

# INVASIVE TREATMENT OF SYMPTOMATIC CAROTID ARTERY STENOSIS – PRESENT STATUS OF CAROTID ENDARTERECTOMY AND CAROTID ANGIOPLASTY

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**SUMMARY** – In this paper we present carotid angioplasty with stenting (CAS) as a relatively new endovascular treatment for carotid stenosis. It has become an established alternative to carotid endarterectomy (CEA) for high-risk patients not eligible for surgery. After presenting data on CEA and CAS and studies comparing CEA and CAS, our results comparing the outcome of patients after CAS and carotid endarterectomy (CEA) are presented. Until December 2004, 183 patients with carotid artery disease (37% of asymptomatic and 63% of symptomatic internal carotid artery stenosis), mean age 68 years, were followed up for 133 days. During the first 24 hours of percutaneous transluminal coronary angioplasty with stenting (stent-PTA), 4 (2.2%) patients had transient ischemic attack (TIA) and 3 (1.5%) patients suffered stroke, and within 30 days post-intervention, another patient presented with TIA and another 2 patients had stroke. Overall 12 of 183 patients (6.6%) had cerebrovascular event (6 TIA and 6 stroke) during the 6-month follow up period. Clinical prognosis of this cohort treated with stent-PTA is comparable with data published in the literature.

**Key words:** *Carotid stenosis – therapy; Endarterectomy – carotid, stents; Cerebrovascular accident – prevention and control*

## Introduction

Stroke is the third leading cause of death after ischemic heart disease and cancer worldwide<sup>1</sup>. Approximately 20% of patients die within the first year of having stroke and another 30% stay disabled. The risk of recurrent stroke is highest within the first 30 days. Altogether, 20% of patients will experience another ischemic event in the following two years.

An important cause of transient ischemic attack (TIA) and stroke is atherosclerotic carotid artery stenosis. It accounts for about 20% of cases of brain infarction and has the highest recurrent stroke risk compared to all other subtypes of stroke<sup>2,3</sup>. Therefore, rapid intervention in this patient group is needed and they should be managed efficiently to minimize the incidence of stroke.

## Symptoms

Unfortunately, only 15% of stroke patients first present with classic TIA symptoms including slurred speech (dysarthria), limb weakness or numbness, transient monocular blindness (amaurosis fugax), unsteadiness (ataxia) or difficult speaking (dysphasia)<sup>4</sup>. However, patients presenting with these symptoms should be examined and screened for carotid stenosis within 24-48 hours of symptom onset. In the absence of treatment, the one-month incidence of stroke following TIA is approximately 5%-10%. Twelve percent of patients will sustain a stroke within the first year, and one-third of patients within 5 years. Therefore, an appropriate treatment may reduce their risk of having a major disabling or fatal stroke.

## Diagnosis

Intra-arterial digital subtraction angiography (DSA) is the gold standard for identification and quantifica-

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tion of carotid artery stenosis. Nonetheless, other non-invasive imaging methods are being increasingly used. Doppler and Duplex ultrasonography (DUS) and contrast enhanced magnetic resonance angiography (CEMRA), when compared with DSA, have a high sensitivity and specificity for occlusion and 70%-99% stenosis<sup>5</sup>. Computed tomography angiography (CTA) has a sensitivity and specificity similar to CEMRA for occlusion, but somewhat lower sensitivity and specificity for detection of 70%-99% stenosis<sup>5</sup>.

In daily practice, DUS is the most often used imaging technique. It is less expensive, reliable and suitable for bedside diagnosis. The most common sites for plaque formation, i.e. the origin of the common carotid artery (12.4%), the internal carotid artery (ICA) just above the bifurcation (22.3%), the origin of the middle cerebral artery (4.1%) and the basilar artery (8.7%) can be examined in a great majority of patients.

U-King-Im *et al.* report that the most cost-effective diagnostic strategy is the use of DUS and CEMRA in carotid artery stenosis. Only if DUS is negative and CEMRA is positive, DSA should be performed<sup>6</sup>.

## Management

Patients with symptomatic carotid artery stenosis should be treated in order to reduce their mostly embolic and in a lesser degree hemodynamic risk of stroke. Depending on the patient's overall condition, his age and degree of stenosis, medication, surgery and less invasive endovascular treatment may be considered.

The standard surgical treatment, carotid endarterectomy, has been widely used. Carotid artery angioplasty with stenting is the second choice and is currently being used in selected patients who are at a high risk of surgery, and in controlled clinical trials.

## Carotid Endarterectomy (CEA)

In 1954, the first endarterectomy was performed in a patient with symptomatic carotid artery stenosis. Over years, it has evolved to become a routine surgical treatment for carotid stenosis although no appropriate clinical trials have confirmed its benefits. In 1998, two large randomized controlled trials of endarterectomy *versus* medical treatment published their results. Although similar in design, there were differences in inclusion and exclusion criteria, methods of determining the degree of stenosis and definitions of outcome events. The Vet-

erans Affairs Trial was the third trial and was terminated when initial results of the two large trials were published in 1991.

## ECST and NASCET

The results of both trials, the European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET), have shown that CEA, when performed with low surgical morbidity and mortality, reduces the risk of stroke in patients with high-grade carotid stenosis<sup>7,8</sup>. Both studies showed that approximately eight patients with >70% stenosis would have to be treated to prevent one ipsilateral stroke in a five-year period after surgery.

For patients with moderate symptomatic stenosis (50% to 69%), NASCET reported greater benefit of endarterectomy compared with medically treated patients, whereas ECST showed no significant benefit. NASCET showed that 15 patients with 50% to 69% stenosis would have to be treated to prevent one stroke within five years. No significant benefit of endarterectomy was shown for patients with symptomatic <50% carotid stenosis in either trial. These results established CEA as the gold standard procedure for the prevention of a recurrent ischemic event in symptomatic patients with ipsilateral carotid stenosis greater than 70%.

Both studies showed that the benefit of endarterectomy was greater for men than for women, for patients aged 75 and older, and for patients with hemispheric symptoms. Also, the patients who had sustained a stroke three months prior to the procedure would benefit more from surgery than those with TIA. Studies suggested that a higher risk of preoperative ischemic event or death existed in patients with diabetes, elevated blood pressure, contralateral carotid occlusion and left-sided disease. Also, patients randomized for surgical treatment within 2 weeks after their last ischemic event benefited more from surgery<sup>9</sup>.

## EUSI Recommendations

In 2003, the European Stroke Initiative (EUSI) Executive Committee updated an overview of established and widely used therapeutic strategies first published in 2000. According to this overview, conventional angiography or one of the noninvasive investigations may be used to visualize and determine the degree of carotid artery stenosis. The patients suitable for CEA are those with stenosis greater than 70% and without a severe

neurological deficit with recent (<180 days) ischemic events. These recommendations apply if the center's perioperative stroke and death rate is less than 6%. CEA may also be performed in patients with 50% to 69% stenosis, free from a severe neurological deficit only if the perioperative stroke and death rate is less than 3%. Centers where complication rates are not similar to those documented in NASCET or ECST should not perform CEA. For patients with stenosis of less than 50% EUSI does not recommend CEA. In addition, all treated patients should remain on antithrombotic therapy before, during and after surgery, and should be followed-up by the surgeon and the neurologist.

### Carotid Angioplasty with Stenting

Carotid angioplasty with stenting (CAS) is a relatively new endovascular treatment for carotid stenosis. Although it does not have a long history, it has become an established alternative to CEA for high-risk patients not eligible for surgery. It is a minimally invasive procedure requiring only a small incision in the groin and local anesthesia.

A stent is a small tube made of nickel-titanium, a bendable metal that springs back after being bent, and is in current practice self-expendable after placement. Emboli protection devices (EPD) have also been designed to protect the brain from embolization during stenting. It is used to catch the small particles that may be dislodged from the plaque into the brain circulation, which may help reduce the incidence of stroke during the procedure. To improve the safety of endovascular treatment, new designs of stents (like drug-eluted stents), delivery systems, and EPD are being constantly designed.

### Risks

The risk of radiation exposure and allergic reaction to the dye used during the procedure is very low. Stents can be overgrown by the surrounding tissue, which may cause restenosis or even occlusion of the vessel. The release of multiple emboli has also been reported during CAS. Some studies have shown that the use of EPD lowers the risk of embolization. Wholey *et al.* have reported on a stroke/death rate of 2.23% when EPD was used. On the other hand, when the procedure was done without protection, stroke/death occurred in 5.29% of treated patients<sup>10</sup>. Cremonesi *et al.* have reported on a stroke/death rate of 1.1% with a cerebral protection device<sup>11</sup>.

### Advantages

Patients treated with CAS avoid surgical incision on the neck with the risk of facial nerve injuries and general anesthesia, and stay shorter in the hospital. This procedure makes possible to treat surgically inaccessible sites of the artery and is most effective in treating restenosis after CEA.

### Trials

To better define the indications for CAS *versus* CEA, several randomized prospective trials have been designed. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) showed no difference in major outcome events between endovascular treatment and carotid endarterectomy, but the 30-day death and stroke rate of carotid surgery was higher than desirable, i.e. 10.0% *versus* 9.9% for CEA<sup>12</sup>. This study also reported that high-grade carotid restenosis was more frequent one year after CAS than after carotid surgery. In the SAPPHERE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) study, 334 patients were included (96 symptomatic and 219 asymptomatic)<sup>13</sup>. This trial has suggested that stenting with protection is not inferior and may be superior to CEA in terms of a combined end point including stroke, myocardial infarction and death.

In North America, the CREST (Carotid Revascularization Endarterectomy *versus* Stent Trial) protocol has been initiated. Its randomization goal is 1200 to 1600 symptomatic patients. In Europe, three ongoing trials, SPACE (Stent Protected Angioplasty *versus* Carotid Endarterectomy), EVA-3S and ICSS (International Carotid Stenting Study, CAVATAS-2), are recruiting symptomatic patients for randomization between CEA and CAS. The SPACE study planned to include 1200 patients by the end of 2005, which was a goal for an interim analysis. First published results were expected in the second half of 2006.

The main inclusion criteria in the SPACE study are:

- symptoms associated with stenosis within the last 6 months
- Rankin scale 0-3
- age  $\geq 50$
- ultrasound confirmed ICA stenosis of 70% and more

The main exclusion criteria are:

- former surgical or endovascular treatment of stenosis

- tandem stenosis with distally higher degree of stenosis
- intracranial bleeding within the last 3 months
- stenosis following radiation
- life expectancy <2 years
- contraindication to contrast media, heparin, ASA, clopidogrel

### EUSI recommendations

As well as for CEA, EUSI made specific recommendations for selection of patients eligible for endovascular procedure. According to this recommendation, carotid PTA with stenting may be performed in patients with contraindications for CEA or with stenosis at surgically inaccessible sites and in patients with restenosis after initial CEA or stenosis following radiation. All patients undergoing CAS should receive a combination of clopidogrel and aspirin immediately before, during and at least for one month after the procedure.

Although several trials showed that CAS is as safe and effective as CEA, its use should still be limited to controlled trials and ethics committee approved case series. One such study started in Graz in 1999.

### Patients and Methods

Until December 2004, 183 patients with carotid artery disease (37% of asymptomatic and 63% of symptomatic ICA stenosis), mean age 68 (range 20-84) years, 64% men, were included. Inclusion criteria were unilateral carotid stenosis and no evidence of a severe permanent neurological deficit. Before CAS, extracranial blood vessels were examined by color duplex ultrasonography and magnetic resonance angiography (MRA). Emboli protection devices were used in 81% of the procedures. Clinical and sonographic assessments were repeated on 1 day, at 1 month, 3 months and 6 months of stent deployment. The mean follow up was 133 days. The study was approved by the local ethics committee, and a signed

*Table 2. Complications in the first 66 procedures*

	<6 months
No complication	57
TIA	4
Stroke/minor stroke	5

informed consent was obtained for all procedures.

### Results

During the first 24 hours of percutaneous transluminal angioplasty with stenting (stent – PTA), four (2.2%) patients had TIA and three (1.5%) patients suffered stroke. Within 30 days post-intervention, another patient presented with TIA and another two patients had stroke. Overall, 12 of 183 (6.6%) patients experienced a vascular event over the 6-month follow up period: six (3.3%) had ipsilateral completed stroke and TIA each (Table 1). One stroke patient died from myocardial infarction within 30 days. It is important to note that during the first 66 procedures, nine patients presented with complications (2 TIA, 5 stroke) (Table 2). The next 117 procedures resulted in a lower complication rate (2 TIA, 2 stroke) (Table 3).

### Conclusion

The clinical prognosis of this cohort of 183 patients treated with stent-PTA is comparable with data published in the literature. However, a learning curve as in all new procedures can be observed. Additional confirmatory results, such as the one from the SPACE study, should be awaited before a decision regarding CAS in routine clinical practice is made.

*Table 1. Clinical results of carotid stenting in 183 patients*

	<24 hours	Day 30	Month 6
No complication	176 (96.2%)	173 (94.5%)	71 (93.4%)
TIA	4 (2.2%)	5 (2.7%)	6 (3.3%)
Stroke/minor stroke	3 (1.6%)	5 (2.7%)	6 (3.3%)

*Table 3. Complications in the next 117 procedures*

	<6 months
No complication	113
TIA	2
Stroke/minor stroke	2

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## Sažetak

### INVAZIVNO LIJEČENJE SIMPTOMATSKE STENOZE KAROTIDNE ARTERIJE – TRENUTNO STANJE KAROTIDNE ENDARTEREKTOMIJE I KAROTIDNE ANGIOPLASTIKE

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U ovom radu predstavlja se karotidna angioplastika sa stentiranjem (CAS) kao relativno nov postupak u liječenju karotidne stenoze koji može biti zamjena za karotidnu endarterektomiju (CEA) kod bolesnika s visokim rizikom koji nisu pogodni za operacijsko liječenje. Nakon prikaza podataka i studija o karotidnoj angioplastici i karotidnoj endarterektomiji prikazuju se vlastiti rezultati usporedbe i ishoda kod bolesnika liječenih karotidnom angioplastikom i karotidnom endarterektomijom. Do prosinca 2004. godine u studiju je uključeno 183 bolesnika sa stenozom karotidne arterije (37% asimptomatskih i 63% simptomatskih stenoza unutarnje karotidne arterije), prosječne dobi 68 (raspon 20-84) godina, od kojih su 64% bolesnika bili muškarci. Prosječno vrijeme praćenja bolesnika bilo je 133 dana. Tijekom prva 24 sata nakon izvođenja karotidne angioplastike 4 (2,2%) bolesnika je zadobilo TIA, a 3 (1,5%) bolesnika moždani udar. Nakon 30 dana još jedan bolesnik je zadobio tranzitornu ishemijsku ataku (TIA), a 2 bolesnika moždani udar. Ukupno je nakon 6 mjeseci 12 od 183 (6,6%) bolesnika imalo cerebrovaskularnu bolest (6 TIA i 6 moždani udar). Ishod bolesnika u ovoj studiji je usporediv s dosadašnjim rezultatima objavljenim u literaturi.

Ključne riječi: *Karotidna stenoza – terapija; Endarterektomija – karotida, stentovi; Cerebrovaskularni incident – prevencija i kontrola*