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).

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
categorical as open cell or closed cell. Open cell stents show in influence the clinical outcome.9,10 Stent designs can be
data are available as to whether different stent designs can
performing CAS involve the use of a so-called protection
general technical perspective, the two main different ways of
technical approaches can be used to place a stent. From the
external 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 compli-
cations, 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 avail-
ability 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.

Recent studies have shown that use of a PD was optional, the decision being
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 certifi-
cation 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.

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 end
points, 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 stan-
dards 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 being 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 certifi-
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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
were included and the data were analyzed.

### Table 1. Interventional Devices (stents; protection devices)

<table>
<thead>
<tr>
<th>Stent Design</th>
<th>Protection Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed cell stent</td>
<td>Wallstent (Boston Scientific)</td>
</tr>
<tr>
<td>Open cell stent</td>
<td>Precise (Cordis)</td>
</tr>
<tr>
<td></td>
<td>Acculink (Guidant)</td>
</tr>
</tbody>
</table>

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### 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>361</td>
</tr>
<tr>
<td>Open cell</td>
<td>127 (22.6%)</td>
<td>75</td>
</tr>
</tbody>
</table>

Total 563 (100%)

154 (25.8%) 418 (74.2%)
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 groups 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).

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 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).

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.\(^5\)\(^6\)\(^12\)\(^--\)\(^15\) Almost all of these studies concluded that PD appear to reduce the thromboembolic complication rate and are strongly recommended in CAS procedures.\(^5\)\(^,\)\(^6\)\(^12\)\(^--\)\(^15\) Even though the lack of controlled studies, the use of these devices has or had become obligatory in the ongoing CREST\(^7\) and in the interrupted EVA-3S\(^8\) trials testing whether CAS and CEA are equally effective.

In SPACE and in the ongoing ICSS trial the use of PD were/are 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 EVA3S trial the protocol was modified during the ongoing study such that PDs were made obligatory.\(^18\) Of course, this dramatic change in the intervention protocol must have had a significant influence on the outcome data. However, EVA3S is comparable to SPACE as an independently controlled prospective study and presents neurological, controlled, multi-center data. The study design of EVA3S 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 EVA3S 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.\(^19\)\(^,\)\(^20\) Why then don’t the data from independently controlled studies support this technical approach? 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).\(^13\)\(^,\)\(^21\) On the other hand, PDs have the potential to produce separate complications such as vasospasms or dissections associated with temporary or permanent carotid occlusion.\(^16\) 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.\(^19\) 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 embolic 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\(^9\) published the results of a retrospective analysis in their patients treated with different carotid stents and showed that the complication rate in asymptomatic patients treated with stents with a small free cell area (closed cell stents) was significantly lower than 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>
<thead>
<tr>
<th>Table 5. Influence of the Use of a Protection Device on the OE Rate for Different Stent Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent Design</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Closed cell</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Open cell</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6. Influence of Predilatation of the Stenosis on the OE Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>OE With Protection</td>
</tr>
<tr>
<td>OE Without Protection</td>
</tr>
</tbody>
</table>

Without predilatation | 204 9 (4.4%, 95% CI: 2.0–8.2%) | 5/67 (5.7%, 95% CI: 1.9–12.9%) | 4/117 (3.4%, 95% CI: 0.9–8.5%) |
| Without predilatation | 359 29 (8.1%, 95% CI: 5.5–11.4%) | 7/58 (12%, 95% CI: 5.0–23.3%) | 22/301 (7.3%, 95% CI: 4.6–10.9%) |
| Total | 563 38 (P=0.14) | 12/145 | 26/418 |
use of a PD. Recently, Schillinger and coworkers10 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.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**


**Table 7.** Distribution of the Occurrence of OEs in all Patients With CAS, in the Nonprotection Group and in the Protection Group

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Navigation</th>
<th>Perinterventional</th>
<th>Postinterventional</th>
<th>HPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>49%</td>
<td>31%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Stents without protection (27/419 pat)</td>
<td>4/27</td>
<td>12/27</td>
<td>6/27</td>
<td>4/27</td>
</tr>
<tr>
<td>15%</td>
<td>44%</td>
<td>26%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Stents with protection (12/145 pat)</td>
<td>...</td>
<td>7/12</td>
<td>5/12</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>...</td>
<td>58%</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

HPS indicates hyperperfusion syndrome.

**Table 8.** Pooled Analysis of SPACE and EVA3S Shows no Significant Difference in the OE Rate in CAS Without or With the Use of a Protection Device (P=0·90, 95%CI: 0·56–1·56)

<table>
<thead>
<tr>
<th>Trial</th>
<th>OE Rate</th>
<th>OE Rate % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonprotection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPACE</td>
<td>26/418</td>
<td>7.3% (5.1–10.2%)</td>
</tr>
<tr>
<td>EVA 3S</td>
<td>5/20</td>
<td></td>
</tr>
<tr>
<td>Protection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPACE</td>
<td>12/145</td>
<td>8.1% (5.5–11.3%)</td>
</tr>
<tr>
<td>EVA 3S</td>
<td>18/227</td>
<td></td>
</tr>
</tbody>
</table>


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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.

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