Protection or Nonprotection in Carotid Stent Angioplasty
The Influence of Interventional Techniques on Outcome Data From the SPACE Trial

Olav Jansen, PhD; Jens Fiehler, PhD; Marius Hartmann, PhD; Hartmut Brückmann, PhD

Background and Purpose—The use of protection devices (PDs) and stents with different cell designs in carotid artery stenting (CAS) is a subject of controversy, and no data on their benefit are available from independently controlled multi-center studies.

Methods—We analyzed data from the prospective randomized SPACE trial, which included 563 patients randomized to CAS and treated per protocol. A total of 145 patients were treated with a PD and 418 without. Of the patients, 436 were treated with an open cell stent and 127 with a closed cell stent. Use of PDs and choice of device was chosen at the individual discretion of the interventionalist.

Results—The outcome event (OE) of the analysis (ipsilateral stroke or ipsilateral stroke death within 30 days) was reached in 26/418 patients (6.2%, 95% CI: 4.1 to 9.0%) in the nonprotection group and in 12/145 (8.3%, 95% CI: 4.3 to 14.0%) patients in the protection group (P=0.40). The OE rate was significantly lower in patients treated with a closed cell stent (5.6% [95% CI: 3.7 to 8.2%]) than in those treated with an open cell stent (11.0%, 95% CI: 6.2 to 17.8%; P=0.029). Predilation showed a tendency to but no significant reduction of OE rate. Overall, 49% of all OEs occurred directly periinterventionally, 10% during the navigation procedure and 41% postinterventionally, including 10% of hyperfusion syndromes. Time point of the event was not influenced by the use of a PD.

Conclusions—This secondary analysis of data from the SPACE trial does not support the need for a PD in CAS. Stent design seems to have an impact on the OE rate. Our analysis demonstrates that the choice of the interventional material may have an impact on the periprocedural complication rate in CAS and that the development of more specific stent systems for the treatment of carotid stenosis may reduce the complication rate significantly. (Stroke. 2009;40:841-846.)

Key Words: stents ■ carotid artery ■ protection ■ cell design

SPACE, a multi-national, multi-center, randomized trial, investigated whether carotid endarterectomy (CEA) and carotid artery stenting (CAS) are equally effective in the treatment of severe symptomatic carotid stenosis.

The primary study end point of SPACE was the rate of ipsilateral stroke (ischemic stroke or intracerebral bleeding with symptoms lasting more than 24 hours) or death of any cause between randomization and day 30 after treatment. Secondary endpoints included: (1) ipsilateral ischemic stroke or vascular death at 6, 12, and 24 months after randomization; (2) disabling ipsilateral stroke defined as a modified Rankin Score of at least 3 or death of any cause between randomization and day 30; (3) any stroke at 30 days, 6, 12, and 24 months after treatment; (4) restenosis of $\geq 70\%_{ECST}$ at 6, 12, and 24 months; and (5) procedural failure, including remaining stenosis of $\geq 70\%_{ECST}$ or vessel occlusion assessed up to 30 days after treatment.

The trial was designed to show noninferiority in primary outcome events (OEs) from randomization until 30 days after therapy between the two arms CEA and CAS. The null hypothesis was that the difference between the event rates in the CAS group and in the CEA group was $\geq 2.5\%$ (noninferiority margin).1

Among symptomatic patients with high-grade stenosis of the carotid artery, SPACE failed to prove noninferiority of CAS for lack of power from 1214 patients recruited. However, there was no statistical difference in the rate of OEs between CEA and CAS. These results can be interpreted differently2: a vascular surgeon may point out that an equal effect between CEA and CAS was not shown with SPACE because equivalence was missed ($P=0.09$, one-sided value for noninferiority).

Interventionalists have focused on the fact that there was no statistical difference in the OE rates between CEA and CAS ($P=0.81$, Chi-Square test). However, in addition to the primary results, the SPACE data can be subjected to various secondary analyses. Keeping in mind that these secondary analyses will not have the scientific value of the primary aim of the trial, they are still highly interesting. SPACE was an independently controlled study concerning peri- and postpro-

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cerebral complications, and therefore even secondary analysis of these data may have much more impact than single-center studies, which currently represent the only available data.

CAS has been performed for nearly 20 years but is still far from being considered a standard procedure. With the availability of different endovascular technologies, a wide range of technical approaches can be used to place a stent. From the general technical perspective, the two main different ways of performing CAS involve the use of a so-called protection device (PD), or not.

Recently, several interventional groups attempted to show the benefit of PDs to reduce the most obvious major complication: the rate of peri-procedural embolism. Although no controlled data are available on the benefit of these devices, some prospective multicenter trials comparing CEA and CAS (CREST, EVA3S) made the use of PDs mandatory in their study protocol. In contrast the use of PDs were optional in other trials such as SPACE and ICSS. Now that the SPACE trial has been concluded, the data on the benefit of these devices, based on the data from the SPACE trial, we analyzed the impact of these technical factors (use of PDs, cell design of the stent) on the rate of primary outcome events (OEs) in the SPACE trial.

Materials and Methods
Study design, inclusion and exclusion criteria, definition of endpoints, and the primary data from the SPACE trial have been published in detail elsewhere.1

Eligibility of Patients
Patients were eligible for SPACE if (1) they had neurological symptoms such as amaurosis fugax, hemispheric transient ischemic attack (TIA), or complete stroke within the previous 180 days and (2) unilateral carotid artery stenosis that was considered to be severe (at least 70% on duplex ultrasound, corresponding to a stenosis level of ≥70%ECST or ≥50%NASCET).

Interventional Procedure
Treatment had to be given within 14 days after randomization. For both treatment modalities—CEA and CAS—detailed quality standards are part of the protocol.

Patients allocated to CAS had to be treated with aspirin 100 mg and clopidogrel 75 mg for at least 3 days before and 30 days after the intervention.

As part of the CAS protocol all patients had to be treated under full heparinization, the effect of the heparin had to be controlled during the procedure. For this, the apparent coagulation time (ACT) had to be between 250 and 350 seconds.

The use of a PD was optional, the decision based on local experience and certification of the treating physician, so it was chosen at the individual discretion of the interventionalist. All stent systems, dilatation catheters, and PDs used had to have CE certification and were approved for use in the study by the endovascular standards committee. Table 1 shows the list of interventional devices that were approved. Because of their technical design, stents were categorized as open cell stents when the cell size was >2.5 mm².

In total, 607 of the 1214 included patients were randomized to the interventional arm. Because of a secondary change in the treatment arm, secondary contraindications for stenting (ie, vessel occlusion) or other protocol violations, the data of ultimately 563 patients treated per protocol (PP) with CAS within the SPACE trial were available for this secondary analysis. Table 2 shows the distribution of the use of different stents and device designs and the use of PDs in these 563 patients.

<table>
<thead>
<tr>
<th>Stent Design</th>
<th>Protection Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed cell Wallstent (Boston Scientific)</td>
<td>GuardWire (PercuSurge)</td>
</tr>
<tr>
<td>Open cell Precise (Cordis)</td>
<td>Epifilter (Boston Scientific)</td>
</tr>
<tr>
<td>Acculink (Guidant)</td>
<td>AngioGuard (Cordis)</td>
</tr>
<tr>
<td></td>
<td>NeuroShield (MediNova)</td>
</tr>
<tr>
<td></td>
<td>Trap NFS (Microvena)</td>
</tr>
</tbody>
</table>

Table 2. Distribution of Patients Treated With Open or Closed Cell Stents and With or Without Protection Devices in 563 Patients

<table>
<thead>
<tr>
<th>Stent Design</th>
<th>With Protection System</th>
<th>Without Protection System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed cell</td>
<td>436 (77.4%)</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>361</td>
<td></td>
</tr>
<tr>
<td>Open cell</td>
<td>127 (22.6%)</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Acculink: 92</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Precise: 35</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>563 (100%)</td>
<td>145 (25.8%)</td>
</tr>
<tr>
<td></td>
<td>418 (74.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Results
Influence of Protection Device on OE Rate
From the 563 patients treated per protocol with a stent, a PD was used in 145 patients (25.8%) and 418 patients were treated without a PD (74.2%). The primary end point of this posthoc analysis (ipsilateral stroke or ipsilateral stroke death within 30 days) was reached by 12 patients (8.3%, 95% CI: 4.3 to 14.0%) in the protection group and 26 patients (6.2%, 95% CI: 4.1 to 9.0%) in the nonprotection group (P=0.40, Table 3). An additional analysis of how many patients suffered a disabling stroke (Rankin 3) or died showed a 5.5% (95% CI: 2.4 to 10.6%) event rate for the protection group and a 4.5% (95% CI: 2.8 to 7.0%) event rate for the nonprotection group. There was no statistically significant difference between the two groups either for any stroke (P=0.395) or for the analysis concerning more disabling strokes (P=0.637).

In the protection group OEs occurred in 7/66 (10.6%) with the use of the EPI-Filter, 2/16 (12.5%) with the Angioguard, 2/23 (8.7%) with the Neuroshield, and 1/16 (6.3%) with the Guardwire.

Influence of Stent Design on OE Rate
Three different stents were used in the SPACE trial. In the majority of the cases the Wallstent was implanted (436/563; 77.4%), whereas in 127/563 (22.6%) either the Acculink stent (92/563) or the Precise stent (35/563) was used. In the patient group treated with the Wallstent, 25/443 developed one or more OEs, resulting in a OE rate of 5.6% (95% CI: 3.7 to 8.2%). Nine of 92 patients who received an Acculink stent had an OE rate of 9.8% (95% CI: 4.6 to 17.8%); 5/35 patients with a Precise stent had a 14.3% OE rate (95% CI: 4.8 to 30.3%). The combined analysis of stents with an open cell design (Acculink stent and Precise stent) gave an OE rate of 11.0% (95% CI: 6.2 to 17.8%, Table 4). The OR for a OE was 2.13 (95% CI: 1.07 to 3.76) for the open cell stent group as compared to the closed cell stent group. This difference was statistically significant for the evaluated population (P=0.029).

Influence of the Protection Device on the OE Rate in Different Stent Design Groups
In the majority of patients treated with a closed cell design stent no protection systems were used (361/436), whereas in more than half of the patients treated with an open cell design stent an additional PD was used (70/127). The additional use of a PD in the closed cell stent group resulted in a small increase in the complication rate (6.7% versus 5.3%), whereas in the open cell stent group the use of a PD showed some benefit (10% versus 12.3%). With the use of a PD only a minor difference was seen between the open cell stent group and the closed cell stent group as compared to no PD. However, the overall influence of the use of a PD on the OE rate was only minor and the difference between the two stent groups was not statistically significant (Table 5).

Influence of Predilatation
In 204/563 cases the stenosis was predilated before the protection device or the stent delivery system was navigated through the stenosis and the final treatment. Cases with predilatation showed a lower OE rate (4.4%) than cases without a predilatation (8.1%), however this was only a trend and the difference was not statistically significant (P=0.14, Table 6).

Time of OEs
Based on the reports in the CRFs, the times when the OEs occurred were secondarily graded into 4 groups: (1) manipulation at the aortic arch, including navigation of the sheet into the common carotid; (2) directly periinterventionally, including placement of a PD, predilatation, application of the stent, and final dilatation; (3) postinterventionally, defined as the occurrence of a OE more than 30 minutes after the final dilatation; and (4) hyperperfusion syndrome (HPS). Only 50% of all OEs occurred directly periinterventionally, whereas 40% of the complications occurred after removing the endovascular devices (including patients with HPS). Ten percent of the complications were directly related to the manipulation in the aortic arch or common carotid. In this analysis no difference could be recognized between the protection group and the nonprotection group; in both subgroups OEs occurred more often directly periinterventionally than postinterventionally (Table 7).

Discussion
Specially in the interventional community there is ongoing discussion about the sense and value of the use of so-called...
cerebral protection devices (PD) during carotid artery stenting (CAS). Several authors have published their uncontrolled monocenter results mostly comparing older data from unprotected interventions with patient groups in which they used PD. Almost all of these studies concluded that PD appear to reduce the thromboembolic complication rate and are strongly recommended in CAS procedures. Despite the lack of controlled studies, the use of these devices has or had become obligatory in the ongoing CREST trial and in the interrupted EVA-3S trials testing whether CAS and CEA are equally effective.

In SPACE and in the ongoing ICSS trial the use of PD were optional, and the decision was left to the treating physician. In the SPACE trial this option resulted in 25% of the procedures being performed with the use of a PD, whereas in 75% the interventionalist decided not to use a protection system. Although the SPACE trial was not designed to evaluate the benefit of PD and patients were not randomized into a protection or nonprotection group, SPACE is an independently controlled prospective study, which has allowed us to investigate the effect of PD in a secondary analysis. One has to point out that there may be a selection bias in the choice as to whether to use a protection device or not because of lack of randomization. With respect to this limitation no statistical difference could be demonstrated between the two groups. Our results demonstrate that the SPACE data do not support the general recommendation for using cerebral PD. In the EVA 3S trial the protocol was modified during the ongoing study such that PDs were made obligatory. Of course, this dramatic change in the intervention protocol must have had a significant influence on the outcome data. However, EVA 3S is comparable to SPACE as an independently controlled prospective study and presents neurological, controlled, multi-center data. The study design of EVA 3S is nearly identical to that of SPACE, which makes it easy to perform a meta-analysis of the two trials and, especially for secondary analysis, the validity can be increased by increasing the number of the patients. Table 8 demonstrates a pooled analysis of the data from SPACE and EVA 3S and investigates the difference between patients treated with or without a PD. Again, this analysis fails to show any difference between the 2 treatment groups.

It would seem reasonable to use a PD to reduce thromboembolic events caused by debris in CAS while a carotid stenosis is being dilated. Reasons may be that in protected CAS, predilatation is often necessary before the PD is placed. In addition, after stent placement and postdilatation, removing the PD can cause microembolization. From a procedural point of view, PD may reduce, but certainly do not eliminate plaque embolization, as demonstrated by periprocedural monitoring with transcranial Doppler (TCD). On the other hand, PDs have the potential to produce separate complications such as vasospasms or dissections associated with temporary or permanent carotid occlusion. All in all, the advantages and disadvantages of PD seem to compensate one another, which may result in the equivalence as shown in this secondary analysis of the SPACE data. Based on the pooled data of EVA3S and the SPACE a randomized trial of more than 40 000 patients would be required to disprove the effect of “protection devices” on the rate of ipsilateral stroke and death (80% power at the 95% level of confidence).

The principle of the CAS procedure is to open the stenosis by dilatation and to prevent future embolization through the scaffolding of the ruptured plaque against the vessel wall by means of a stent. Therefore, after placement of the stent the struts of the stent represent a protection system against peri- and postprocedural embolic events. Because the final dilatation of the stenosis, which is the most emboligenic part of the CAS procedure, is usually performed after the stent is placed, protection is also provided during this most dangerous part of the intervention.

Bosiers and coworkers published the results of a retrospective analysis in their patients treated with different carotid stents and showed that the complication rate in symptomatic patients treated with stents with a small free cell area (closed cell stents) was significantly lower than that in patients treated with open cell stents. The secondary analysis of the SPACE data also showed statistical significance between different stent designs, with a lower rate of OEs in patients treated with a closed cell stent than in those who received an open cell stent. Interestingly, this difference tended to be stronger in patients treated without the additional

### Table 5. Influence of the Use of a Protection Device on the OE Rate for Different Stent Designs

<table>
<thead>
<tr>
<th>Stent Design</th>
<th>Total</th>
<th>With Protection System</th>
<th>Without Protection System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed cell</td>
<td>24/436</td>
<td>5/75</td>
<td>19/361</td>
</tr>
<tr>
<td></td>
<td>5.5% (95% CI: 3.6–8.1%)</td>
<td>6.7% (95% CI: 2.2–14.9%)</td>
<td>5.3% (95% CI: 3.2–8.1%)</td>
</tr>
<tr>
<td>Open cell</td>
<td>14/127</td>
<td>7/70</td>
<td>7/57</td>
</tr>
<tr>
<td></td>
<td>11% (95% CI: 6.2–17.8%)</td>
<td>10% (95% CI: 4.1–19.5%)</td>
<td>12.3% (95% CI: 5.1–23.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>563</td>
<td>12/145</td>
<td>26/418</td>
</tr>
</tbody>
</table>

### Table 6. Influence of Predilatation of the Stenosis on the OE Rate

<table>
<thead>
<tr>
<th></th>
<th>OE</th>
<th>OE With Protection</th>
<th>OE Without Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>With predilatation</td>
<td>204</td>
<td>9 (4.4%, 95% CI: 2.0–8.2%)</td>
<td>5/67 (5.7%, 95% CI: 1.9–12.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4/117 (3.4%, 95% CI: 0.9–8.5%)</td>
</tr>
<tr>
<td>Without predilatation</td>
<td>359</td>
<td>29 (8.1%, 95% CI: 5.5–11.4%)</td>
<td>7/58 (12%, 95% CI: 5.0–23.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22/301 (7.3%, 95% CI: 4.6–10.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>563</td>
<td>38 (P=0.14)</td>
<td>12/145</td>
</tr>
</tbody>
</table>
use of a PD. Recently, Schillinger and coworkers\(^\text{10}\) published a consecutive patient series treated at 10 European centers to analyze the impact of different stent designs on neurological adverse events and mortality. In contrast to the SPACE data analysis they found no superiority of a specific stent design. However, in their population up to 90% of all patients were treated with a protection system, which may blot out the influence of a different stent design. The same effect could be demonstrated with the SPACE data. An additional drawback of the analysis from Schellinger et al is that the data were taken from nonrandomized uncontrolled registry datasets, which imply the likelihood that not all adverse events were recorded. Compared to this the data from the SPACE trial are more precise and allows to speculate that closed cell stents do not benefit from the additional use of a PD because the protection effect of the stent is good enough. However, in open cell stents the use of a PD may help to reduce the periprocedural embolic rate.

Another approach for assessing the potential effect of PD is to analyze the timing of the complications. Based on the evaluation of the CRFs we found that only half of the complications developed directly during the actual stent and angioplasty procedure; 40% of the OEs (including 10% of hyperperfusion syndromes) occurred when the catheter devices were displaced from the treated carotid and 10% of the OEs during the navigation procedure at the aortic arch. Not all of these complications can be avoided by the use of a PD. Even in patients treated with a PD, half of the complications occurred directly perinterventionally, showing that PDs do not eliminate periprocedural embolic events but they may potentially enhance the risk of periprocedural OEs.

We suggest from our analysis of these data that the stent design has strong impact on the periprocedural complication rate in CAS. PD may be beneficial in open cell stents but show a lower effect in closed cell stents. When considering cost aspects as well, it is more reasonable to develop and prefer a stent system in which the protection effect has been optimized and to avoid using additional costly protection devices.

The data used for secondary analysis in the present study were taken from the SPACE trial.\(^\text{1}\) This posthoc analysis can only generate a hypothesis, which must be substantiated in further prospective trials. Nevertheless, the results of this secondary analysis demonstrate that the choice of the material has a direct impact on the periprocedural complication rate in CAS and that the development of more specific stent systems for the treatment of carotid stenosis can reduce the complication rate significantly.

### Disclosures

O.J. has received speaker’s fees from Penumbra and Boston Scientific. J.F. has received speaker’s fees from Cordis Neurovascular.

### References


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In the article entitled “Protection or Nonprotection in Carotid Stent Angioplasty: The Influence of Interventional Techniques on Outcome Data From the SPACE Trial” by Jansen et al., the authors would like to note an error in the Abstract, 2nd and 3rd lines under Results. The sentence “The outcome event (OE) of the analysis ... in the protection group and in 12/145 ... patients in the nonprotection group (P=0.40).” should read “The outcome event (OE) of the analysis ... in the nonprotection group and in 12/145 ... patients in the protection group (P=0.40).” In other words, “protection group” and “nonprotection group” should be transposed. The authors regret this error.

The corrected version can be viewed online at http://stroke.ahajournals.org.