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Carotid Artery Stenting With Proximal Cerebral Protection for Patients With Angiographic Appearance of String Sign

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Objectives The aim of this study was to assess the safety and effectiveness of carotid artery stenting (CAS) with proximal cerebral protection in patients showing string sign at carotid angiography.

Background Presence of string sign is a well-known factor for adverse events in patients with severe carotid artery disease undergoing CAS.

Methods We used retrospective analysis of a cohort of patients who underwent carotid angiography with the intention to undergo carotid stenting and had angiographically documented string sign in the target lesion.

Results From October 2006 to August 2007, 25 patients (21 men and 4 women, mean age 70.9 ± 8.7 years) presented with string sign during carotid angiography. This was 6.0% of a total of 416 patients studied during the time of the study. Twenty patients (80.0%) were symptomatic, and 5 (20.0%) were asymptomatic. Carotid artery stenting was performed successively in all patients. Proximal cerebral protection was applied in all but 1 patient. The 30-day death/stroke rate was 0%. At 12-month follow-up neurological events did not occur; 1 patient developed a nonfatal myocardial infarction, and another patient died from noncardiac cause. The 12-month death/stroke rate was 4.0%.

Conclusions Carotid stenting under proximal cerebral protection seems to be a feasible and safe procedure to manage patients with severe carotid stenosis in presence of angiographic string sign. Further prospective trials are required to prove efficacy of CAS in larger study populations. (J Am Coll Cardiol Intv 2010;3:298–304) © 2010 by the American College of Cardiology Foundation

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High-grade internal carotid artery (ICA) stenosis might be associated with angiographic appearance of a long, thin, tapered, post-stenotic segment of markedly reduced caliber with reduced anterograde flow. This angiographic appearance is called string sign, slim sign, or atherosclerotic pseudo-occlusion (1,2). Presence of string-sign detected at carotid angiography has been correlated to high morbidity and mortality risk (3). The natural history of patients with string sign is poorly characterized, and therefore management of those patients remains controversial. Previous studies in

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which endarterectomy was performed to treat those patients reported conflicting results. Alternatively, carotid artery stenting (CAS), with various protection devices, has been used as treatment modality in string sign patients with acceptable results (4). Nevertheless, string sign is a well-known anatomical and functional feature for adverse events, and patients presenting with string sign were excluded from most clinical trials on CAS. That was because of the possible presence of thrombus at the lesion site, which is associated with elevated risk for distal embolization and subsequent neurological complications.

To determine the feasibility and safety of CAS with proximal protection devices, which potentially minimizes the risk of distal embolization, we evaluated the acute and 12-month outcome of 25 patients presenting with angiographic appearance of string sign.

Methods

Patient population. The study cohort consisted of patients who underwent carotid angiography and had angiographically documented string sign in the target lesion. Indication for treatment was set by a board certified neurologist together with an interventionalist experienced in carotid stenting. String sign was defined as the angiographic appearance of a long, thin, tapered post-stenotic segment of the ICA with markedly reduced antegrade flow in presence of a subocclusive stenosis (2). Appearance of the string sign had to be certified by at least 2 interventionalists experienced in carotid stenting, 1 of whom was unaware of the patient's clinical condition.

From October 2006 to August 2007, in 2 different institutions, selective carotid angiography was performed in 25 patients (21 men [84.0%], and 4 [16.0%] women, mean age of 70.9 ± 8.7 years) presenting with string sign. That was 6.0% of the total 416 CAS procedures performed in both institutions during the period of the study. Immediately after the diagnostic angiography, CAS was attempted in all 25 patients. Twenty (80.0%) patients were symptomatic—defined as the presence of stroke, transient ischemic attacks (TIAs), or amaurosis within 6 months before the angiography—and 5 (20.0%) were asymptomatic. The demographic, clinical, and angiographic data of the patients treated are summarized in Table 1.

Indications for treatment in symptomatic patients were: single TIA in 5 (20%) patients, repeated and recent TIAs in 11 (44.0%), recent major stroke in 3 (12.0%), and acute stroke suitable for emergent reperfusion as indicated by the guidelines for acute ischemic stroke management in 1 (4.0%) patient (5).

Procedural details. All procedures were performed by experienced operators working in large volume centers (>200 CAS/year) and having large experience in both carotid stenting (>50 CAS/year) and in use of proximal protection devices. If not already receiving therapy, all patients received a loading dose of clopidogrel (300 mg) orally; a loading dose of aspirin (250 mg) was given only in patients not already taking aspirin daily. Before the procedure a bolus dose of heparin (70 to 100 IU/kg of body weight) was administered to maintain an activated coagulation time of 250 to 300 s throughout the procedure. Diagnostic carotid and cerebral angiography was performed in standard orthogonal angiographic views with the transfemoral approach and selective catheterization of the common carotid artery (CCA) (Fig. 1). Subsequently, a diagnostic catheter (4-F or 5-F) was advanced over a hydrophilic, floppy 0.035-inch wire (Glidewire, Terumo Europe NV, Leuven, Belgium) that had been previously placed into the external carotid artery (ECA). This wire was exchanged through the diagnostic catheter to a medium-support, 300-cm long, floppy-tip 0.035-inch wire (Hi-Torque SupraCore 35, Guidant, Santa Clara, California). Then the proximal protection device—either Mo.Ma (Invatec, Roncadelle, Italy) in 16 patients or the Gore Flow Reversal System (W. L. Gore, Inc., Flagstaff, Arizona) in 5 patients—was advanced into the CCA. In case of the Mo.Ma device, the distal balloon was advanced in the proximal part of the ECA. Application of proximal protection device was not possible in 1 patient (4.0%), because of the presence of a type III aortic arch. This patient was treated with a guiding catheter and a filter-type distal protection device. The number and type of protection devices used are presented in Table 2. Proximal protection was applied with the consecutive inflation of the balloons, first with the balloon placed in the ECA and then the balloon placed in the CCA. Flow-blockage (in case of Mo.Ma device) and flow-reversal (in case of Gore Flow Reversal System) were angiographically documented, and

Abbreviations and Acronyms

CAS = carotid artery stenting
CCA = common carotid artery
CEA = carotid endarterectomy
ECA = external carotid artery
ICA = internal carotid artery
MACCE = major cardiac and cerebral event
TIA = transient ischemic attack

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back-pressure was registered. After this, the lesion was carefully crossed with a 0.014-inch steerable coronary guidewire. Pre-dilation of the stenotic lesion was performed in 17 (68.0%) patients with low-profile coronary balloons of 2.5 to 3.5 mm in diameter. In all patients a single self-expanding stent was successfully deployed that was post-dilated with slightly undersized balloons (5.0 to 5.5 mm in diameter) to achieve a good stent apposition and adequate lumen diameter (Table 2, Figs. 2 and 3).

Independent neurological evaluation was routinely performed, typically by different neurologist–whoever was on-call–before and immediately after the procedure as well as at discharge and at 30 days after procedure. All patients underwent routine carotid ultrasound at 24 h and 30 days after procedure to evaluate stent patency. All patients were prescribed aspirin (100 mg daily) indefinitely and clopidogrel (75 mg daily) for 30 days after index procedure. Clinical follow-up was routinely scheduled at 1 month and 6 and 12 months for all patients.

Definitions. Post-procedural carotid and cerebral flow was categorized according to the Thrombolysis In Myocardial Infarction grading system (6). Grading of the angiographic images was made by an independent investigator who was unaware of the clinical characteristic and the clinical outcome of the patient. Procedural success was defined as the successful treatment of the culprit lesion in the ICA together with restoration of normal antegrade flow (Thrombolysis In Myocardial Infarction flow grade 3). Clinical success was defined as procedural success without the occurrence of any major cardiac and cerebral event (MACCE). A MACCE was defined as occurrence of any death of cardiovascular or neurological cause, myocardial infarction, new ischemic stroke, or symptomatic intracerebral hemorrhage. Major stroke was defined as a stroke that caused more than 4 points worsening in the National Institutes of Health Stroke Scale or worsening of at least 1 point in the modified Rankin Scale during follow-up. Any other stroke that did not fulfill the aforementioned criteria was classified as minor stroke.

The procedures were performed after signed informed consent form was obtained from every patient or from his/her closest relatives in cases where the patient was declared unable to consent.

Table 1. Patient Clinical and Angiographic Data (n = 25)

Patient age, yrs	70.9 ± 8.7
Age ≥80 yrs	10 (40.0)
Male	19 (76.0%)
Cardiovascular risk factors	
Smokers	9 (36.0)
Hypertension	19 (76.0)
DM	3 (12.0)
Dyslipidemia	20 (80.0)
Family history of CAD	9 (36.0)
NIHSS	13.9 (5–30)
History of CAD	9 (36.0)
History of PAD	5 (20.0)
Previous CABG	1 (4.0)
Left internal carotid involvement	13 (52.0)
Right internal carotid involvement	12 (48.0)
Symptomatic status	20 (80.0)
Presence of thrombus	13 (52.0)
Asymptomatic	5 (100)
Symptomatic	8 (40.0)
Contralateral ≥50% stenosis	3 (4.0)
Calcification	16 (64.0)
Unfavorable aortic arch	
Type II	12 (48.0)
Type III	1 (4.0)
Vessel tortuosity	
Distal to the lesion	7 (28.0)
Proximal to the lesion	2 (8.0)
ECA stenosis	6 (24.0)

Data reported as mean ± SD, n (%), or mean (range).

CABG = coronary artery bypass grafting; CAD = coronary artery disease; DM = diabetes mellitus; ECA = external carotid artery; NIHSS = National Institutes of Health Stroke Scale; PAD = peripheral artery disease.

Results

Procedural and clinical success was achieved in all patients (100%). Neurological complications during the in-hospital period did not occur. One patient developed a groin hematoma that was treated conservatively without blood transfusion and resolved within 5 days.

Proximal protection was successfully applied in all but 1 patient (96.0%). One patient developed acute myocardial infarction at day 21 after procedure that was treated successfully with primary percutaneous coronary intervention. Thus, the 30-day MACCE rate was 4.0%, whereas the stroke/death rate during the same period was 0%.

Follow-up at 12 months was available for all patients. Neurological events did not occur. One patient died from no cardiovascular or neurological cause—bronchogenic carcinoma—3 months after CAS procedure. The 12-month MACCE rate was thus 4.0%, whereas the 12-month death/stroke rate was 4.0%.

Routine examination by carotid duplex ultrasonography at discharge and at 30 days showed patent stents in all 25 treated patients. Ultrasound examination at 6 months was available in 19 (76.0%) patients. All stents appeared patent without significant restenosis.

Discussion

Pre-occlusive atherosclerosis with or without presence of thrombus is the most common cause of angiographic string sign. It usually occurs in the very proximal part of the ICA. Circumferential enlargement of the plaque produces hemo-

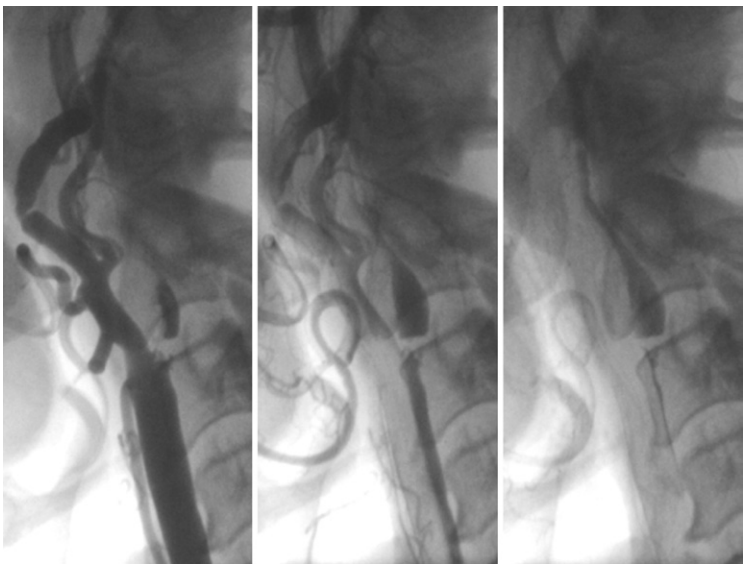

Figure 1. Angiographic Appearance of String Sign

The **left panel** shows the external carotid artery filled with contrast, whereas the internal carotid artery shows a tight, flow-limiting lesion at the ostium. The **middle** and the **right panel** show the internal carotid artery with reduced caliber, whereas the contrast in the external carotid artery is already washed away.

dynamically significant stenosis with reduction of the flow distal to the stenosis, which leads to lumen collapse of the distal extracranial and the intracranial ICA producing the string sign (7,8). Despite the angiographic narrow appearance of the distal collapsed ICA, the more distal artery is usually not diseased and resumes normal flow and diameter after revascularization, either surgical or endovascular (9).

String sign was observed only in 25 of 416 CAS patients (6.0%). This figure might underestimate the real incidence of string sign. Previous studies have indicated the difficulty of Duplex ultrasound in differentiating patients with total occlusion of the ICA with those with string sign (1,10) Wide application of modified duplex scanning protocols in patients with phenomenally occluded ICA might increase the number of patients diagnosed with string sign instead of total occlusion of ICA (10).

Table 2. Cerebral Protection Devises and Stents*

Protection devices	
Mo. MA	16 (64.0)
Gore Flow Reversal System	8 (32.0)
FiterWire EZ	1 (4.0)
Stents	
Precise	10 (40.0)
Cristallo	9 (36.0)
Carotid Wallstent	3 (12.0)
Acculink	2 (8.0)
Exponent	1 (4.0)

Data reported as n (%). *Mo.Ma, Invatec, Roncadelle, Italy; Gore Flow Reversal System, W. L. Gore, Inc., Flagstaff, Arizona; FilterWire EZ, Boston Scientific, Natick, Massachusetts; Precise RX, Cordis, Miami Lakes, Florida; Cristallo, Invatec; Carotid Wallstent, Boston Scientific; RX Acculink Carotid stent, Abbott Park, Illinois; and Exponent Carotid Stent System, Minneapolis, Minnesota.

Previously, patients presenting with angiographic string sign were considered as candidates for urgent carotid endarterectomy (CEA). Early studies have demonstrated that patients suffering from string sign are at higher risk for perioperative complications and stroke when treated with CEA (3,11). By contrast, data from the NASCET (American Symptomatic Carotid Endarterectomy Trial) showed perioperative safety comparable to that of patients who underwent CEA with less severe stenosis but a lesser degree of stroke reduction (12). Another study reported that CEA performed in the presence of string sign and critical carotid stenosis did not affect the outcome (13). In the ECST (European Carotid Surgery Trial), symptomatic patients with high-grade stenosis and post-stenotic narrowing of the ICA who were treated medically showed significantly lower rates of ipsilateral stroke compared with those with lesser degree of stenosis (14). This led some centers to abandon emergent CEA management and treat those patients pharmacologically with anticoagulation and/or aspirin (9).

Percutaneous treatment of patients with string sign with CAS is also a matter of contradiction. It has been associated with a higher risk of thromboembolic complications and has even been considered as a contraindication for CAS. This was due to the possible presence of thrombus or ruptured, unstable plaque leading to the string sign itself, which might predispose to elevated rates

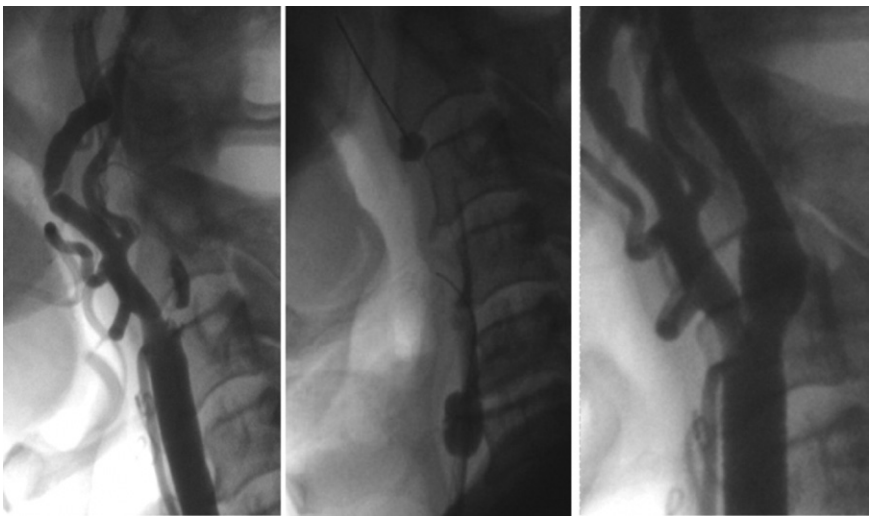

Figure 2. Carotid Stenting Procedure With Proximal Protection Device in a Patient With String Sign

Angiographic appearance of string sign at baseline **(left)**, during proximal cerebral protection **(middle)** with 1 balloon occluding the external carotid artery and 1 balloon occluding the common carotid artery and staining of a modest quantity of contrast. Final angiographic result after stent placement and removal of the protection device **(right)**.

of cerebral embolism and stroke. Most of the CAS studies and registries cite string sign among their exclusion criteria (15–17). Previous studies have reported, contrary to the dominant clinical impression, encouraging results for patients with string sign undergoing carotid stenting (4,18). The relatively low rate of MACCE observed in our study confirm the encouraging results of these reports. The increasing experience in CAS techniques, the improvement of devices, and the availability of new proximal cerebral protection systems led us to the assumption that CAS might be a feasible and safe option to treat symptomatic patients with string sign. Given that the majority of the patients were symptomatic with elevated risk for complications and the degree of difficulty of these procedures, the outcome of our patients is considered favorable (19). A significant role in these encouraging results was played by the close cooperation among different specialties (cardiologists, neurologists, and vascular surgeons) managing patients with advanced carotid artery disease, collaborating within a solid multidisciplinary team. Careful patient selection and adequate experience in complex CAS procedures as well as in the usage of proximal protection devices should be considered mandatory to achieve low rates of periprocedural complications.

Previously, the annual risk of stroke in symptomatic patients with ICA near-occlusion who have been treated medically was 11.1% (12). Even though direct comparison

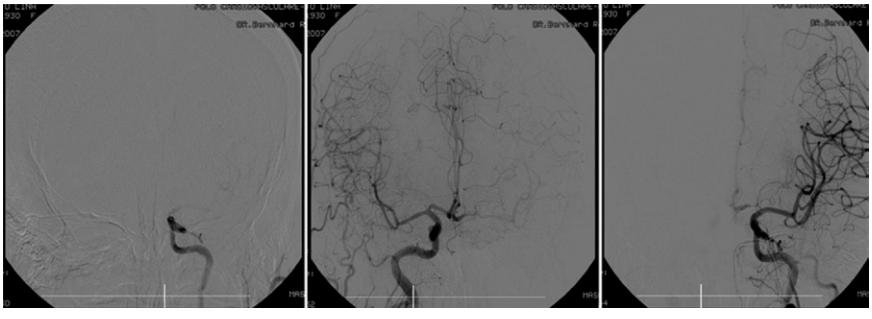

Figure 3. Intracerebral Angiography Before and After Carotid Stenting in a Patient With String Sign

Intracerebral angiography obtained from the patient shown in Figure 2 with selective injection into the common carotid arteries. The **left panel** shows reduced intracranial flow of the left internal carotid artery at baseline. The **middle panel** shows intracranial arteries after injection of the right common carotid artery, and the **right panel** shows flow after stent implantation in the left carotid artery.

between previous data and ours cannot be done, the low annual death/stroke rates observed in our study demonstrate that CAS might be a considerable treatment option in symptomatic patients with string sign. It should be noted, however, that the small numbers of patients included in this study together with its retrospective nature signify that larger, prospective trials, testing CAS in patients with string sign, are required before real clinical efficacy of this endovascular treatment modality is granted.

In patients with string sign, the indications for performing CAS are yet unclear, especially for the asymptomatic ones. The main reason for proceeding with CAS in the asymptomatic patients was the angiographically documented presence of fresh thrombus at the site of carotid stenosis. In cases like that, the multidisciplinary team—consisting of the interventionalist, a vascular surgeon, and a neurologist—felt that there was high probability for embolization and unanimously decided to proceed into CAS.

Proximal protection devices were used in 96.0% of the cases. Use of proximal protection devices seems to be better in cases of string sign, because they offer the advantage of complete protection during all phases of the procedure, even before lesion crossing. Application of a distal type of protection device—either filter or occlusion balloon—would be rather difficult, because the estimation of the caliber or the anatomy of the distal ICA to accommodate a distal type of protection device is almost impossible. Furthermore, crossing the culprit carotid lesion with a filter or occlusion balloon could create emboli to the brain with potentially devastating results, especially in the presence of fresh thrombus. Importantly, as seen from our series, significant stenosis of the ECA is not a contraindication for application of the proximal protection devices. In 6 of 24 patients treated with proximal protection device who had significant ECA stenosis, we identified no complications. At the end of the procedure, ECA remained intact without any damage. This observation is in accordance with previous reports indicating that significant ECA stenosis does not preclude application of proximal clamping as protection device during CAS (20).

Study limitations. The major limitation of the study is its retrospective nature. The number of patients included in this study is small, and therefore the comparison of the present results with other published reports must be interpreted with great caution. Not all patients had ultrasound follow-up at 6-months; therefore, asymptomatic restenosis might have not been identified in the rest of the patients.

Conclusions

Carotid stenting in patients with string sign seems to be a feasible alternative to CEA, with low procedural complications and favorable outcome. Application of carotid stenting in all patients requires careful patient selection from an experienced multidisciplinary team able to identify and treat patients with advanced carotid artery disease. Whether universal application of carotid stenting as a treatment modality in patients with carotid disease and sting sign will reduce future stroke events needs to be clarified further with larger controlled trials.

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Key Words: carotid stenting ■ proximal protection ■ string sign.