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FOCUS ISSUE: TRANSCATHETER CARDIOVASCULAR THERAPEUTICS

The PROFI Study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting)

A Prospective Randomized Trial

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Objectives The objective of this study was to compare the cerebral embolic load of filter-protected versus proximal balloon–protected carotid artery stenting (CAS).

Background Randomized trials comparing filter-protected CAS with carotid endarterectomy revealed a higher periprocedural stroke rate after CAS. Proximal balloon occlusion may be more effective in preventing cerebral embolization during CAS than filters.

Methods Patients undergoing CAS with cerebral embolic protection for internal carotid artery stenosis were randomly assigned to proximal balloon occlusion or filter protection. The primary endpoint was the incidence of new cerebral ischemic lesions assessed by diffusion-weighted magnetic resonance imaging. Secondary endpoints were the number and volume of new ischemic lesions and major adverse cardiovascular and cerebral events (MACCE).

Results Sixty-two consecutive patients (mean age: 71.7 years, 76.4% male) were randomized. Compared with filter protection (n = 31), proximal balloon occlusion (n = 31) resulted in a significant reduction in the incidence of new cerebral ischemic lesions (45.2% vs. 87.1%, p = 0.001). The number (median [range]: 2 [0 to 13] vs. 0 [0 to 4], p = 0.0001) and the volume (0.47 [0 to 2.4] cm^3 vs. 0 [0 to 0.84] cm^3, p = 0.0001) of new cerebral ischemic lesions were significantly reduced by proximal balloon occlusion. Lesions in the contralateral hemisphere were found in 29.0% and 6.5% of patients (filter vs. balloon occlusion, respectively, p = 0.047). The 30-day MACCE rate was 3.2% and 0% for filter versus balloon occlusion, respectively (p = NS).

Conclusions In this randomized trial of patients undergoing CAS, proximal balloon occlusion as compared with filter protection significantly reduced the embolic load to the brain. (J Am Coll Cardiol 2012;59:1383–9) © 2012 by the American College of Cardiology Foundation

Stroke is the third leading cause of death in industrialized countries and the major cause of functional impairment (1). Carotid artery stenosis is an important cause of stroke (2). Carotid endarterectomy (CEA) has been established as an effective treatment for symptomatic as well as for asymptomatic patients (3). Carotid artery stenting (CAS) has emerged as an alternative to CEA (4). Current data support the use of embolic protection devices for CAS (5). Randomized trials comparing CAS with CEA revealed lower periprocedural stroke rates with surgery (6–10). As protection devices for CAS, filters were used in these trials.

Proximal balloon occlusion is an alternative to filter protection, which, by occluding the external and common carotid artery (CCA), induces reversed flow in the target vessel before the lesion is crossed and stented. Whether this results in a more effective cerebral embolic protection than a filter device has never to our knowledge been studied in a randomized trial. Diffusion-weighted magnetic resonance imaging (DW-MRI) has been shown to be a sensitive tool in identifying new ischemic cerebral lesions caused by emboli during CAS (11–13) and can therefore serve as a surrogate endpoint. The primary objective of the present study was to compare the incidence, the number, and volume of new cerebral ischemic lesions after filter-protected versus proximal balloon–protected CAS.

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From the Medical Care Center Prof. Mathey, Prof. Schofer, Hamburg University Cardiovascular Center, Hamburg, Germany. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

CAS = carotid artery stenting

CCA = common carotid artery

CEA = carotid endarterectomy

DW-MRI = diffusion-weighted magnetic resonance imaging

MACCE = major adverse cardiovascular and cerebral events

Methods

Study design. The PROFI (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting) study is a prospective randomized, single-center trial. The study was approved by the Freiburg ethics committee (clinic trial code 010/1707). At that time, the operator had experience in CAS in more than 1,000 patients. All patients gave their written informed consent. Between May 2010 and August 2011, eligible patients were randomized in a 1:1 fashion to get either filter or proximal balloon protection for the CAS procedure. Before and 12 to 24 h after CAS, a cerebral DW-MRI was performed.

The primary endpoint was the incidence of new cerebral ischemic lesions as assessed by DW-MRI. Secondary endpoints were the number and volume of new cerebral ischemic lesions, major adverse cardiovascular and cerebral events (MACCE) (defined as death, stroke, myocardial infarction, and vascular complications) at 30 days, bleeding complications, and device crossover.

The inclusion and exclusion criteria are summarized in Table 1.

Procedure. Patients were on dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg/day) before the intervention and for 4 weeks after. Carotid artery stenting was performed by a single experienced operator (J.S.) (14) as described in detail previously (11). The protocol specified use of the Cristallo ideale stent (Invatec, Roncadelle, Italy), the Emboshield Protection System for filter protection (Abbott Vascular, Abbott Park, Illinois), and the MO.MA ultra system (Invatec) for proximal balloon occlusion, respectively.

Diffusion-weighted magnetic resonance imaging. Cerebral DW-MRI scans were obtained before and 12 to 24 h after CAS using a 1.5-T scanner (Magnetom Sonata, Siemens, Erlangen, Germany). Images were reviewed by 2 independent physicians (A.W. and F.H.), both blinded to the protection device used. Echo planar imaging with the following parameters was used: TR = 3,000 ms, TE = 84 ms, 19 slices with a slice thickness of 6 mm, field of view = 230 mm, diffusion values b = 0, 500, 1,000 s/mm^2, fat saturation, time of acquisition = 71 s. Additionally, apparent diffusion coefficient maps were obtained. A new lesion after CAS was defined as a focal hyperintense area detected by the fluid-attenuated inversion recovery sequence, corresponding to a restricted diffusion signal in the diffusion-weighted imaging sequence, confirmed by apparent diffusion coefficient mapping to rule out a shine-through artifact. The number, volume, and location of new ischemic lesions on DW-MRI at follow-up were assessed.

Follow-up assessments. Patients underwent neurological examination by an independent neurologist prior to carotid artery stenting and before discharge and were monitored for at least 24 h. A follow-up visit with neurological evaluation and a duplex ultrasound of the target vessel was scheduled at 30 days.

Definitions. Patients were considered symptomatic if they had an ipsilateral neurological ischemic event within 6 months before the procedure.

Diameter stenosis for patient screening was determined by ultrasound using the peak systolic velocity ratio, the ratio of the peak systolic velocity in the internal carotid artery to the peak systolic velocity in the distal CCA, with a value of <2.0 for $<50\%$ stenosis, >4.0 for 70% stenosis with the additional value of >5.0 for 90% stenosis but less than near occlusion. Diameter stenosis for evaluation of the procedural result was determined angiographically by visual estimate before and after stenting.

Procedural success was defined as residual stenosis after stenting $\leq 30\%$ and the absence of complications.

Stroke was defined as a new neurological deficit with focal symptoms and signs consistent with focal cerebral ischemia, lasting at least 24 h. Stroke was considered minor if a neurological deficit resolved completely within 30 days or did not lead to an impairment in daily activities as judged by the independent neurologist. Otherwise, stroke was defined as major.

Balloon intolerance was defined as transient neurological symptoms during balloon occlusion which promptly disappeared after balloon deflation.

Myocardial infarction was defined as an increase in creatine kinase-MB 3 times the upper reference limit

Table 1 Inclusion and Exclusion Criteria

Inclusion criteria
Patient age ≥18 yrs
Symptomatic ICA stenosis ≥60% on ultrasonography
Asymptomatic ICA stenosis ≥80% on ultrasonography
No occlusion of the ipsilateral external carotid artery
Patent contralateral ICA
Complete circle of Willis (assessed by MR angiography)
Lesion passage with the filter possible without pre-dilation (assessed by MR angiography)
Sufficient landing zone (>4 cm) for the filter (assessed by MR angiography)
Patients provided written informed consent
Exclusion criteria
Ischemic stroke within previous 48 h
Total occlusion of the target vessel
Contraindication for MRI (pacemaker, claustrophobia)
Previous major stroke, severe enough to confound the assessment of endpoints
Contraindications for antiplatelet and/or anticoagulant therapy
In-stent restenosis
Coagulation disorders
Gastric ulcer or gastrointestinal bleeding within the last 30 days
Untreated hyperthyreosis
Allergy to contrast agent, aspirin, or clopidogrel

ICA = internal carotid artery; MR = magnetic resonance; MRI = magnetic resonance imaging.