Open Versus Endovascular Treatment for Patients with Post-Carotid Endarterectomy Restenosis: Early and Long-term Results

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Background: The aim of this study is to assess and compare the short- and long-term results of carotid artery stenting (CAS) and redo surgery in patients with restenosis after carotid endarterectomy (CEA).

Methods: From January 1988 to December 2014, 44 consecutive patients were treated for carotid restenosis (CR): 23 redo-CEA (52.3%) and 21 CAS (47.7%). Data from these patients were prospectively collected in a dedicated database. Early results and 3-year end points were analyzed and compared between groups with $\chi^2$ test, Kaplan–Meier curves, and Breslow test.

Results: Demographic characteristics and comorbidity were similar in both groups, except for arterial hypertension and chronic renal insufficiency which were higher in the CAS group. CR was symptomatic in 7 patients in the redo-CEA group (30.4%) and 1 (4.8%) in CAS ($P = 0.04$). No differences were found in the time period between primary CEA and reintervention, critical carotid stenosis, or contralateral carotid occlusion. Median follow-up was 61.5 months. In the redo-CEA group, 1 patient (4.3%) had a perioperative transient ischemic attack and 3 (13%) experienced cranial nerve injury with complete regression at 30 days. No differences were found between groups in terms of early and long-term mortality, neurologic morbidity, and overall morbidity. The rate of secondary restenosis and freedom from reintervention was similar in both groups during follow-up.

Conclusions: Both CAS and redo-CEA are suitable options for patients with CR. CAS might be the treatment of choice due to the risk of cranial nerve injuries in redo-CEA. When CAS is contraindicated, redo-CEA remains a safe and effective treatment option.

INTRODUCTION

Recurrent carotid stenosis after carotid endarterectomy (CEA) has become a controversial issue. With an incidence ranging from 2% to 38% in different reports, its management remains open to debate.

Some studies have reported a lower risk of neurologic events associated with carotid restenosis (CR) compared with primary stenosis and it has been described that carotid myointimal lesions post-CEA may regress in up to 10% of patients followed by duplex scanning. However, results from multicenter clinical trials such as Carotid Revascularization Endarterectomy versus Stenting Trial have demonstrated clinical significance of restenosis >70% with a greater risk of stroke than patients without a high-grade CR. Furthermore, some studies comparing patients having surgery for CR...
versus those without it recommend a more aggressive approach in patients with asymptomatic high-grade CR.6

The increased incidence of cranial nerve injuries and wound complications in redo-CEA due to fibrotic tissue in the surgical field7 and the promising results of carotid artery stenting (CAS) led to a paradigm shift in recent years toward an endovascular approach as the treatment of choice in the majority of centers. Nevertheless, several articles have called into question the early results and long-term durability of CAS compared with CEA of late,8 making it necessary to review the indications for endovascular treatment of carotid stenosis.

The aim of this study is to compare the major adverse events as well as early and long-term results of redo-CEA and CAS for patients with CR after CEA in a single-setting center.

MATERIALS AND METHODS

The protocol of this study was revised and approved by the Ethics Committee of our hospital and all patients signed an informed consent.

Design

Data from patients treated for carotid stenosis were prospectively collected in a dedicated database including demographic data, past medical history, preoperative characteristics, imaging studies, procedural details, operative outcomes, intra- and postprocedural complications, and follow-up data. The records of patients treated for CR were reviewed retrospectively for this study and a post hoc analysis of this database was performed comparing between the 2 treatment groups.

Patients

This study included all patients who underwent intervention for CR (redo-CEA or CAS) between January 1988 and December 2014 at our institution. Patients with a follow-up time less than 6 months were excluded (n = 3). Over this period, 44 consecutive patients were treated for CR: 23 patients underwent open repair (OR) and 21 CAS. In general, intervention was recommended for any patient with a symptomatic stenosis greater than 50% or high-grade asymptomatic restenosis (>70%) using the North American Symptomatic Carotid Endarterectomy Trial criteria. Patients were considered to be asymptomatic in the absence of transient ischemic attack (TIA) or stroke within 6 months from the intervention. All patients underwent duplex ultrasound followed by either a computed tomography (CT) angiography, a magnetic resonance imaging angiography (MRI), or a carotid angiography before intervention to assess the degree of stenosis, presence of intracranial cerebral artery occlusive disease, and severity of contralateral disease.

The selection of either open or endovascular treatment was made at the surgeon’s discretion. Patients with previous neck irradiation, high cervical lesions, or past cranial nerve injuries were considered at high risk for OR and underwent CAS. Patients with severe vessel tortuosity, difficult aortic arches, images suggesting mural or mobile intraluminal thrombus in the arteriography, or ulcerated lesions considered at high risk for embolization by the radiologist were considered inadequate for endovascular treatment and therefore an open approach was preferred. In recent years, CAS was the treatment of choice for CR in our center. Therefore, only 5% of CR interventions after 2001 were done with OR.

Operative Technique

All redo-CEAs were performed by vascular surgeons with systemic heparin. The selection of anesthesia was at the discretion of the operating surgeon and anesthetist. Routine shunting was used in all the patients under general anesthesia. In those cases with local anesthesia, a carotid shunt was used depending on clinical neurologic changes during carotid clamping. Patients received aspirin (100 mg/day) before the intervention and the therapy was continued indefinitely in all patients.

CAS Technique

All CAS procedures were done by an interventional neuroradiologist under local anesthesia and a percutaneous access to the common femoral artery was used. Before selective catheterization, patients underwent systemic heparinization. Primary stenting was performed in all the patients except for the first one of the series in which a single percutaneous transluminal angioplasty (PTA) was carried out. We used Carotid WALLSTENT (Boston Scientific, Natick, MA) and postdilatation PTA was performed selectively after stent deployment. All patients underwent a completion angiography. A cerebral protection device was used in 2 patients with lesions which were considered at risk for embolization in the preoperative angiography. All patients received aspirin (100 mg/day) and clopidogrel (75 mg/day) for 3–5 days before intervention. Aspirin was continued for 6 weeks after CAS, whereas
clopidogrel was continued indefinitely. All the patients received long-term statin therapy.

Early Evaluation and Follow-up

After intervention patients were evaluated independently for development of stroke, TIA, and amaurosis fugax at the intensive care unit and those with cranial nerve injuries underwent evaluation by an experienced otolaryngologist too. TIA was defined as any postoperative neurological event of less than 24-hr duration and stroke was defined as any postoperative neurological event of more than 24-hr duration with or without residual impairment.

After discharge, patients were followed up with duplex ultrasound scanning of both extracranial carotid arteries as well as clinical evaluation at our outpatient department at 1, 3, 6, 12 months, and yearly thereafter.

Our end points were cranial nerve injury, myocardial infarction (MI), TIA, and stroke at 30 days after intervention as well as restenosis and reintervention during follow-up. We used a cutoff of <30% stenosis to indicate normal to minimal disease and severity of CR was classified into <70% or >70% according to duplex velocity.

Statistical Analysis

Continuous data were compared with unpaired Student’s t-test and discrete variables with χ² or Fisher’s exact test. Time to occurrence of events during follow-up (survival, stroke-free survival, freedom from secondary restenosis, freedom from >70% secondary restenosis, and freedom from secondary reintervention) was analyzed using the Kaplan–Meier life-table analyses and statistical comparisons between the 2 groups were made by the Breslow test (generalized Wilcoxon). Statistical significance was defined as P < 0.05. SPSS 20.0 statistical software (SPSS, Inc., Chicago, IL) was used for statistical analysis.

RESULTS

Patient Characteristics

Between 1988 and 2014, 47 patients were treated for CR in our center, which represents a 4.9% of the total CEA operations in that period; 3 of these patients were excluded from analysis due to a follow-up time of less than 6 months. Of the 44 patients included, 23 (52.3%) underwent OR and 21 (47.7%) CAS. Demographic and clinical preoperative characteristics were comparable for both groups, except for arterial hypertension and chronic renal insufficiency, which were significantly higher in the CAS group (Table I). The OR group had a significantly higher number of patients with symptomatic carotid disease as indication for redo surgery (30.4% vs. 4.8%, P = 0.04). No differences were found between groups regarding critical carotid stenosis, contralateral occlusion, or time from initial CEA to reintervention. Mean time interval to CEA was 38.9 months compared with 26.6 months for CAS (P = 0.41).

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (23)</th>
<th>CAS (21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>67.32 ± 8.9</td>
<td>69.86 ± 7.4</td>
<td>0.32</td>
</tr>
<tr>
<td>Female gender</td>
<td>8 (34.8%)</td>
<td>6 (28.6%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Smoker (prior or current)</td>
<td>21 (91.3%)</td>
<td>19 (90.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>15 (65.2%)</td>
<td>20 (95.2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (60.9%)</td>
<td>12 (57.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14 (60.9%)</td>
<td>14 (66.7%)</td>
<td>0.76</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (4.3%)</td>
<td>5 (23.8%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14 (60.9%)</td>
<td>15 (71.4%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>1 (4.3%)</td>
<td>6 (28.6%)</td>
<td>0.04</td>
</tr>
<tr>
<td>On dialysis</td>
<td>1 (4.3%)</td>
<td>1 (4.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Critical carotid stenosis</td>
<td>11 (47.8%)</td>
<td>6 (28.06%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Contralateral occlusion</td>
<td>2 (8.7%)</td>
<td>5 (23.8%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Indications for procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>7 (30.4%)</td>
<td>1 (4.8%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>16 (69.6%)</td>
<td>20 (95.2%)</td>
<td></td>
</tr>
<tr>
<td>Mean time from primary CEA (months)</td>
<td>38.9</td>
<td>26.6</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Bold values are statistically significant. COPD, chronic obstructive pulmonary disease; SD, standard deviation.
Median time interval was 14 months in the OR group (range 9–189) and 8 in the CAS group (range 4–191).

Intraoperative Details

Of the 23 operations, 14 of them (60.8%) were done under local anesthesia and 9 (39.2%) under general anesthesia with routine shunting.

In 3 cases the local anesthesia was converted to general due to pain (2 patients) or neurologic findings during clamping (1 patient).

Repair technique consisted of Dacron patch angioplasty with endarterectomy when there were atherosclerotic plaques in 17 patients (73.9%) and gioplasty with endarterectomy when there were atherosclerotic plaques in 17 patients (73.9%) and gioplasty with endarterectomy when there were atherosclerotic plaques in 17 patients (73.9%) and gioplasty with endarterectomy when there were atherosclerotic plaques in 17 patients (73.9%). Dacron common-to-internal carotid re-endarterectomy with primary closure in 2 patients (8.7%).

Intraoperative Details

DISCUSSION

The reported incidence of post-CEA CR ranges from 2% to 38%. However, only around 10% of the patients develop severe restenosis and the rate of CR after the second year is <2%. While some authors recommend an aggressive approach in patients with asymptomatic high-grade CR, others prefer a nonoperative approach with optimal medical treatment and surveillance. As a result of the lack of prospective randomized studies, this issue remains open to debate and most of the guidelines for carotid surgery suggest the same indications to treat CR than for primary stenosis, suggesting that CAS should be the treatment of choice in these patients.

Table II. Early (30 days) perioperative outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>OR (23)</th>
<th>CAS (21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Ipsilateral stroke</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Ipsilateral TIA</td>
<td>1 (4.3%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Contralateral stroke/TIA</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Total cranial nerve injury</td>
<td>3 (13%)</td>
<td>0 (0%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Transient</td>
<td>3 (13%)</td>
<td>0 (0%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Permanent</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
</tbody>
</table>

95% confidence interval [CI] 0.19–3.75 (Fig. 1). None of the late deaths were secondary to stroke.

The rate of freedom from >30% restenosis at 6, 12, 24, and 36 months was 95.2%, 76.2%, 71.1%, and 65.6% for repeat CEA and 70.2%, 70.2%, 58.3%, and 58.3% after CAS (P = 0.39, Breslow 0.73, HR 1.22, 95% CI 0.47–3.18). There were 6 patients in the OR group and 2 in the CAS group with severe (>70%) secondary restenosis during follow-up which was asymptomatic in all of them, but life-table analysis showed no significant difference between groups (P = 0.37, Breslow 0.81, HR 0.38, 95% CI 0.08–1.91) (Fig. 2).

All these patients who developed severe secondary restenosis underwent further reintervention: in the OR group, a carotid artery stent was placed in all patients but one, who underwent a repeat CEA; and all patients in the CAS group were treated with single in-stent PTA. No postoperative events were registered after these secondary reinterventions. The rate of freedom from repeat intervention for re-recurrence was 100%, 90%, 84.7%, and 79.1% for OR and 90%, 90%, 90%, and 90% for CAS, respectively (P = 0.31, Breslow 1.04, HR 0.37, 95% CI 0.07–1.821).

Early (30 Days) Perioperative Outcome

Mortality, neurologic morbidity, and overall morbidity were similar in both groups (Table II). There were no perioperative MIs or deaths in either group. In the OR group, one patient had a TIA with resolution within hours, no abnormality demonstrated at MRI, and no permanent neurologic deficit. The cranial nerve injury rate was 13% (3 patients with deficit of a laryngeal nerve) in this group and 0% in the CAS group (P = 0.23). However, none of these patients had a permanent cranial nerve injury at the otolaryngological examination at 30 days.

Follow-up Results

The median follow-up was 86 months (range 6–223) for the OR group and 38 months (range 6–126) for the CAS group.

No ipsilateral or contralateral strokes were encountered in either group and no patient had stent or carotid artery occlusion during follow-up. Therefore, survival and stroke-free survival rates at 3 years were equal.

Patient estimated survival at 3 years was similar for the OR and CAS groups (80.8% vs. 89.1%, P = 0.66, Breslow 0.2, hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.19–3.75) (Fig. 1). None of the late deaths were secondary to stroke.

The rate of freedom from 30% restenosis at 6, 12, 24, and 36 months was 95.2%, 76.2%, 71.1%, and 65.6% for repeat CEA and 70.2%, 70.2%, 58.3%, and 58.3% after CAS (P = 0.39, Breslow 0.73, HR 1.22, 95% CI 0.47–3.18). There were 6 patients in the OR group and 2 in the CAS group with severe (>70%) secondary restenosis during follow-up which was asymptomatic in all of them, but life-table analysis showed no significant difference between groups (P = 0.37, Breslow 0.81, HR 0.38, 95% CI 0.08–1.91) (Fig. 2).

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DISCUSSION

The reported incidence of post-CEA CR ranges from 2% to 38%. However, only around 10% of the patients develop severe restenosis and the rate of CR after the second year is <2%. While some authors recommend an aggressive approach in patients with asymptomatic high-grade CR, others prefer a nonoperative approach with optimal medical treatment and surveillance. As a result of the lack of prospective randomized studies, this issue remains open to debate and most of the guidelines for carotid surgery suggest the same indications to treat CR than for primary stenosis, suggesting that CAS should be the treatment of choice in these patients. Results of studies showing similar rates of perioperative stroke
and death for CAS and redo-CEA in these patients and a non-negligible risk for cranial nerve injuries with open surgical interventions justify this trend toward a preferred endovascular approach in CR. Even though some groups have reported similar cranial nerve injury rates in redo-CEA compared with primary CEA,15,16 scar tissue present in a previously operated field can make dissection and nerve identification difficult, increasing the risk of local complications. In our series, we recorded a 13% rate of cranial nerve injury, similar to that reported in previous series which ranges from 3.7% to 21%.7,17,18 However, all 3 injuries were transient and otolaryngological examination at first month after discharge showed no permanent cranial nerve injury in these patients, supporting the results of studies showing no statistically significant differences between CAS and redo-CEA in permanent nerve injury rates.19

AbuRahma et al.19 retrospectively evaluated 192 patients in the largest single-center comparison of CAS versus redo-CEA in patients with CR. They reported similar perioperative stroke rates (3% vs. 1%, \(P = 0.5573\)) and combined early and late stroke rates (3% vs. 2%, \(P = 0.6347\)).

More recently, Fokkema et al.20 carried out an individual patient data meta-analysis including 13 studies and 1132 patients treated by CAS (\(n = 653\)) or redo-CEA (\(n = 479\)). The results showed no differences in terms of stroke, death, and restenosis at short-term follow-up.

However, most of these studies have been conducted in centers with excellent results in stroke/death rates. Therefore, this outcomes might not be attained in every department and it might be advised that this type of pathology should be treated only by experienced surgeons in high-volume centers.

These findings supporting that, unlike CAS for primary stenosis, CAS for CR attains similar results than CEA, have been explained by some authors by a supposedly fairly stable plaque in restenotic lesions occurring in the first years after intervention, and attributed to neointimal fibrous hyperplasia.15,19,21 This hyperplastic lesions are supposed to have a lower potential for embolization than atherosclerotic plaques developed later during follow-up. However, no differences have been
found in transcranial Doppler-detected microembolization for early and late restenosis treated with CAS.22

Although most authors agree that both treatment options have similar mortality and neurological complication rates, there is still controversy regarding rates of recurrent restenosis and tertiary interventions in the long-term setting. In our series, we found a trend toward a higher severe recurrent restenosis rate in the OR group during follow-up; however, this was not statistically significant. Dorigo et al.17 in a series of 41 redo-CEA and 58 CAS for severe post-CEA restenosis also found an increased incidence of >80% restenosis in the redo-CEA group (28.3% vs. 6.5%, P = 0.01). Similar results were reported by Bet
tendorf et al.23 AbuRahma et al.19 showed a higher rate of >50% in-stent restenosis in the CAS group but similar rates of freedom from >80% restenosis at 4 years. Attigah et al.16 also found no difference regarding the incidence of severe restenosis, with similar results to those reported by studies evaluating durability of these procedures.15,18

This disparity between studies could be partially explained by different criteria on CAS duplex surveillance between groups. Several authors have reported increased in-stent velocities due to the altered properties of vessels after CAS, leading to the revised velocity criteria suggested by Lal et al.24 Although some of the groups changed criteria for the CAS group in recent years, most of them used the same criteria for redo-CEA and CAS surveillance in these studies, which could have contribute to a potential bias.

Considering that post-CEA restenosis has been found to be the most important predictive factor for in-stent restenosis after CAS,25 duplex scanning surveillance is required in both early and long-term follow-up in these patients and further studies are needed to assess the long-term outcomes of these procedures.

Advances in medical therapy for patients with carotid artery disease, together with stroke/death rates in CR treatment close to the upper limit acceptable for asymptomatic patients suffering carotid stenosis, have raised controversy on whether a nonsurgical approach should be considered for asymptomatic CR.15 However, the results from the meta-analysis published by Fokkema et al.20 showed no difference in the primary outcome of both asymptomatic and symptomatic patients, with a stroke/death rate of 2% and 2.1% for CAS and redo-CEA, respectively, in the first group. Therefore, identification of high-risk patients who would benefit from CR intervention is a challenge that should be pursued in future studies to be able to offer the best option for the patient in each specific situation.

This study has some limitations. It is a retrospective study; nevertheless, all the data in the dedicated

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**Fig. 2.** Freedom from >70% restenosis. S, standard deviation.
database were collected prospectively. The limited number of patients and event rate could have lowered the ability to detect significant differences, leading to a type II error. On the other hand, our median follow-up is one of the longest reported in studies comparing treatment options for CR, allowing us to therefore identify long-term outcome trends. Finally, a bias in the choice of treatment may exist due to the paradigm shift toward an endovascular approach of CR in the last years in our center. Outcomes in these patients treated with CAS in recent years may have also been influenced by improvement in best medical treatment of late. Nonetheless, our 2 groups were homogeneous in both demographic and clinical preoperative characteristics, contributing to the accuracy of the comparisons between groups.

CONCLUSION

Our data suggest that both CAS and redo-CEA are suitable options for patients with an indication for treatment for post-CEA CR. CAS might be considered the treatment of choice due to the increased risk for cranial nerve injuries in redo-CEA operations. When CAS is contraindicated, redo-CEA remains a safe and effective treatment option. Further studies are required to assess the long-term results of these treatments and to identify asymptomatic high-risk patients who would benefit from surgical or endovascular intervention.

REFERENCES