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The Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy Trial

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Key Words
Stroke · Ischaemia · Secondary prevention · Stenting · Carotid surgery · Clinical trials

Abstract
The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) Trial is investigating if both treatment modalities are equivalent in the treatment of severe symptomatic carotid stenoses. Patients with symptomatic (transient ischaemic attack or minor stroke) stenosis (above 50% following the North American Symptomatic Endarterectomy Trial criteria) eligible for both methods can be recruited into this trial. The primary endpoint is the incidence of an ipsilateral stroke or death between randomisation and day 30 after treatment. Surgeons as well as the interventionalists have to demonstrate their expertise prior to participation in the trial. Funding is mostly by public institutions (Federal Ministry of Education and Research and German Research Foundation). An external monitoring is applied. Thirty-two centres are currently taking part in the SPACE Trial that has been running in Germany, Austria and Switzerland for 3 years, and they have been able to recruit a total of around 670 patients. The definitive results of this study cannot be expected before 3–5 years.

Methods

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) Study is investigating whether carotid endarterectomy and stent-supported percutaneous angioplasty of the carotid artery are equivalent in the treatment of severe symptomatic carotid stenoses with respect to incidence of an ipsilateral stroke (cerebral infarction and/or cerebral bleeding with longer than 24 h of continuing functional impairment) or death from any cause, reckoned from the time of randomisation up to the 30th ± 3 days following treatment.

The following further endpoints have been defined:

(a) ipsilateral stroke (cerebral infarction and/or cerebral bleeding) or death from vascular causes within the control period of 24 months ± 14 days from the time of randomisation,

(b) restenosis with a level of at least 70% in duplex sonography, corresponding to a stenosis level of at least 70% according to the criteria of the European Carotid Surgery Trial (ECST) or at least 50% according to the criteria of the North American Symptomatic Endarterectomy Trial (NASCET), after 6, 12 and 24 months, each ± 14 days, reckoned from the time of randomisation,

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Table 1. Inclusion and exclusion criteria of the SPACE Trial

	Clinical	Angiological
a	Inclusion criteria	
	• Symptomatic stenosis (transient ischaemic attack or stroke) of the carotid bifurcation or the internal carotid artery within the last 180 days • Modified Rankin scale score ≤2 • Above 50 years of age • Possibility for follow-up examinations • Written informed consent	• Stenosis of the carotid bifurcation or the internal carotid artery of at least 70% proven by duplex sonography or angiography corresponding to a stenosis level of at least 70% according to the criteria of ECST or at least 50% according to the criteria of NASCET
b	Exclusion criteria	
	• Intracranial bleeding within the last 90 days • Uncontrolled arterial hypertension • Known intracranial angioma • Life expectance less than 2 years • Contraindications for heparin, ASS, or clopidogrel • Contraindications for contrast media • Planned simultaneous surgery	• Occlusion of the common or the internal carotid artery • Stenosis due to external compression • Stenosis due to dissection • Recurrent stenosis after surgery or stenting • Stenosis due to fibromuscular dysplasia • Floating thrombus • Additional intracranial stenosis with higher grade

(c) procedural technical failure (treatment impossible for technical reasons, serious adverse events during and/or due to the treatment, occlusion of the vessels or restenosis with a level of stenosis of at least 70% in duplex sonography on the 6th day ± 1 day and 30th day ± 3 days following treatment,

(d) incidence of any ipsilateral stroke (cerebral infarction and/or cerebral bleeding with continuing functional impairment of ≥3 on the modified Rankin scale) or death from any cause, reckoned from randomisation up to the 30th ± 3 days following treatment,

(e) incidence of strokes with any localisation and any degree of severity within 30 ± 3 days following intervention and

(f) incidence of strokes with any localisation and any degree of severity within 24 months ± 14 days following intervention.

The precondition for the randomisation of a patient according to the information above is the presence of a clinically symptomatic high level of stenosis (≥70% in duplex sonography, corresponding to a stenosis level of at least 70% according to the criteria of the ECST or at least 50% according to the criteria of the NASCET) of the internal carotid artery or the carotid bifurcation, taking into consideration the inclusion and exclusion criteria listed in table 1.

A multidisciplinary team comprising neurologists, vascular surgeons and interventionalists decides on the indications for treatment of the patient. A specially important feature is that the disciplines participating in the SPACE Study must demonstrate in advance their expertise in the treatment of patients with symptomatic stenosis of the carotid artery. Quality committees have been formed for all disciplines (neurologists, vascular surgeons and interventionalists), which define the treatment guidelines and evaluate the personal qualifications of the staff involved. All stent systems used must have CE certification, with the same also applying for dilatation catheters and the protection systems. In the case of interventional treatment, the use of a protection system was quite deliberately left open. In the light of continuing discussion within the specialist communities on the benefits and risks of such protection systems, no standard procedure should be prescribed in this respect. This is, for example, one of the main differences between this trial and the CREST Study (Carotid Revascularization Endarterectomy vs. Stent Trial) running in the United States as well as the French EVA-3S Trial (Endartérectomie Versus Angioplastie chez les patients ayant une Sténose carotide Symptomatique Serrée), in which the use of a protection system is mandatory.

Although the SPACE Study is being financially supported by two companies (with a total of 175,000 EUR), the co-operation does not involve any obligation to use certain materials. Major funding comes from the German Research Foundation (DFG) and the Federal Ministry of Education and Research (BMBF). A further quality feature of the SPACE Study is that an external monitoring is applied, which monitors the quality of the data in the individual centres and the proper observation of the treatment guidelines.

With regard to the statistical case number estimation, it was assumed that the frequency of ipsilateral strokes or death within a period reckoned from the time of randomisation up to the 30th day ± 3 days following treatment, due to endovascular treatment, would correspond to that for surgical treatment, although this frequency may exceed that of surgical treatment by a maximum of 2.5%. If one assumes identical event frequencies of a maximum of 5% for the target size, defines the equivalency threshold as 2.5% and the 1st-level error rate (unilateral test decision) at 5%, this produces a target number of 950 patients per group, in order to be able to confirm the equivalency with a reliability of 80%.

Trial Status

After receiving positive votes from various ethics committees, recruiting for the SPACE Study began in March 2001. There are now 32 centres taking an active part in the study, with further centres currently in the certification process (see Appendix). The original planning envisaged that in the first 2 years, at least 2 patients should be randomised in every associated centre every month. These expectations have not been able to be fulfilled so far; the average recruiting rate is currently 1 patient per centre and month only. By means of an interim analysis at the end of the 3rd year – which will be done in the near future – a decision will be made as to whether the study will be terminated or continued in accordance with the criteria described above.

To date, 667 patients have been recruited into the SPACE trial (up to 18/02/2004); 338 of them were treated by carotid endarterectomy and 329 by stent-supported angioplasty. Further information and contact facilities for the SPACE Study are listed on the homepage (www.space.stroke-trial.com).

Appendix

Participating Centres of the SPACE Trial

University of Kiel; University of Lübeck; University of Hamburg; Hospital Hamburg Altona; Hospital Hamburg Barmbek; Hospital Hamburg Wandsbek; University of Dortmund; University of Essen; Alfried Krupp Hospital Essen; Wedau Hospital Duisburg; University of Aachen; University of Göttingen; Hospital Köln/Porz; Hospital Mühlhausen; University of Mainz; University of Homburg/Saar; Hospital Ludwigshafen am Rhein; University of Heidelberg at Mannheim and Heidelberg; Hospital of Ludwigsburg; University of Freiburg; Hospital Augsburg; Vascular Centre at the Isarkanal, Munich; University of Munich, Grosshadern; Medical Centre Technical University of Munich; Hospital Wagner Jauregg, Linz; University of Vienna; University of Innsbruck; University of Graz; Hospital St. Gallen; University of Bern.

Steering Committee

W. Hacke (Department of Neurology, University of Heidelberg); M.G. Hennerici (Department of Neurology, University of Heidelberg); J.H. Allenberg (Department of Vascular Surgery, University of Heidelberg); P.C. Maurer (Department of Vascular Surgery, Technical University of Munich); H. Zeumer (Department of Neuroradiology, University of Hamburg); O. Jansen (Department of Neuroradiology, University of Kiel).

Safety Committee

P. Marx, Berlin (Head); K. Poeck, Aachen; L. Solymosi, Würzburg; H. Schweiger, Bad Neustadt an der Saale; S. von Sommoggy, Vogtareuth.