-14 days	13/320 (4.1)	24/352 (6.8)	1.68 (0.87-3.24)	0.12
>14 days	49/1495 (3.3)	98/1446 (6.8)	2.07 (1.48-2.89)	<0.0001
Fatal or disabling stroke				
0-7 days	1/226 (0.4)	9/287 (3.1)	8.29 (1.07-64.28)	0.04
8-14 days	5/320 (1.6)	9/352 (2.6)	1.64 (0.55-4.83)	0.37
>14 days	21/1495 (1.4)	37/1446 (2.6)	1.81 (1.07-3.06)	0.03

* CEA represents reference group.

CAS: carotid artery stenting, CEA: carotid endarterectomy, CI: confidence interval

Supplementary Table II Baseline characteristics of the combined trial population according to available or missing information on timing of treatment			
	Patients WITH information about timing of treatment n=4138	**Patients WITHOUT information about timing of treatment** n=459	**P value**
Age at treatment (years)	69.5±9.3 [63,70,77]	67.9±8.8 [61,68,75]	0.001
Treatment group (CEA), n (%)	2045 (49)	226 (49)	0.94
Male, n (%)	2891 (70)	317 (69)	0.72
History of diabetes, n (%)	1026 (25)	125 (27)	0.26
History of hypertension, n (%)	3122 (75)	339 (74)	0.37
History of hypercholesterolemia, n (%)[a]	2314 (69)[¶]	33 (70)[¶]	0.82
Any smoking history (current/past), n (%)	2627 (63)	334 (73)	<0.001
History of coronary heart disease, n (%)	1148 (28)	108 (24)	0.06
History of peripheral artery disease, n (%)[b]	334 (16)[≠]	0 (0)[≠]	1
Degree of ipsilateral carotid stenosis, n (%)[c]			
Moderate (50-69%)	735 (18)	149 (32)	<0.001
Severe (70-99%)	3403 (82)	310 (68)	
Contralateral severe carotid stenosis (≥70%) or occlusion, n (%)[c]	412 (15) [α]	43 (15) [α]	1
Type of most recent ipsilateral ischaemic event before randomization, n (%)			

TIA	1535 (37)	147 (32)	0.02
Retinal ischaemia	710 (17)	72 (16)	
Hemispheric stroke	1865 (45)	239 (52)	
modified Rankin Score (mRS) at baseline[d]			<0.001
mRS=0 , n (%)	2027 (49)	273 (59)	
mRS=1 , n (%)	1103 (27)	106 (23)	
mRS=2 , n (%)	676 (16)	47 (10)	
mRS=3 , n (%)	238 (6)	33 (7)	
mRS=4 , n (%)	50 (1)	0 (0)	
mRS=5 , n (%)	4 (0.1)	0 (0)	
History of stroke before most recent event, n (%)[b]	736 (34)[§]	0 (0)[§]	0.55

Mean ± standard deviation (SD) and [25th, 50th, 75th percentile] in case of non-normal distribution; interquartile range (IQR): 25th - 75th percentile] or number (%)

CAS: carotid artery stenting, CEA: carotid endarterectomy; TIA: transient ischemic attack

[a] Data collected in EVA-3S, ICSS and CREST only. [¶] Information available in n=3369 (patients with information about timing of treatment), and n=47 (patients without information about timing of treatment)

[b] Data collected in EVA-3S and ICSS only. [≠] Information available in n=2148 (patients with information about timing of treatment), and n=2 (patients without information about timing of treatment); [§] Information available in n=2164 (patients with information about timing of treatment), and n=2 (patients without information about timing of treatment)

[c] Degree of stenosis measured by NASCET method or equivalent non-invasive method. [α] Information available in n=2761 (patients with information about timing of treatment), and n=288 (patients without information about timing of treatment);

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

[e] The date of the most recent ipsilateral ischaemic event before randomization 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 randomization and treatment took place within 7 days of the qualifying event), were retrieved where available.

Reference List

(1) Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006 October 7;368:1239-47.

(2) Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006 October 19;355:1660-71.

(3) 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 March 20;375:985-97.