Flow Reversal Versus Filter Protection
A Pilot Carotid Artery Stenting Randomized Trial

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Background—Carotid artery stenting (CAS) has become an alternative treatment for patients presenting symptomatic carotid artery stenosis. The improvement in clinical outcomes with CAS has been associated with the development of embolic protection devices. The trial aim is to compare flow reversal versus filter protection during CAS through femoral access.

Methods and Results—Patients were randomly enrolled in CAS using flow reversal or filter protection. The primary end points were the incidence, number, and size of new ischemic brain lesions after CAS. The secondary end points included major adverse cardiac and cerebrovascular events, transient ischemic attack, and definitive ischemic brain lesions on fluid-attenuated inversion recovery magnetic resonance image at a 3-month follow-up. Ischemic brain lesions were assessed by a 3T magnetic resonance image. Neurological outcomes were evaluated by means of the National Institutes of Health Stroke Scale and the modified Rankin Scale (mRS). Forty consecutive patients were randomly assigned. Compared with flow reversal (n=21), filter protection (n=19) resulted in a significant reduction in the incidence (15.8% versus 47.6%, P=0.03), number (0.73 versus 2.6, P=0.05), and size (0.81 versus 2.23 mm, P=0.05) of new ischemic brain lesions. Two patients, 1 from each group, presented transient ischemic attack at 3-month follow-up. There were no major adverse cardiac and cerebrovascular events in the hospital or at 3-month follow-up.

Conclusions—In this small sample size trial, filter protection was more effective than flow reversal in reducing ischemic brain lesions during CAS through femoral approach.

Clinical Trial Registration—URL: http://portal2.saude.gov.br/sisnep/. Unique identifier: 0538.0.004.000-10.
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Key Words: carotid artery angioplasty stenting ◼ embolic protection devices ◼ flow reversal ◼ ischemic brain lesions ◼ magnetic resonance image

Ischemic stroke is the third cause of death and the first cause of long-term disability in the adult population worldwide. Carotid artery stenosis is associated with ≥15% of all ischemic strokes. Carotid endarterectomy is the standard treatment for symptomatic atherosclerotic carotid artery stenosis aiming at ischemic stroke prevention. Carotid artery stenting (CAS) is an emerging treatment option for patients presenting carotid stenosis. The improvement in clinical outcomes with CAS has been associated with operators’ experience, high volume centers, and development of embolic protection devices (EPDs). Distal protective techniques using filter devices are the most widely used EPDs during CAS. Proximal protective techniques are promising strategies to protect the brain during CAS procedures. In proximal protection techniques, common and external carotid arteries are occluded promoting flow arrest, or flow reversal, of the target internal carotid artery, which establishes brain protection to cross and treat carotid stenosis. Randomized trials comparing proximal protection devices against filter protection revealed superiority of the former in preventing embolic complications to the brain. The present trial is aimed at comparing flow reversal and filter protection during CAS using a femoral approach.

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Methods

Study Design, Patient Population, and End Points
This study is a randomized, prospective, open-label (blinded outcomes), single-center, superiority trial. The trial complied with the principles of the Declaration of Helsinki and followed the CONSORT Statement for pragmatic trials assessing nonpharmacological treatments using a policy of intention-to-treat analysis. The study statement and the
WHAT IS KNOWN

• The improvement in clinical outcomes with carotid artery stenting has been associated with development of embolic protection devices.
• Proximal protective techniques have been associated with better outcomes than distal protective techniques during carotid artery stenting procedures.

WHAT THE STUDY ADDS

• Proximal protective strategy using flow reversal was associated with worse outcomes than distal protective strategy using filter protection during carotid artery stenting.
• Filter protection during carotid artery stenting resulted in excellent outcomes.

written informed consent were approved by the institutional review board (number: 14837/2010). All patients, or their legal representatives, signed the consent forms before allocation. The trial was registered in Brazil by the Ministry of Health—SISNEP (Web site: http://portal2.saude.gov.br/sisnep; registration number: 0538.004.000-00-10).

We prospectively randomized patients presenting carotid atherosclerotic stenosis from March 2011 to July 2012. Patients who presented internal carotid artery stenosis ≥50% in a carotid ultrasound study underwent a 3T magnetic resonance image (MRI) to assess the brain ischemic injury pattern, age-related white matter change15 score, and the angiographic anatomy focusing on the carotid stenosis and on the intracranial collateral pattern.

The inclusion and exclusion criteria were analyzed (Table 1).14,16 The patients were invited to participate in the study if all enrollment criteria were met. Patients were blindly randomized in 2 groups in a 1:1 ratio using a virtual flip coin Web site based method (http://www.random.org). The first group underwent CAS with flow reversal using the GORE flow-reversal system (WL Gore and Associates, Flagstaff, AZ), and the second group underwent CAS with the filter wire EZ (Boston Scientific, Natick, MA), both procedures used a femoral approach.

New ischemic brain lesions on diffusion-weighted MRI (DWI-MRI) at 3-month follow-up were used as a surrogate outcome measure of treatment efficacy.17 The primary end points were the incidence, number, and size of new brain ischemic signs on DWI-MRI 24 hours after CAS. The secondary end points included major adverse cardiac and cerebrovascular events, which are defined as stroke, symptomatic myocardial infarction, vascular complications, or death. Other secondary outcomes include transient ischemic attack during the first 24 hours after treatment and at 3-month follow-up, and remnant ischemic brain lesions on fluid-attenuated inversion recovery (FLAIR-MRI) at 3-month follow-up.

CAS Procedure

All procedures were performed by a unique experienced intervention-al neuroradiologist using a flat-panel detector system, Innova 4100 (General Electric, Fairfield, CT). The operator (D.G.A.) had worked with Interventional Neuroradiology since 2002 performing >450 cases of CAS, of which 26 cases without protection, 412 cases using filter devices, and 39 cases using proximal protection devices. The operator was informed of which protective technique was randomized immediately before starting CAS, and he was blinded to clinical and radiological assessments postprocedure.

The antiplatelet regimen recommended was aspirin (300 mg daily) and clopidogrel (75 mg daily) 25 days before treatment or aspirin (300 mg attack) and clopidogrel (300 mg attack) 24 hours before the procedure and continuing for 3 months afterward. Aspirin 300 mg daily was maintained indefinitely. After femoral punctures, 7500 IU of heparin was administered intravenously. At the time of angioplasty, an atropine bolus was infused intravenously (0.5–1.0 mg). All cases were performed with the patient under general anesthesia. The closed-cell Wallstent (Boston Scientific, Natick, MA) was used for all procedures. All patients were discharged mostasis was achieved with the use of the Angioseal (St. Jude Medical Daig Division Inc, De Veau Place, MN). All patients were discharged

Table 1. Eligible Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Eligible Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age ≥18 y</td>
<td>Life expectancy ≥1 y</td>
</tr>
<tr>
<td>Symptomatic ICA stenosis ≥50%*</td>
<td>Asymptomatic ICA stenosis &gt;60%*</td>
</tr>
<tr>
<td>Symptoms were defined as ischemic stroke, transient ischemic attack, hypoperfusion symptoms, or retinal ischemia</td>
<td>At least 1 patent intracranial collateral (ipsilateral posterior communicate artery or anterior communicate artery and bilateral A1 segments of cerebral anterior artery)</td>
</tr>
<tr>
<td>Presence of ≥1 arterial femoral pulse</td>
<td>ECA diameter ≤6 mm</td>
</tr>
<tr>
<td>Absence of any arterial branch emerging below ECA occlusion site</td>
<td></td>
</tr>
</tbody>
</table>

Contraindication to general anesthesia

Patients presenting any high- or medium-risk sources for cardioembolism†

Contraindication for antiplatelet therapy

CAS indicates carotid artery stenting; ECA, external carotid artery; and ICA, internal carotid artery.

*Based on the criteria defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET).14
†Based on TOAST criteria.16

bolus was infused intravenously (0.5–1.0 mg). All cases were performed with the patient under general anesthesia. The closed-cell Wallstent (Boston Scientific, Natick, MA) was used for all procedures. All patients were discharged mostasis was achieved with the use of the Angioseal (St. Jude Medical Daig Division Inc, De Veau Place, MN). All patients were discharged 24 hours after treatment if no contraindication occurred. Two times were registered: the overall procedure time and protection time (flow-reversal time or time from the filter opening until its removal).

Image Assessment

A 3T MRI and a magnetic resonance angiography (Philips Achieva Duo—Philips Medical Systems, Best, The Netherlands) were performed...
before CAS. Post-treatment MRI was obtained between 6 and 24 hours after CAS and at 3-month follow-up. All images were assessed by 2 blinded, independent neuroradiologists. For discrepant findings, a third neuroradiologist made the final decision. Echo planar imaging with the following parameters was used: TR, 7.2943 ms; TE, 3.403 ms; 50 slices, slice thickness of 5 mm; field of view, 256 mm; diffusion values, b, 0, 500, 1000, and 3000 s/mm²; fat saturation; time of acquisition, 71 s. Additionally, apparent diffusion coefficient maps were obtained. A new ischemic brain lesion after CAS was defined as a focal hyperintense area detected as a restricted diffusion signal in the DWI sequence, confirmed by apparent diffusion coefficient mapping to rule out a shine-through artifact. The incidence, number, mean diameter, and site of new ischemic lesions on DWI-MRI were assessed. The FLAIR-MRI sequence was obtained to assess leukoaraiosis patterns defined by the age-related white matter change score on the baseline MRI and to evaluate remnant ischemic brain lesions at 3-month follow-up. Carotid ultrasound was performed to all patients before CAS and at 3-month follow-up.

Neurological Assessment
All patients were examined by 2 blinded certified vascular neurologists in-hospital and at 3-month follow-up. The neurologists measured outcomes with the National Institutes of Health Stroke Scale and the modified Rankin Scale (mRS). National Institutes of Health Stroke Scale scores were obtained 1 hour before treatment, 24 hours after treatment, and at 3-month follow-up. The mRS scores were obtained 1 hour before treatment and at 3-month follow-up. A stroke was defined as an ischemic neurological deficit (National Institutes of Health Stroke Scale score ≥4) that persisted for ≥24 hours.

Statistical Analysis and Literature Review
We calculated the sample size, using a Web site based method (http://www.sealedenvelope.com), by assuming that the proportions of patients presenting brain ischemic lesions on DWI-MRI would be 50% in the filter group and 10% in the flow-reversal group. A sample size of 34 patients, 17 per group assigned, was necessary to detect a decrease in embolic complication rate from 50% to 10% (at 80% power and 0.05 significance). Therefore, a sample size of 40 patients was chosen. The null hypothesis was that the 2 EPDs were equal concerning efficacy and security. Continuous variables were presented as mean (range±SD) or median, and the Student t or Mann–Whitney test was used, as appropriate. Categorical variables were presented as number and percentages and compared among groups using χ², Pearson’s χ², or Fisher exact tests, as appropriate. One independent blinded investigator received all data collected for statistical analysis. The SPSS Statistics software version 17.0 (Chicago, IL) was used for statistical analysis.

Aiming at comparing the primary end points obtained in the present study with those in the earlier trials, a literature review was performed to evaluate the incidence of new ischemic brain lesions after
carotid interventions. PubMed was searched for studies published through January 20, 2013, using the key words “carotid” and “ischemic lesions” in titles or abstracts. Only studies clearly reporting incidence of new ischemic brain lesions on DWI-MRI after carotid interventions and modalities of carotid interventions were included. Moreover, studies that reported use of different devices in the same groups of study were excluded.

**Results**

**Patient Population and Procedures**

A total of 117 patients were screened, and 40 patients were randomized, of which 21 and 19 patients were allocated in the flow-reversal and filter groups, respectively. A total of 77 patients were not randomized because 1 patient declined to participate, 18 did not meet inclusion criteria, and 58 patients presented exclusion criteria. Among all patients excluded, 10 did not have a patent intracranial collateral, 4 presented a large external carotid artery diameter (>6 mm), 3 presented a superior thyroid artery emerging below the external carotid artery, 1 had no femoral arterial pulse, 16 presented contralateral internal carotid artery stenosis ≥50%, 11 presented contralateral carotid artery occlusion, 1 presented a creatinine clearance <40 mL/min, 14 had a recent stroke, 1 presented contraindication for antiplatelet therapy, 3 had a recent myocardial infarction, 2 presented contraindication to general anesthesia, and 10 patients presented a source for cardioembolism. A flow chart of enrolled patients is shown in the Figure.

All CAS procedures were successfully accomplished, and all patients were discharged 24 hours after treatment. All patients had MRI and neurological assessment between 6 and 24 hours after the procedure. Two patients, 1 from each group, did not have an MRI and carotid ultrasound at 3 months; therefore, they were excluded from the secondary analysis. A neurological assessment was performed in all patients at 3-month follow-up. No patient had carotid restenosis on carotid ultrasound. There were no clinical, technical, or device-related complications. The overall mean procedure time was significantly longer in the flow-reversal group compared to the filter group.

**Table 2. Baseline Characteristics of Patients per Group Assigned**

<table>
<thead>
<tr>
<th>Clinical, Radiological, and Procedural Data</th>
<th>Total (N=40)</th>
<th>Flow-Reversal Group (n=21)</th>
<th>Filter Group (n=19)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>25 (62.5)</td>
<td>12 (57.1)</td>
<td>13 (68.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>69.1 (49–82, SD=7.55)</td>
<td>69.9 (56–82, SD=9.1)</td>
<td>68.2 (59–82, SD=5.46)</td>
<td>0.47</td>
</tr>
<tr>
<td>Left carotid stenosis, n (%)</td>
<td>23 (57.5)</td>
<td>10 (47.6)</td>
<td>13 (68.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Carotid stenosis grade, mean (NASCET, %)</td>
<td>66.4 (50–95, SD=13.87)</td>
<td>67.8 (50–95, SD=13.35)</td>
<td>64.79 (51–95, SD=14.62)</td>
<td>0.29</td>
</tr>
<tr>
<td>Asymptomatic patients, n (%)</td>
<td>7 (17.5)</td>
<td>3 (14.3)</td>
<td>4 (21.1)</td>
<td>0.57</td>
</tr>
<tr>
<td>Symptomatic patients, n (%)</td>
<td>33 (82.5)</td>
<td>18 (85.7)</td>
<td>15 (79.0)</td>
<td>0.57</td>
</tr>
<tr>
<td>Ipsilateral stroke, n (%)</td>
<td>24 (60.0)</td>
<td>12 (57.1)</td>
<td>12 (63.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Transient ischemic attack, n (%)</td>
<td>6 (15.0)</td>
<td>5 (23.8)</td>
<td>1 (5.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Retinal infarct, n (%)</td>
<td>3 (7.5)</td>
<td>1 (4.8)</td>
<td>2 (10.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>High blood pressure, n (%)</td>
<td>39 (97.5)</td>
<td>20 (95.2)</td>
<td>19 (100)</td>
<td>0.48</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>16 (40.0)</td>
<td>8 (38.1)</td>
<td>8 (42.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>28 (70.0)</td>
<td>14 (66.6)</td>
<td>14 (73.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Tobacco smokers, n (%)</td>
<td>13 (32.5)</td>
<td>6 (28.5)</td>
<td>7 (36.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>9 (22.5)</td>
<td>5 (23.8)</td>
<td>4 (21.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous myocardial infarct, n (%)</td>
<td>6 (15.0)</td>
<td>3 (14.2)</td>
<td>3 (15.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Baseline NIHSS, mean (median)</td>
<td>1.62; 1 (0–8; SD=2.02)</td>
<td>1.52; 1 (0–7; SD=1.86)</td>
<td>1.74; 1 (0–8; SD=2.23)</td>
<td>0.92</td>
</tr>
<tr>
<td>Baseline mRS, mean (median)</td>
<td>1.57; 2 (0–4; SD=1.33)</td>
<td>1.62; 1 (0–4; SD=1.39)</td>
<td>1.53; 2 (0–4; SD=1.30)</td>
<td>0.82</td>
</tr>
<tr>
<td>ARWMC score, mean (median)</td>
<td>2.97; 3 (0–5; SD=1.20)</td>
<td>2.95; 3 (1–5; SD=1.22)</td>
<td>2.84; 3 (0–5; SD=1.21)</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean procedural time, min</td>
<td>19.74 (10.61–33.58; SD=5.17)</td>
<td>22.41 (16.61–33.58; SD=4.68)</td>
<td>16.78 (10.61–22.91; SD=4.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean protection time, min</td>
<td>4.88 (2.83–7.55; SD=1.21)</td>
<td>4.49 (2.83–7.55; SD=1.44)</td>
<td>5.32 (4.26–6.98; SD=0.71)</td>
<td>0.02</td>
</tr>
<tr>
<td>Predilatation, n (%)</td>
<td>15 (37.5)</td>
<td>8 (38.1)</td>
<td>7 (36.8)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

ARWMC indicates age-related white matter change; mRS, modified Rankin Scale; NASCET, North American Symptomatic Carotid Endarterectomy Trial; and NIHSS, National Institutes of Health Stroke Scale.

**Table 3. Primary End Points Obtained**

<table>
<thead>
<tr>
<th>New Ischemic Brain Lesions on DWI-MRI Between 6 and 24 h After Procedure</th>
<th>Total (N=40)</th>
<th>Flow-Reversal Group (n=21)</th>
<th>Filter Group (n=19)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, n (%)</td>
<td>13 (32.5)</td>
<td>10 (47.6)</td>
<td>3 (15.8)</td>
<td>4.85 (1.08–21.76)</td>
<td>0.03</td>
</tr>
<tr>
<td>Number (mean)</td>
<td>1.72 (0–18; SD=3.98)</td>
<td>2.61 (0–18; SD=5.13)</td>
<td>0.73 (0–5; SD=1.75)</td>
<td>...</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean diameter (mm)</td>
<td>1.56 (0.0–9.5; SD=2.49)</td>
<td>2.23 (0.0–9.5; SD=2.77)</td>
<td>0.81 (0.0–6.4; SD=1.96)</td>
<td>...</td>
<td>0.05</td>
</tr>
<tr>
<td>Incidence of ipsilateral lesions, n (%)</td>
<td>7 (46.1)</td>
<td>7 (70.0)</td>
<td>0 (0.0)</td>
<td>...</td>
<td>0.07</td>
</tr>
<tr>
<td>Incidence of bilateral lesions, n (%)</td>
<td>6 (53.9)</td>
<td>3 (30.0)</td>
<td>3 (100)</td>
<td>...</td>
<td>0.07</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and DWI-MRI, diffusion-weighted magnetic resonance image.
group, whereas the mean protection time was significantly longer
in the filter group (Table 2). Baseline characteristics of patients
did not differ significantly between the 2 groups (Table 2).

Primary End Points
The primary end points are summarized in Table 3. All 40
patients were included in the primary analysis. Compared
with flow reversal (n=21), filter protection (n=19) resulted in
a significant reduction in the incidence (15.8% versus 47.6%,
P=0.03), number (0.73 versus 2.6, P=0.05), and size (0.81
versus 2.23 mm, P=0.05) of new ischemic brain lesions. Flow
reversal was associated with a tendency toward increased inci-
dence of ipsilateral ischemic lesions more than those who had
filter protection (70% versus 0.0%, P=0.07). In addition, flow
reversal showed a greater tendency toward increased incidence
of ipsilateral lesions than bilateral (70% versus 30%, P=0.07).

Secondary End Points
Secondary end points are summarized in Tables 4 and 5. Two
patients, 1 from each group, presented transient ischemic attack
related to the stented carotid territory at 3-month follow-up,
and they completely recovered from neurological deficits. No
patient presented major adverse cardiac and cerebrovascular
events in-hospital or at 3-month follow-up. About the incidence
of definitive ischemic brain lesions at 3 months, no difference
was observed between the 2 groups. However, compared with
flow reversal (n=20), filter protection (n=18) resulted in a sig-
nificant reduction in the number (0.40 versus 0.0, P=0.05)
and size (1.34 versus 0.0 mm, P=0.05) of definitive ischemic
brain lesions at 3-month follow-up. Among 10 patients in the
flow-reversal group presenting ischemic brain lesions on early
DWI-MRI, 4 (40%) patients presented 8 definitive ischemic
lesions with a mean diameter of 1.34 mm. Among patients of
the filter group, no patient presented definitive ischemic lesions.
Considering the overall number of ischemic lesions, only 8
(11.5%) of 69 lesions remained on FLAIR-MRI at 3-month
follow-up, whereas 61 (88.5%) of 69 lesions disappeared.

Discussion
This is the first randomized trial comparing flow reversal with
the GORE flow-reversal system (GORE) and filter protection
with the Filterwire EZ (Boston Scientific) during CAS using
a femoral approach. Baseline characteristics of patients were
similar and did not differ significantly between the 2 groups
(Table 2). Concerning CAS procedures, the mean procedure

time was longer in the flow-reversal group, which can be
explained by the flow-reversal device that is more complex,
thus necessitating more technical steps during the CAS proce-
dure. On the contrary, procedure time was shorter in the filter
group, whereas protection time was significantly longer in this
group than in the flow-reversal group. Despite significant differ-
ences obtained between the 2 groups on procedure and protec-
tion times, all procedures were performed in up to 34 minutes.
Therefore, these findings probably could not justify differences
in the primary end points obtained but did prove that filter pro-
tection device is simpler to use than flow-reversal system.

This trial was the first that showed better results using filter pro-
tection than a proximal protective technique during CAS. Aiming
to avoid bias, all procedures were performed by the same opera-
tor, in the same angiography suite, using the same MRI, the same

Table 5. Secondary End Points Obtained on FLAIR-MRI

<table>
<thead>
<tr>
<th>Remnant Ischemic Brain Lesions on FLAIR-MRI at 3-Mo Follow-up</th>
<th>Total (N=38)</th>
<th>Flow-Reversal Group (n=20)</th>
<th>Filter Group (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, n (%)</td>
<td>4 (10.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Number (mean)</td>
<td>0.21 (0–3; SD±0.70)</td>
<td>0.40 (0–3; SD±0.34)</td>
<td>0 (0.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean diameter (mm)</td>
<td>0.70 (0.0–9.0; SD±2.13)</td>
<td>1.34 (0.0–9.0; SD±2.83)</td>
<td>0 (0.0)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

FLAIR-MRI indicates fluid-attenuated inversion recovery magnetic resonance image.
stent, and the same dosages of heparin, aspirin, and clopidogrel. Moreover, patients presenting cardioembolic sources of cerebral emboli were excluded to avoid polluting the DWI-MRI results.

Ischemic brain lesions during CAS by femoral access have been criticized because instrumentation of an atherosclerotic aortic arch could release plaque debris to the brain during carotid catheterization. All of the ischemic brain lesions (100%) obtained in the filter group and 30% in the flow-reversal group were bilateral, which supports the hypothesis of aortic arch instrumentation as an inherent source of embolic complications during CAS by femoral approach. However, the high incidence of ipsilateral ischemic lesions observed in the flow-reversal group suggests that worse results in this group were not related exclusively to aortic arch instrumentation.

A possible explanation of the origins of ischemic brain lesions with proximal protection devices was reported in a recent study assessing microembolic signals during CAS monitored by transcranial Doppler. In this study, Montorsi et al11 monitored all phases of the procedure and found lower incidence of microembolic signals with proximal balloon occlusion than that with filter protection in almost all phases of the procedure, except during the retrieval and deflation of devices. Authors showed that deflation of proximal balloon occlusion was associated with higher microembolic signals counting than retrieval of filter devices. In addition to the results of Montorsi et al,11 the worse results obtained in the flow-reversal group in the present study could be attributed to the larger diameter (9.5 Fr) of the GORE balloon sheath and its higher rigidity than the guiding catheter (7.0 Fr) used in the filter group. The larger size and the high rigidity of the GORE balloon sheath possibly increased shear stress in the artery walls during carotid catheterization, promoting the release of microemboli from plaques.

An unexpected low incidence rate of new ischemic brain lesions (15.8%) was obtained with procedures using filter protection in a population, in which 79% of patients were symptomatic. Moreover, all ischemic brain lesions (100%) observed in the filter group were bilateral. Therefore, we reviewed the literature to compare our results with those in the earlier trials.

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**Table 6. Literature Review of Studies Assessing Incidence of New Brain Ischemic Lesions on DWI-MRI After Carotid Interventions**

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Year</th>
<th>Carotid Intervention (n)</th>
<th>DWI-MRI, n (%)</th>
<th>Carotid Intervention (n)</th>
<th>DWI-MRI, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnaudigel et al20</td>
<td>2008</td>
<td>F (1363)</td>
<td>504 (36.9)</td>
<td>CEA (754)</td>
<td>75 (10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Posacioglu et al21</td>
<td>2008</td>
<td>F (56)</td>
<td>7 (12.5)</td>
<td>CEA (59)</td>
<td>16 (27.1)</td>
<td>0.041</td>
</tr>
<tr>
<td>Paionbo et al22</td>
<td>2008</td>
<td>F (98)</td>
<td>20 (20.4)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Grunwald et al23</td>
<td>2009</td>
<td>U (197)</td>
<td>67 (34.0)</td>
<td>...</td>
<td>...</td>
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CEA indicates carotid endarterectomy; CF, carotid artery stenting (CAS) with filter protection by cervical access; CFR, CAS with flow reversal by cervical access; DB, CAS with distal balloon protection; DWI-MRI, diffusion-weighted magnetic resonance image; F, CAS with filter protection; FR, CAS with flow reversal by femoral access; NR, not reported; PB, CAS with proximal balloon occlusion; and U, unprotected CAS.

*Reference refers to the present study in this article.
Twenty-seven studies before January 20, 2013, were found. We included a systematic review of Schnaudigel et al.20 and all studies after that.11-13,17,21-42 Results of this review are summarized in Table 6.11-13,17,20-42 The high variability in methods makes it difficult to compare between procedures and protection techniques accurately among the different studies reviewed. Accordingly, higher variable rates of ischemic brain lesions during CAS using several protection techniques and EPD can be seen in the reviewed studies. Furthermore, the filter protection results of the present trial were among the best CAS results reported and were even similar to some standard carotid endarterectomy results (Table 6). Therefore, we think that our excellent results with filter protection may be because of a considerable operator experience with CAS, to the general anesthesia, which minimized the risk of movement accidents and to the filter protection device profile. It is possible that, beyond protection technique, characteristics of EPD profiles may play an important role in CAS outcomes. Therefore, future CAS trials should compare different protection techniques using same EPD for each arm, and the Filterwire EZ should be tested against other embolic protection devices to confirm our results.

Although the present trial was not powered to detect differences in clinical outcomes, absence of major adverse cardiac and cerebrovascular events and the lower rates of transient ischemic attack (5.0%) were in accordance with best results of large carotid intervention trials.41 In addition to the increased incidence of ischemic lesions in the flow-reversal group, a higher number of definitive ischemic lesions on FLAIR-MRI at 3 months were observed in the flow-reversal group than in the filter group (Table 2). Nevertheless, no observed remnant lesions were related to neurological deficits. In addition, in the 2 patients who presented transient ischemic attack, no ischemic brain lesions on FLAIR-MRI were detected at 3 months. Concerning microembolic complications to the brain, at present no definitive association between ischemic brain lesions and neurological deficit or cognitive impairment has been demonstrated. In fact, the majority (88.5%) of new early ischemic brain lesions did not result in definitive lesions at 3-month follow-up.

A criticism of the method exists about the operator learning curve and new devices assessed in trials. The operator of the present trial (D.G.A.) performed 450 CAS procedures, of which 412 cases using filter devices, 27 cases using proximal protection devices with flow arrest, and 12 cases using proximal protection with flow-reversal before the start of the randomization.18 Although the operator experience was lower with the new GORE device, and this may be seen as a limitation of our study, the EMPIRE study showed a low major adverse cardiac and cerebrovascular event rate (1.8%) in the 56 roll-in patients (2 roll-in cases per institution), which suggested that experienced interventionalists can learn to use the GORE flow-reversal system quickly and efficiently among the different studies reviewed. Accordingly, strict enrollment criteria, which led to the exclusion of a high number of patients. Therefore, because of explanatory model of the study and an experienced operator performing all procedures, extrapolation of our results to general clinical practice should be considered with caution.

Conclusions

In this small sample size trial, filter protection was more effective than flow-reversal in reducing the incidence, number, and size of new ischemic brain lesions during CAS through femoral approach. Moreover, filter protection was associated with a shorter procedure time than that of flow-reversal. Large trials designed to assess clinical outcomes are necessary to confirm our findings.

Disclosures

None.

References


Flow Reversal Versus Filter Protection: A Pilot Carotid Artery Stenting Randomized Trial

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