Carotid artery stenting: current role of proximal neuroprotection and technical advancements in stroke prevention

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For more than 50 years, carotid endarterectomy has been considered the gold standard therapy to prevent stroke in patients with carotid artery disease. Carotid artery stenting (CAS) has emerged in the last 15 years as minimally invasive alternative to surgery, especially in patients at high surgical risk. Recent randomized trials have challenged this concept reporting a relatively high incidence rate (4–6%) of post-CAS neurological adverse events. The aim of this study is to evaluate the current role of CAS in all-comers with advanced carotid disease, managed with mandatory proximal neuroprotection in a high-volume centre. From our database, the last 393 consecutive patients, from January 2011 to August 2013, undergoing CAS under proximal neuroprotection were analysed (mean age 72 ± 8 years). Indications included symptomatic stenoses ≥ 60% (n = 87; 22%) and asymptomatic stenoses ≥ 80% (n = 306; 78%). In an intention-to-treat approach, CAS success rate was 100%. The in-hospital all stroke/death rate was 1% (minor stroke 1%, major stroke 0%, and death 0%), and the rate of myocardial infarction was 0.3%. The minor stroke rate was 2.3% in symptomatic patients and 0.7% in asymptomatic patients. Carotid artery stenting performed in a high experience centre with the use of proximal embolic protection device is safe and has a low incidence rate of stroke.

KEYWORDS
Carotid artery stenosis; Carotid artery stenting; Proximal embolic protection

Introduction

For more than 50 years, carotid endarterectomy (CEA) has been considered the standard treatment for severe asymptomatic and symptomatic carotid stenoses. Carotid artery stenting (CAS) has emerged in the last 15 years as minimally invasive alternative to surgery, but its role remains highly controversial as recent randomized trials reported a relatively high incidence rate of CAS-related neurological adverse events. However, some experts debate these findings and the design of the trials, mainly questioning the insufficient expertise of the operators selected and the constant use of the embolic protection devices (EPDs).

Today, the operators have more efficient devices for preventing brain damage. The proximal EPD has shown to reduce the risk of stroke in many studies. The different stent structures give us the possibility to tailor the procedure to different subsets of lesions. We believe that the operator expertise, both in terms of skill and patients’ selection, and the use of newest technologies are the cornerstone to cut down the incidence of CAS neurological adverse events.

The aim of this study is to describe the current role of CAS in the management of consecutive patients with advanced carotid disease, managed with mandatory proximal neuroprotection in a high-volume centre.
Methods

We analysed retrospectively all consecutive patients (393 CAS procedures) affected by severe carotid artery disease treated in our laboratory from January 2011 to August 2014 with stenting under a proximal neuroprotection device. Our population is 66.1% of all the CAS procedures (595) performed in our laboratory from January 2011 to August 2014. Indications for treatment were symptomatic patients with a diameter stenosis of ≥60% or asymptomatic patients with a diameter stenosis of ≥80%. Symptomatic was defined the patient who had ipsilateral neurological symptoms in the last 6 months. Contraindications to the use of proximal neuroprotection device were the presence of severe peripheral artery disease, preventing the use of large sheath required by proximal neuroprotection devices and the association with severe disease of external carotid artery and common carotid artery. Occlusion of contralateral internal carotid artery is a relative contraindication, in the presence of an adequate function of circle of Willis. The clinical endpoints were in-hospital stroke, myocardial infarction (MI), or death. Stroke was defined as a new neurological deficit that persist ≥24 h categorized as minor stroke if the clinical features either resolved completely within 30 days or persisted ≥30 days with the National Institutes of Health Stroke Scale (NIHSS) ≤3; as major stroke if features persisted ≥30 days with the NIHSS ≥4. Fatal stroke was defined as death attributed to a stroke. Myocardial infarction was defined according to the universal definition. All patients provided informed consent for both the procedure and subsequent data collection and analysis for research purposes.

Procedure description

All patients were treated with aspirin (100 mg daily or a loading dose of 250 mg the day before the procedure in naïve patients) and clopidogrel (75 mg daily and or a loading dose of 300 mg the day before the procedure in naïve patients). During the procedure, unfractionated heparin was administered to obtain an activated clotting time of ≥250 s. Using transfemoral access, an angiogram of the aortic arch and selective bilateral carotid and intracranial angiograms were obtained. The Mo.Ma™ Ultra (Medtronic, Inc., Minneapolis, MN, USA) was the only proximal EPD used. Pre-dilatation of the lesion was at discretion of the operator and it was performed in case of severely calcified lesions and in stenoses >85–90%. The diameter of the stents was adapted to the reference diameter of the internal and common carotid artery. The choice of stent type was at discretion of the operator, based on the morphological features of the plaque and vessel anatomy. Two types of stent structures were used. The closed-cell design stent was preferred in the case of straight vessels and soft plaques, whereas the hybrid-cell design stent was preferred in the case of tortuous vessel to accommodate the vessel anatomy. Post-dilatation was mandatory as our common practice. After post-dilatation, control angiograms of the ipsilateral extra- and intracranial carotid were performed in two planes to ensure the correct placement of the stent, exclusion of vessel dissection, spasm, or intracranial embolization. After verification of the technical result, the protection system was retrieved. During the intervention, neurological monitoring was repetitively performed by the operator. The day after the procedure a neurological examination was performed by a neurologist and in case of new focal neurological deficits a cerebral computed tomography was performed at the onset of symptoms and 48 h later.

Statistical methods

Continuous variables are presented as means ± standard deviation, and categorical variables as frequencies (%). Normality of the distribution of continuous variables was tested by means of the Kolmogorov–Smirnov goodness-of-fit test. All analyses were based on an intention-to-treat approach. Exploratory univariate analysis was performed to assess the predictors of stroke by means of logistic regression analysis. The result was reported in adjusted odds ratio (OR) with associated confidence intervals (CIs). Statistical analysis was performed using the SPSS software (version 16.0; SPSS, Inc., Chicago, IL, USA).

All patients gave their informed consent to the procedures. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

We analysed 393 CAS belonging to our database from January 2011 to August 2013. Baseline clinical characteristics are summarized in Table 1. About 73% of patients were male and mean age was 72 ± 8 years. Eighty-seven patients (22%) were symptomatic. Pre-dilatation was performed in case of severely calcified lesions or stenoses >85–90% and post-dilatation in 100%. In 135 (34.3%) patients was implanted a hybrid-cell design stent and in 258 (65.6%) patients a closed-cell design stent. The procedural success rate was 100%. In-hospital outcome is reported in Table 2.

We observed 4 (1%) cases of in-hospital stroke, all of them

<table>
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<tr>
<th>Table 1 Baseline characteristics</th>
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<tr>
<td>Patients, n</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Age (year), mean ± SD</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Hypercholesterolaemia, n (%)</td>
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<td>Coronary artery disease, n (%)</td>
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<td>Symptoms in the last 6 months</td>
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<tr>
<td>Antiplatelet therapy with ASA</td>
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<td>Statins therapy</td>
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ASA, acetylsalicylic acid.
minor. Two events occurred in asymptomatic patients and 2 in symptomatic patients. One event occurred during the procedure in cathlab, and the other during the following hours in the medical ward. One patient had in-hospital MI due to major bleeding and severe anaemia. No death was observed. The risk of stroke was higher in symptomatic compared with asymptomatic patients (OR 3.5, 95% CI 0.49–25.76), although not statistically significant because of the low rate of events.

Discussion

The main idea of this paper is that CAS, if performed in a high experience centre with the use of proximal EPD and associated with a tailored strategy based on the clinical and morphological aspects of each patient, is safe and has a low incidence rate of stroke.

Today, the main debated issue of carotid stenting is the relative high risk of neurological events showed in the recent trials comparing CAS with CEA. However, these randomized studies were burdened by several limitations:

(i) limited endovascular expertise required for the operators performing CAS;
(ii) limited use of proximal neuroprotection EPD. The distal filter devices may not adequately protect the brain in all settings, due to incomplete apposition to the vessel wall, lack of protection during placement of the device, and passage of microemboli smaller than the filter pore size;
(iii) many CAS procedures were performed with implantation of stents with an open-cell design. This stent frame may have insufficient lesion scaffolding properties and allow for intra-strut plaque prolapse, which could lead to embolization.

The CAVATAS trial, performed in the late 1990s, randomized 504 symptomatic patients at a low-to-moderate risk for surgery to CEA or CAS. This study was criticized because of a low stenting rate (26%). An EPD was unavailable at the time. The incidence rate of death or stroke at 30 days was 10.0% in the endovascular group and 9.9% in the surgical group. The SAPPHIRE study randomized 334 patients at a high risk for surgery to CAS with the systematic use of EPD or CEA. Only an open-cell design stent was allowed. The primary endpoint showed a trend in favour of CAS (12.2% vs. 20.1%). The SPACE study, which included 1200 participants, found no difference between patients allocated to CAS or CEA, with an event rate of 6.8 and 6.3% at 30 days, respectively. The EPD was used in a minority of CAS patients and both open-cell and closed-cell design stents were used. The EVA-3S trial, which included 527 patients, was stopped prematurely because of a significantly increased event rate among patients allocated to endovascular treatment (death or stroke 9.6 vs. 3.9%). The EPD was used in 78–97% of procedures and closed-cell design stents in 60%, whereas open-cell design stents in 40% of cases. The ICSS study randomized 1713 symptomatic patients. The use of EPD was not mandatory in this trial, and both closed-cell and open-cell design stents were used. The incidence rate of disabling stroke or death at 120 days did not differ (4.0% in the CAS group and 3.2% events in the CEA group), but there was an excess of overall strokes in the endovascular arm (HR 1.92, 95% CI 1.27–2.89; P = 0.002). Finally, the CREST trial randomized 2502 symptomatic and asymptomatic patients with embolism protection or CEA. Only an open-cell design stent was allowed. The 4-year rate of stroke or death was 6.4% with CAS and 4.7% with CEA (HR 1.50; P = 0.03). Periprocedural event rates differed between the CAS and CEA for stroke (4.1 vs. 2.3%, P = 0.01) and MI (1.1 vs. 2.3%, P = 0.03), but beyond 30 days, the incidence rates of ipsilateral stroke with both CAS and CEA were low (2.0 vs. 2.4%; P = 0.85). Importantly, in the second half of the study, the rate of stroke in the CAS arm, but not in the CEA arm, showed a significant reduction, suggesting a learning curve effect in the endovascular arm.

Although the insufficient expertise, both in terms of skills and in patient selection, may be the main factor leading to a relative high risk of stroke after CAS in the real world, today the technical limitation mentioned above could be overcome by the recent technology advancements.

Proximal embolic protection

Proximal EPD protects the brain by interrupting or reversing the blood flow at the level of the carotid bifurcation at the time of the procedure. The main advantages of proximal protection include crossing of the lesion under protected conditions as well as the blockage of both macro- and microemboli. Finally, with proximal protection, there is no placement of a device in the distal internal carotid artery, and this may reduce the risk of arterial spasm, dissection, or intimal damage. The MoMa III system

Table 2  In-hospital events

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
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<tr>
<td>Patients, n</td>
<td>393</td>
<td>306</td>
<td>87</td>
</tr>
<tr>
<td>Any stroke, n (%)</td>
<td>4 (1.0)</td>
<td>2 (0.7)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Major stroke, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minor stroke, n (%)</td>
<td>4 (1.0)</td>
<td>2 (0.7)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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MI, myocardial infarction.
consists of an 8F or 9F sheath with an effective working channel of 5F and 6F sheaths, respectively, and two independently inflatable balloon catheters. The distal balloon occludes the external carotid artery, whereas the proximal balloon occludes the common carotid artery. When inflated, both balloons prevent flow in the internal carotid artery at the lesion site. As a result, the carotid lesion can be crossed and treated under flow blockage, preventing cerebral embolization. After the lesion is treated, three 20 mL syringes of carotid blood are aspirated and checked for debris before deflating the distal and then the proximal balloons, re-establishing cerebral blood flow. The available clinical experience consisted of five multicentre registries and one large-scale single-centre registry, and has been summarized in a meta-analysis. Among 2397 patients, 31% of them being symptomatic, the 30-day rate of composite stroke, MI, or death was 2.25% composed by 1.71, 0.02, and 0.40%, respectively.

Stent design

Recently, it has been recognized that the stent itself may substantially add to embolic protection in CAS through adequate scaffolding of the plaque once the EPD has been removed. The ideal properties of a carotid stent are a well-balanced mix of high flexibility and conformity, to accommodate tortuous anatomy, as well as high plaque coverage, to prevent late embolization of debris. Stent structure is characterized by sequential aligned annular rings interconnected by bridges, and the design may be either open-cell or closed-cell, depending on the density of the bridges between the rings.

Open-cell design stents present some of the segments free from the adjacent rings, allowing greater adaptation to the vessel anatomy at the price of less plaque coverage and higher risk of tissue prolapse. Closed-cell design stents are characterized by higher density of bridge interconnection, which reduces their conformability and increases the probability of malapposition, but at the same time, offers greater plaque coverage. A hybrid configuration with an open-cell design of the proximal and distal segments combined with a closed-cell design of the central segments has been recently developed. The impact of stent design on CAS clinical outcomes has not been adequately addressed. Schillinger et al.11 analysed 1684 patients undergoing CAS and did not found a superiority of a specific carotid stent design with respect to neurological complications. Timaran et al.12 did not found significant difference in subclinical cerebral embolization, as detected by transcranial Doppler and diffusion-weighted magnetic resonance imaging, in 40 patients randomized to CAS with open- or closed-cell design stents. An insight into the impact of stent design and in the pathophysiology at the lesion level at the time of CAS comes from a prospective single-centre study enrolling 40 consecutive patients and designed to evaluate the rate of stent malapposition, plaque prolapse, and thin cap fibroatheroma rupture according to stent configuration by optical coherence tomography (OCT).13 On OCT analysis, the frequencies of malapposed struts were higher with closed-cell compared with open-cell and hybrid design stents (34.5 vs. 15 and 16.3%, respectively; P < 0.01). Plaque prolapse was more frequent with open-cell than closed-cell (68.6 vs. 23.3%; P < 0.01) and hybrid stents (30.8%; P < 0.01). Significant differences were also noted in the rates of fibrous cap rupture between closed-cell and open-cell (24.2 vs. 43.8%; P < 0.01), and between closed-cell and hybrid design (39.6%; P < 0.01) stents, but not between open-cell and hybrid design stents (P = 0.4).

This study showed that, while stent malapposition was more common following closed-cell design stent implantation, plaque prolapse was more common in patients treated with open-cell design devices, but a correlation to clinical events remains to be demonstrated.

Conclusions

Carotid artery stenting is a reasonable therapeutic alternative to treat carotid artery atherosclerosis in well-experienced high-volume centres. These data suggest that the use of technical advancements may significantly contribute in improving clinical in-hospital outcomes.

Conflict of interest: none declared.

References


