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Multicenter Evaluation of Carotid Artery Stenting With a Filter Protection System

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OBJECTIVES The aim of this study was to evaluate the feasibility and safety of carotid artery stenting (CAS) with a filter protection system.

BACKGROUND Neurologic events linked to the embolization of particulate matter to the cerebral circulation may complicate CAS. Strategies designed to capture embolic particles during carotid intervention are being evaluated for their efficacy in reducing the risk of these events.

METHODS Between September 1999 and July 2001, a total of 162 patients (164 hemispheres) underwent CAS with filter protection (NeuroShield, MedNova Ltd., Galway, Ireland) according to prospective protocols evaluating the filter system at three institutions.

RESULTS Angiographic success was achieved in 162 of the procedures (99%) and filter placement was successful in 154 (94%) procedures. Carotid access was unsuccessful in two cases (1%) and filter placement in eight cases (5%). Of the latter, five procedures were completed with no protection and three were completed using alternative protection devices. On an intention-to-treat basis, the overall combined 30-day rate of all-stroke and death was 2% (four events: two minor strokes and two deaths). This includes one minor stroke in a patient with failed filter placement and CAS completed without protection. There was one cardiac arrhythmic death and one death from hyperperfusion-related intracerebral hemorrhage. There were no major embolic strokes.

CONCLUSIONS Carotid artery stenting with filter protection is technically feasible and safe. Early clinical outcomes appear to be favorable and need to be confirmed in a larger comparative study. (J Am Coll Cardiol 2002;39:841–6) © 2002 by the American College of Cardiology Foundation

The efficacy of carotid endarterectomy (CEA) in preventing stroke is dependent on the perioperative incidence of stroke and death (1). Accordingly, the American Heart Association has set guidelines for the performance of CEA. On the basis of these guidelines, CEA should only be performed if the combined rate of perioperative stroke and death can be kept ≤6% in symptomatic patients and ≤3% in asymptomatic patients with severe extracranial carotid stenoses (1). Extrapolating these guidelines to the performance of carotid artery stenting (CAS), experienced groups have reported outcomes that are consistent with these recommendations (2–4). However, despite advanced stenting techniques, neurologic events may still complicate CAS and remain an obstacle to its widespread acceptance. Obstructive carotid artery lesions are known to contain friable thrombotic and atherosclerotic components that have the potential to embolize during intervention and may be responsible for the majority of the neurologic events during CAS. This has been demonstrated in an ex vivo human carotid artery model by Ohki et al. (5), as well as by several transcranial Doppler (TCD) studies during CAS (6). A number of "distal protection" strategies, designed to capture embolic debris released during carotid intervention, are currently being evaluated for their efficacy in minimizing the risk of embolic neurologic events. One such strategy is the placement of a temporary intravascular filter that captures embolic matter in the distal internal carotid artery (ICA) during intervention (6). The aim of this study was to prospectively investigate CAS with a filter protection system.

MATERIALS AND METHODS

Between September 1999 and July 2001, a total of 162 patients (164 hemispheres, 164 procedures) underwent elective CAS with a filter protection system (NeuroShield, MedNova Ltd., Galway, Ireland) according to prospective protocols examining the feasibility and safety of the system during CAS at three institutions: New York, 64 cases (40%); Milan, 50 cases (30%); and Sheffield, 50 cases (30%). The enrollment criteria were identical and included patients with symptomatic or asymptomatic extracranial ICA stenosis of ≥50% and ≥70% (diameter obstruction) respectively, as determined by carotid angiography. Additionally, all enrolled patients satisfied the following criteria: 1) age ≥18 years; 2) ability to understand the procedure and sign a written consent; 3) a negative pregnancy test in women of childbearing age; 4) suitable lesion for treatment with angioplasty and stenting (based on the absence of significant calcification, thrombus and extremely tortuous anatomy); 5)

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Abbreviations and Acronyms

CAS = carotid artery stenting
CEA = carotid endarterectomy
CREST = Carotid Revascularization Endarterectomy vs. Stenting Trial
ECA = external carotid artery
ICA = internal carotid artery
NIHSS = National Institutes of Health Stroke Score
TCD = transcranial Doppler

sufficient space for filter placement distal to the lesion; and 6) ICA diameter ≥4 mm but ≤6 mm.

Exclusion criteria included: 1) breastfeeding women; 2) stroke within seven days before the procedure; 3) National Institute of Health Stroke Score (NIHSS) of ≥15 within seven days before the procedure or baseline major ipsilateral stroke that is likely to confound the determination of the study clinical end points; 4) more than one ipsilateral carotid lesion requiring treatment; 5) the presence of a cardiac source of embolus (such as atrial fibrillation); 6) the presence of known intracranial tumors or vascular malformation; 7) renal insufficiency (creatinine ≥2.5 mg/dl); and 8) comorbidity with a life expectancy of ≤1 year.

The primary end points included: 1) technical success (angiographic and device success) and 2) procedural and 30-day incidence of minor stroke, major stroke, myocardial infarction and death.

All procedures were performed according to the guidelines of the Institutional Review Board or the local medical ethics committee. All patients signed a written consent. All patients had a complete neurologic evaluation performed by a neurologist that included an assessment of the NIHSS before and within 24 h after the procedure. Additionally (at Lenox Hill), clinical events were adjudicated, based on patient chart review, by an independent clinical events committee that was selected to include a neuroradiologist, a neurologist and a surgeon.

Clinical and procedural data were documented by a dedicated research coordinator using a special case report form and were entered into a computerized database. Thirty-day follow-up that included queries regarding potential neurologic events was completed on each patient. Imaging studies were utilized in determining occurrences of end points whenever necessary.

Patients were premedicated with clopidogrel (Plavix, Pfizer Inc., New York, New York) 75 mg once a day and aspirin 100 to 325 mg twice a day for a minimum of seven days before the procedure. Clopidogrel was continued for 30 days after CAS (14 days in Sheffield) and aspirin was continued indefinitely. All carotid stenting procedures were performed using a standard technique as previously described (7). A 7F/90-cm long guiding sheath (Shuttle, Cook Inc., Indianapolis, Indiana) was used to access the carotid artery. A single bolus of intravenous heparin (5,000 U or 70 U/kg) was administered at the beginning of the procedure. The filter system was employed according to the manufacturer's instructions as described later. Glycoprotein IIb/IIIa antagonists were not utilized.

Device description. The Generation-II NeuroShield (MedNova Ltd.) is a temporary intravascular filtration system designed to capture atheromatous material released during the carotid interventional procedures (Fig. 1). The system is composed of three major components: 1) the filter guidewire, 2) a delivery catheter and 3) a retrieval catheter.

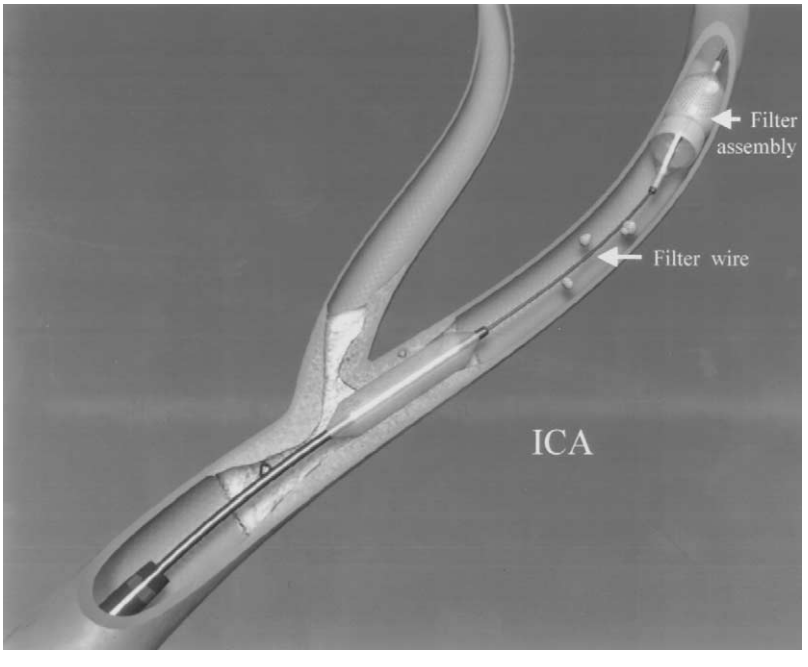

Figure 1. Application of the NeuroShield filter system during carotid artery stenting. The filter is mounted on a filter wire that is used to cross the lesion and deliver interventional balloon and stent catheters. ICA = internal carotid artery.

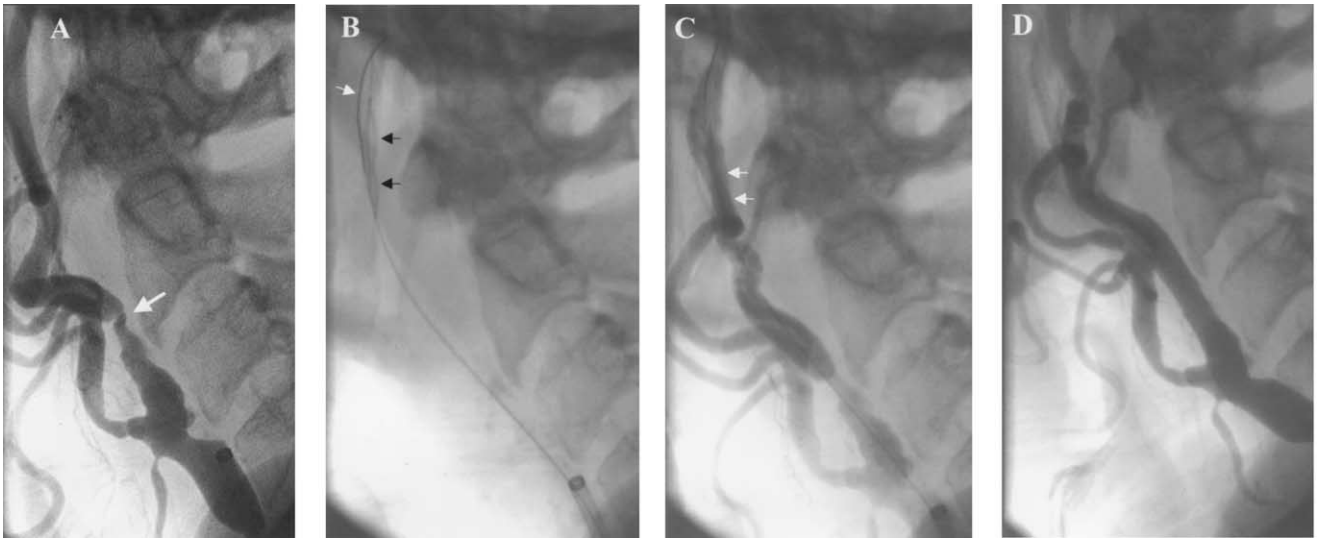

Figure 2. Carotid angiogram demonstrating flow preservation during carotid artery stenting with the filter protection system. **(A)** Preprocedural angiogram showing a high-grade stenosis of the internal carotid artery. **(B)** The filter **(the bottom two arrows)** is positioned distal to the lesion. In this case a "buddy wire" **(the white arrow)** was required to facilitate filter placement. **(C)** Carotid angiogram demonstrating flow through the filter **(arrows)**. **(D)** Final angiography: the stented site is widely patent.

The filter assembly is located at the distal end of 0.014-inch guidewire that is used to cross the lesion (Fig. 1). The filtration element, made of polyurethane, has four proximal entry ports and multiple distal perfusion pores (100 to 150 μm) that allow blood flow to the cerebral circulation (Fig. 2). The filter is available in diameters of 4 to 6 mm and is sized to the selected distal ICA segment (1:1). A preshaped Nitinol expansion system assists in filter deployment and apposition to the arterial wall.

Filter deployment and retrieval are performed using dedicated catheters. At the commencement of an interventional procedure, the filter system is loaded into the delivery catheter. The system is then advanced through the guiding sheath and across the target lesion into the distal ICA. The delivery catheter is withdrawn and, as it is withdrawn, the filter is deployed. After the delivery catheter is removed, an angiogram is obtained to document blood flow through the filter and document device placement distal to the target lesion (Fig. 2C). The filter guidewire is used to deliver the balloon and stent delivery catheters. Following the completion of the procedure, the filter assembly is recovered using the retrieval catheter. This is advanced over the guidewire and through the stented lesion, then further over the deployed filter assembly. As the retrieval catheter distal pod contacts the proximal edge of the filter assembly, the Nitinol expanders collapse and the filter assembly is rewrapped, fully contained within the retrieval catheter. The entire device is then removed from the patient with the captured emboli contained in the filtration element. In cases where the filter delivery catheter system is unable to cross the lesion on the initial attempt because of lesion severity or vessel tortuosity, a gentle predilation (using a 2-mm balloon) or a side-wire "buddy wire" was used to facilitate the system advancement (Fig. 2).

DEFINITIONS

Technical success. *Device success:* successful placement and retrieval of the NeuroShield filter device. *Angiographic success:* successful stent deployment resulting in ≤30% residual diameter stenosis.

Stroke. *Minor stroke:* an arterio-occlusive brain infarction characterized by the sudden onset of a neurologic deficit that persists for ≥24 h. In all cases, patients must be nondisabled. *Major stroke:* an arterio-occlusive brain infarction characterized by the sudden onset of a neurologic deficit (NIHSS ≥9) persisting for a minimum of 30 days.

Procedural event. A procedural event is the occurrence of any clinical event during the procedure, from the time femoral arterial access is obtained and until vascular access site hemostasis is successfully achieved.

30-day outcome. The 30-day outcome was the composite incidence of the clinical end points within the first 30 days.

Statistical analysis. The primary end points were analyzed on an intention-to-treat basis. All values were expressed in mean ± SD.

RESULTS

Table 1 summarizes the patient clinical and angiographic characteristics. The mean age of the patients was 68 ± 8 years (range 51 to 85 years, 11 patients (7%) were ≥80 years). Seventy-seven patients (48%) had symptoms attributable to the treated artery within the three months before the procedure. Of these, 61% had transient ischemic attacks, 23% had stroke and 16% had amaurosis fugax. One patient was treated using the filter system after he developed intolerance symptoms during CAS with the distal-balloon protection.

Immediate outcome. Angiographic success was achieved in 162 (99%) of the patients. Successful filter placement and

Table 1. Clinical and Angiographic Characteristics

Age (yrs) (mean ± SD)	68 ± 8
Age ≥80 yrs	11 (7%)
Men (n, %)	28 (87%)
Symptomatic lesions	77 (48%)
Hypertension	31 (80%)
Diabetes	12 (31%)
Hyperlipidemia	26 (67%)
Coronary artery disease	21 (54%)
Prior ipsilateral CEA	13 (8%)
Stenosis severity (mean ± SD)	82 ± 9%
Lesion length (mm) (mean ± SD)	12 ± 6
Contralateral ICA stenosis of ≥50%	49 (30%)
Contralateral ICA occlusion (n, %)	18 (11%)

CEA = carotid endarterectomy; ICA = internal carotid artery.

retrieval was achieved in 154 (94%) of the procedures. An additional maneuver, such as a gentle predilation (using a 2-mm diameter balloon) and/or a "buddy wire" placement, was necessary in 12 (8%) of the cases to facilitate the filter placement. In these cases, high-grade lesions and/or severe distal vessel tortuousity made the initial attempt unsuccessful. Failure to place the filter occurred in eight cases (5%) because of inability of the device to cross-sever stenoses with tortuous distal anatomy despite additional maneuvers (buddy wire and predilation) in two cases. The procedure was completed with no protection in five patients and with an alternative protection system in three; distal balloon protection (GuardWire, Percusurge Inc., Sunnyville, California) in two patients, and a different filter protection device (Angioguard, Cordis Inc., Miami, Florida) was negotiated through the lesion in one patient after an additional balloon dilation. Preserved flow through the ICA was angiographically documented in all of the procedures where the filter was successfully placed. There was no device failure following deployment, and all filters were successfully retrieved in a completely collapsed condition. Macroscopically visible particles were retrieved in 54 (35%) of the filters. Pathohistologic analysis of the filter contents was performed in a subset of 11 consecutive patients. This revealed multiple debris (mean number of particles per filter was 12, range 0 to 41) that included fibrin, cholesterol clefts, organized thrombi and red and white blood cell aggregates.

Nonflow-limiting spasm that resolved after removal of the filter (with/without intravascular nitroglycerin) occurred in five cases (3%). Flow-limiting spasm at the filter site occurred in three patients (2%). This resolved completely with the filter removal in one patient, by advancing the filter few millimeters in one, and by intravascular nitroglycerin administration in the third patient. All three procedures were successfully completed with filter protection with no associated clinical sequelae. There were no vascular dissections.

There were two procedural minor strokes (1%). One patient developed blurred vision during a CAS procedure in which the filter placement was unsuccessful. The intervention was successfully completed without distal protection. The second patient, a known case of von Willebrand's disease whose aspirin had been withheld on the advice of the hematologist, developed dysphasia immediately following successful filter retrieval. Both patients recovered completely within 48 h. Of the 154 patients in whom the filter was successfully deployed, there was one embolic neurologic event (0.6%).

30-day outcome. On an intention-to-treat basis, the overall combined rate of all strokes and deaths at 30 days was 2% (four events). These include the two procedural minor strokes and two deaths. One patient suffered prolonged brady/tachyarrhythmia following a control arch aortogram, and a temporary transvenous pacer was placed before stenting and was removed following successful intervention. Subsequently, the patient developed an asystolic cardiac arrest and she could not be resuscitated. Autopsy demonstrated a perforated right ventricle with hemopericardium, and fatal arrhythmias were given as the cause of death. A second patient developed massive ipsilateral intraventricular/subarachnoidal hemorrhage four days following an uncomplicated CAS and died within 24 h from the onset. This constituted the only neurologic death and was thought to be due to reperfusion injury. All the remaining patients were asymptomatic, with no neurologic events or myocardial infarctions.

DISCUSSION

Carotid artery stenting without distal protection has been associated with embolic minor stroke rates of 2% to 5% and major stroke rates of 1% to 1.5% (2–4). In the largest report of CAS, a multicenter registry by Wholey et al. (8) that included 5,210 patients, the rates of minor and major embolic strokes were 2.7% and 1.5%, respectively. Distal protection has the potential to reduce the risk of embolization and enhance the safety of CAS. Preliminary results of a multicenter trial of CAS using the distal balloon protection have already shown a favorably low rate of embolic events (9). Moreover, the ability of the distal balloon protection to reduce the microembolic load has been demonstrated (10).

The present study demonstrates that the application of a filter protection system during CAS is feasible and safe. The risk of atheroembolic complications in patients who had successful filter placement appears to be favorably low and notable for the absence of major embolic events. This series represent the largest experience with a single-design filter system during CAS, and it confirms the results of two prior smaller series that evaluated various filter designs during CAS. Parodi et al. (11) reported the successful application of an umbrella-shaped filter system during CAS in six patients with no complications. In a recent report, Reimers et al. (12) reported no neurologic events during CAS using various filter designs in a series of 84 patients. The ability of the NeuroShield filter system to capture embolic particles during the carotid intervention has been demonstrated in an ex vivo human carotid artery model (13). In the current study, macroscopically visible particles were detected in 30%

Figure 3. Retrieved filter showing macroscopically visible captured material.

of the filters (Fig. 3), clinically confirming the prior ex vivo observation. Moreover, the retrieval of these particles in the filters provides further clinical evidence of the particulate matter release during CAS.

Embolic profile during CAS. The majority of CAS-associated neurologic events occur during the procedure, less commonly within the immediate 2 to 4 h following the intervention, and rarely thereafter. Transcranial Doppler studies have shown that stent deployment, predilation and postdilation are the most emboligenic phases of the unprotected CAS procedure, and that the risk of embolization after CAS is completed is very low (10,14). Gensori et al. (14), using TCD, reported a very low emboligenic potential in a group of patients within the 24 h following CAS. Therefore, it is intuitive that the successful application of any protection strategy during balloon dilations and stent deployment will result in significant reduction in the risk of embolic neurologic events during CAS.

Distal protection strategies. Two additional approaches for distal protection during CAS are under evaluation (6). The first involves the use of a distal balloon that interrupts flow though the ICA during intervention. The proximal blood column, potentially containing embolic material, is then aspirated before re-establishing the blood flow. The second approach involves reversing the flow within the ICA. This is achieved by occluding the CCA, diverting the blood into the ECA or simultaneously occluding the ipsilateral CCA and the ECA and diverting the blood into the guiding catheter that is externally connected to the contralateral femoral vein. Preliminary experience has shown that all of these strategies are effective in capturing embolic matter. However, each of these strategies has its inherent advantages and limitations. The utility of any distal protection system in the individual patient depends on the lesion anatomy, the adequacy of collateral circulation, the ease of use and, most importantly, the efficacy in reducing the risk of embolic events. Although the filter protection offers the advantage of a constant cerebral perfusion during CAS, allowing more time for careful and precise intervention, microscopic particles smaller than the size of the filter pores ($\leq$100 μm) may not be captured. The clinical significance of these particles, however, is uncertain (15). On the other hand, although both balloon occlusion systems are more applicable in severe lesions and tortuous vessels, intolerance may occur rapidly in 5% to 10% of the patients who have poor collateral blood supply due to incomplete circle of Willis (4). Confirming the early observation, the current series demonstrates that following successful placement, the flow through the filter is preserved and that the filter system is well tolerated. The crossing profile of the Generation-II system used in this study made it difficult to cross high-grade obstruction and/or tortuous anatomy, resulting in 5% failed filter placements in this series. Recent experience with the new Generation-III (authors' personal experience) has shown that this is more applicable in the tortuous anatomy. Compared with Generation-II, the new system has a lower profile and over-the-wire design with a free (nonmounted) filter. Using this system, the lesion is first crossed using a bare 0.014 178 guidewire. The filter is then delivered and retrieved over the wire in a similar fashion to the older version.

Future directions. The introduction of distal protection into the CAS procedure has set the stage for a randomized comparison of CAS with the traditional surgical treatment of carotid obstructions, such as CEA (16). Several trials are being commenced (16). The largest is the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), a randomized controlled trial of CEA versus CAS with filter protection in the symptomatic patients with extracranial carotid internal carotid stenosis (16). A second study is the Carotid Revascularization with Endarterectomy or Stenting Systems, evaluating CAS with distal protection in asymptomatic patients as well as those patients excluded from CREST. These and other ongoing trials will further define the role of CAS in stroke prevention.

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