Risk factors for restenosis after carotid artery angioplasty and stenting

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Objectives: With carotid artery stenting (CAS) becoming an ever-increasing procedure, we sought to determine risk factors for in-stent restenosis after CAS.

Methods: Consecutive patients undergoing CAS between January 2002 and October 2004 at a tertiary care hospital were retrospectively reviewed. Patient, filter, and stent selection were left to the discretion of the attending surgeon. High-risk patients were defined by significant comorbidities or a hostile neck (prior surgery or radiation, or both), and risk factor analysis was performed. In-stent restenosis was defined as >60%, and selective angiography was performed on patients with an in-stent restenosis >80% by duplex ultrasound imaging.

Results: Reviewed were 101 patients (55 men, 46 women) who underwent 109 CAS procedures. Comorbidities were typical for patients with atherosclerosis. In addition, 38% (n = 41) of procedures were performed in patients who had prior neck surgery, of which 29% (n = 32) had previous ipsilateral carotid endarterectomy. Seventeen patients (16%) had a history of neck cancer, and all had prior neck radiation. Median follow-up was 5 months (range, 0 to 30 months). Neurologic complications included three transient ischemic attacks (2.8%) and one nondisabling stroke (0.9%). There were two myocardial infarctions (1.9%) and no peri-procedural deaths (30 days), for a combined stroke, myocardial infarction, and death rate of 2.9%. Asymptomatic in-stent restenosis developed in 12 carotids (11%), five of which required endovascular intervention, with a mean of 6 months to restenosis. Univariate Cox proportional hazard regression models were used to determine risk factors for the development of restenosis. Prior stroke, transient ischemic attack, amaurosis fugax, and prior neck cancer were all significant risk factors. When these significant risk factors from univariate analysis were put into multivariate analysis, however, the only marginally significant risk factor was prior neck cancer (P = .06). Kaplan-Meier analysis revealed a cumulative freedom from in-stent restenosis at 24 months of 88% ± 6% in patients without neck cancer compared with 27% ± 17% (P = .02) in patients with neck cancer.

Conclusions: CAS has been shown to be safe and effective in high-risk patients, with minimal adverse events. (J Vasc Surg 2006;44:1010-5.)

Carotid endarterectomy (CEA) is the treatment of choice for patients with symptomatic carotid artery stenosis1 and selected patients with asymptomatic stenosis.2 The reported perioperative risk of stroke or death in multicenter studies is 3% to 7.5%.3-5 The operation is exceedingly durable, with nearly 95% of patients being free from either neurologic events or death3-5 and 80% to 90% of patients free from restenosis during the first 5 years.6-11

With the inception of carotid artery angioplasty and stenting (CAS) with embolic protection devices (EPD), a shift has taken place in the treatment in those patients deemed to be at high risk. High-risk patients include those with clinically significant cardiac disease, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal-nerve palsy, recurrent stenosis after endarterectomy, and previous radical neck surgery or radiation to the neck.5 Recently, CAS with embolic protection in high-risk patients with severe carotid artery stenosis has been shown to be at least equivalent to CEA with respect to stroke, myocardial infarction (MI), or death.3 The primary end points of combined death, stroke, or MI ≤30 days were lower in those patients undergoing protected CAS (4.8%) compared with those who underwent CEA (9.8%). The Carotid Revascularization using Endarterectomy or Stenting Systems (CARESS) trial demonstrated no significant difference of combined stroke or death rate at 30 days (3.6% CEA vs 2.1% CAS) or at 1 year (13.6% CEA vs 10.0% CAS). Similarly, no significant differences were found in the combined end point of death, stroke, or MI at 30 days (4.4% CEA vs 2.1% CAS) or at 1 year (14.3% CEA vs 10.9% CAS).5

Because CAS use is increasing, it is important to define its durability and to identify those patients that may be at risk for recurrent stenosis. Reports of carotid in-stent restenosis are 1% to 75%12-19; however, the earlier studies with higher restenosis rates looked at very few patients and incorporated angioplasty alone. Subsequent studies paid little attention to the risk factors for recurrent stenosis in patients who had undergone CAS.

Numerous studies have shown that the presence of restenosis is frequently asymptomatic and does not necessarily require intervention.12,18 For this reason, it would be beneficial to identify those patients who are at increased risk
for restenosis that would require reintervention to ensure that long-term patency is maintained. In addition, several reports have questioned the validity of duplex ultrasonography for detecting in-stent restenosis after CAS, citing a change in the biomechanical properties of the artery leading to a potential error in interpretation.\textsuperscript{20,21} The purpose of this study was to identify risk factors in already high-risk patients that would predict an increased risk for in-stent restenosis.

METHODS

All patients undergoing CAS between the years 2002 and 2004 were retrospectively reviewed. Patient demographics, clinical presentation, radiology records, operative notes, and clinical outcomes were obtained and available for review in all cases. Symptomatic disease was diagnosed if the patient experienced a transient ischemic attack (TIA) or stroke referable to the carotid lesion. All comorbidities were documented from history and physical examination. Diagnosis of carotid artery stenosis was made by duplex ultrasound imaging, computed tomographic (CT) angiogram, or magnetic resonance angiogram (MRA) with confirmation using angiogram.

Inclusion criteria for CAS were two or more coronary vessels with \( \geq 70\% \) stenosis, an ejection fraction <30\%, a New York Heart Association functional class of III or higher, bronchopulmonary obstructive disease, recurrent stenosis after a previous CEA, previous radical neck surgery or radiation therapy, surgically inaccessible lesions, and contralateral occlusion of the ICA. All patients were given aspirin and clopidogrel in the perioperative period.

All complications occurring \( \leq 30 \) days of the CAS were considered perioperative morbidity. Stroke was defined as any localized neurologic deficit lasting >24 hours and confirmed by magnetic resonance imaging or head CT scan. A TIA was defined as a neurologic deficit lasting <24 hours. MI was defined by the vascular attending as documented electrocardiographic changes with concordant serum elevation of creatine kinase and troponin.

All procedures were performed by vascular surgeons in the general operating room suites using an OEC 9800 system (GE OEC Medical Systems, Salt Lake City, Utah) and later on a Siemens Axiom Artis VBIID system (Berlin and München, Germany).

Survival, neurologic events, and restenosis rates are presented as defined by the Society of Vascular Surgery/International Society for Cardiovascular Surgery Ad hoc Committee’s recommended standards for carotid endarterectomy.\textsuperscript{25} Recurrent carotid artery stenosis is defined as the reappearance of a stenosis with a diameter reduction of >60\% in the stented internal carotid artery as determined by a duplex scan. Lesions believed to be >80\% were confirmed by angiogram results.

Patients were kept in the hospital overnight. Carotid duplex scans were obtained at 1, 6, and 12 months and yearly thereafter. All duplex scans were performed by registered vascular technicians in an approved vascular laboratory accredited by the Intersociety Commission on Accreditation of Vascular Laboratories. Velocity criteria were defined as 50\% to 60\% stenosis (peak systolic velocity [PSV], 125 to 170 cm/s); 60\% to 69\% (PSV, 170 to 210 cm/s); 70\% to 79\% (PSV, >210 cm/s); 80\% to 99\% (end-diastolic velocity, >145 cm/s). Criteria were not altered to account for intra-arterial stents.

Statistical analysis. Time to restenosis was analyzed using survival analysis methods. Survival curves were estimated by the Kaplan-Meier method (SPSS Inc, Chicago, Ill). Univariate and multivariate Cox proportional hazard regression models were used to determine risk factors for the development of restenosis. Because some patients underwent bilateral procedures, a marginal risk set model\textsuperscript{23} was used to account for within-patient correlation.

Risk factors investigated included procedure side, gender, smoking, coronary artery disease, prior coronary artery bypass grafting (CABG), previous MI, congestive heart failure (CHF), hypertension, hypercholesterolemia, chronic obstructive pulmonary disease (COPD), prior stroke, TIA, amaurosis fugax, prior ipsilateral CEA, prior neck radiation, and prior neck cancer. For each risk factor, the hazard ratio and associated 95\% confidence interval from univariate analysis was reported. Multivariate analysis was conducted for those risk factors with significant \( P \) values (<.05) from univariate analysis. All analyses were conducted in Stata 9.0 (StataCorp, College Station, Texas).

RESULTS

Patient characteristics. A total of 101 patients (55 men, 46 women) underwent 109 CAS procedures. Comorbidities were typical for patients with atherosclerosis (Table I). Neurologic symptoms referable to the lesion that was ultimately stented were present in 40\% (\( n = 43 \)), including stroke, 22\% (\( n = 24 \)); TIA, 21\% (\( n = 23 \)); or amaurosis fugax, 6\% (\( n = 7 \)). Forty-eight percent (\( n = 52 \)) of carotids

Table I. Demographics of 101 patients undergoing 109 carotid angioplasty and stenting procedures

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70 ± 9 (44-90)</td>
</tr>
<tr>
<td>Male gender</td>
<td>55 (55)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80 (79)</td>
</tr>
<tr>
<td>Smoking</td>
<td>41 (41)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>66 (61)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>24 (22)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32 (32)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>15 (14)</td>
</tr>
<tr>
<td>Congestive cardiomyopathy</td>
<td>20 (20)</td>
</tr>
<tr>
<td>COPD</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Prior ipsilateral CEA</td>
<td>29 (32)</td>
</tr>
<tr>
<td>Prior neck Radiation</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Stroke</td>
<td>24 (22)</td>
</tr>
<tr>
<td>TIA</td>
<td>23 (21)</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

CABG, Coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; TIA, transient ischemic attack. *Data are presented as mean ± SEM (range) or number of patients (% of total).
stented were in a neck that had prior surgery, 29% (n = 32) of previously stented carotids had an ipsilateral CEA, and 16% (n = 17) of procedures were in patients with a head and neck cancer (n = 14) or lymphoma (n = 3) in the neck.

Clinical outcomes. Distal EPDs were used in 84% (n = 92) of the cases. The EPD and stent systems included the Percusurge (Medtronic, Redmond, Wash) in 7 (6.4%), the Accunet/Acculink (Guidant, Indianapolis, Ind) in 47 (43%), and the Filter Wire and Wallstent (Boston Scientific, Marlborough, Mass) in 35 (32%). The technical success rate was 100%.

Neurologic complications included three TIAs (2.8%) and one nondisabling stroke (0.9%). There were two MI (1.9%) and no periprocedural deaths (30 days) for a combined stroke, MI, and death rate of 2.9%.

Follow-up and case report. Median follow-up was 5 months (mean, 7 months; range, 0.1 to 30 months). Asymptomatic >60% in-stent restenosis developed in 12 carotids (11%) at a median time to detection of 7 months. Five carotids (4.6%) developed asymptomatic >80% in-stent restenosis by duplex imaging and required endovascular intervention with a median of 7 months (range, 1 to 9 months) to detection restenosis. No patient had neurologic symptoms.

Table II summarizes the clinical outcomes in the patients who required reintervention for in-stent restenosis. The seven (6.4%) carotids that went on to develop an asymptomatic >60% stenosis are being monitored with serial duplex examinations.

Risk factor analysis. Univariate Cox proportional hazard model with "within-patient correlation" corrected using marginal risk set method indicated that prior stroke, TIA, amaurosis fugax, and prior neck cancer were significant risk factors (Table III); however, when these significant risk factors from univariate analysis were put into multivariate analysis, none were significant. The only marginally significant risk factor was prior neck cancer (P = .06). The results indicate that prior neck cancer could be a risk factor for restenosis. Kaplan-Meier analysis revealed a cumulative freedom from in-stent restenosis of 88% ± 6% in patients without neck cancer compared with 27% ± 17% (P = .02) in patients with neck cancer. Fig 1 shows the Kaplan-Meier estimated survival curves for patients with and without prior neck cancers.

DISCUSSION

The development of improved endovascular technology, specifically EPDs, has advanced the treatment of carotid stenosis by CAS in high-risk patients. In fact, indications for CAS are expanding with the demonstration of excellent results. As we gain greater experience with endovascular techniques, however, it is essential to correctly
identify patients that would benefit from CAS. With advances in medical management, those patients deemed to be high risk are living longer and therefore should be offered treatment with proven durability. With this in mind, we reviewed the results of a single institution’s experience in an attempt to determine predictors of restenosis.

CAS with an EPD has been shown to be equivalent to CEA in high-risk patients. Accordingly, high-risk patients were reviewed retrospectively to determine if any risk factors were associated with recurrent carotid artery stenosis. Univariate analysis identified prior stroke, TIA, amaurosis fugax, and neck cancer as significant risk factors for restenosis. When these factors were analyzed by multivariate analysis, a history of head and neck cancer was found to be a marginally significant risk factor for the development of early in-stent restenosis. This was confirmed by Kaplan-Meier survival curves comparing freedom from in-stent restenosis in patients with prior neck cancer with those without.

The incidence of recurrent stenosis in CEA has been well studied. Published restenosis rates after CEA are 2.7% to 19%. Earlier studies tended to have higher restenosis rates because more primary closures were being performed. Ouriel investigators. A review of the global carotid registry, which included 12,392 procedures, found the restenosis rate after CEA to be 2.7%, 2.6%, and 2.4% at 1, 2, and 3 years, respectively. Thus, the results presented in this study and in the previously mentioned studies are favorable compared with restenosis rates after CEA.

As CAS becomes more prevalent and is applied more broadly to patients with carotid disease, it is imperative to continue to review risk factors to best determine who is at risk for recurrence because durability of the procedure will come into question. Recent studies suggest that previous CEA is a risk factor for restenosis. Zhou et al reviewed 208 CAS procedures in 188 patients and found a 3.4% incidence of in-stent restenosis. Risk factor analysis identified patients with previous CEA to be at risk for in-stent restenosis.

Although previous CEA was not a risk factor for in-stent restenosis in this current study, it highlights the point that these patients need to be monitored closely. Risk factors that were previously associated with recurrent carotid stenosis after CEA include small carotid arteries, female sex, and primary closure. Although size of the vessel was not studied and primary closure was not a technical issue, we found no difference between men and women with respect to restenosis. Furthermore, the risk of restenosis was not associated with prior stroke, TIA, hypertension, smoking, coronary artery disease, previous MI, prior CABG, CHF, COPD, chronic renal insufficiency, device used, or prior ipsilateral CEA.

The current study found that patients with a history of head and neck cancer or a cancer in the neck were at a marginally significantly increased risk for development of early in-stent restenosis after CAS. The freedom from restenosis was significantly lower in patients with prior neck cancer. Interpretation may be difficult, however, because no standardized duplex criteria for patients with carotid stents exist. In addition, the total number of patients with in-stent restenosis was low. Regardless, it seems to warrant a vigilant follow-up in patients with neck cancer.

Despite the time to restenosis occurring in the typical time frame for a neointimal hyperplastic response, these lesions did not go on to become symptomatic. A combination of factors may influence in-stent restenosis, including radiation therapy and previous neck surgery. Although both ionizing radiation and prior neck surgery were not significant risk factors for restenosis on their own, prior neck cancer serves as a marker that stratifies patients into treatment modalities that may be enough to incite in-stent restenosis. The exact dose of radiation was not determined, but current regimens for malignant lymphomas and head and neck cancers include high-dose radiation to the tumor bed. Unfortunately, the carotid arteries are frequently in the field of treatment.

Radiation-associated vascular injury has been investigated and shown to cause damage consistent with atherosclerosis. Intimal proliferation, selective disruption of the internal elastic lamina, and necrosis has been noted in both small and large vessels. The mechanism of carotid artery stenosis secondary to radiotherapy is believed to be a combination of direct vessel wall damage, leading to intimal proliferation, necrosis of the media, periadventitial fibrosis, and accelerated atherosclerosis. In addition, the indirect effect of radiation-induced obliteration of the adventitial vasa vasorum may contribute. Little data currently exist on the mechanism of in-stent restenosis; however, local changes in flow dynamics and vascular wall damage are prime suspects. In addition to these effects, radiation may further exacerbate vessel wall damage and changes in the local hemodynamics, increasing the rate of in-stent restenosis after CAS. Furthermore, the effect of radiation may be long-term, predisposing to progressive restenosis.

Diagnosis of recurrent stenosis after CAS remains problematic, and in the case of this study, one patient with a presumed 80% to 99% stenosis underwent an angiogram that found 60% stenosis. Stringent follow-up is imperative to determine which patients have hemodynamically significant lesions. Duplex ultrasonography is noninvasive, safe, free of complications, and readily available.

Some authors have raised concerns of the utility of current velocity criteria and the need to refine the criteria for patients with carotid stents. A study by Lal et al found...
shows that the presence of a stent in the carotid artery changes the biomechanical properties of the artery, ultimately affecting the velocity and therefore the diameter and mimicking an in-stent restenosis. The stent ultimately decreases the compliance of the vessel, leading to falsely elevated velocities. Willfort-Ehringer et al.\(^\text{42}\) discuss positive remodeling forces of the stent placement and negative arterial remodeling of neointimal proliferation. The two forces seemed to counteract each other. The presence of the radiation is certainly a factor that affects the arterial wall. The hyperplasia may certainly be enough to overcome any positive remodeling from stent placement, thus increasing the likelihood of restenosis.

To date, there are no standardized criteria for the detection of restenosis in previously stented carotids. For this reason, our laboratory used duplex ultrasonography for screening. All hemodynamically significant stenoses were confirmed by arteriography. The focus of this study was not to define a new set of criteria for restenosis in patients with previous carotid stent placement.

Upon reintervention, all patients with >80% in-stent restenosis had an endovascular approach to treatment. Although balloon angioplasty was used in all cases, stent placement was performed in selected cases. The optimal management of in-stent restenosis has yet to be determined. Zhou et al.\(^\text{17}\) and Levy et al.\(^\text{34}\) were proponents of angioplasty or cutting balloons, whereas others have used open conversion.\(^\text{43}\) The exact etiology of in-stent restenosis is unclear in this patient population, and the ideal treatment approach to halt the process has yet to be determined. The patients in this study were only treated with angioplasty and selective stenting. Continued follow-up will determine if this is a viable treatment approach.

Although exact rates of restenosis after CEA in radiated necks are unclear, certainly perioperative risk factors are increased, especially that of nerve injury.\(^\text{44}\) In addition, surgery is difficult because of arterial, periarterial, and cutaneous sclerosis and risk of infection.\(^\text{45}\) In contrast, CAS offers an approach that circumvents any dissection in these difficult fields. In addition, this procedure can be performed with minimal risk of stroke, death, or MI. Thus, although CAS in patients with prior neck cancer had a higher rate of in-stent restenosis compared with patients without prior neck cancer, it is still the intervention of choice in this patient population. Only a direct comparison of CEA vs CAS in radiated necks would answer the question of which is the procedure of choice. Although the study is limited by the short follow-up period and only a moderately sized population, which could lead to a type II error, it confirmed the safety and efficacy of CAS and identified patients with an increased risk of in-stent restenosis. In addition, given the low number of events, the study is limited by the number of factors adjusted. This precluded a more extensive multivariable model, and some risk factors may have been excluded.

**CONCLUSION**

It is clear that CAS with EPD is a safe procedure that may be performed with a low incidence of stroke, TIA, MI, or death. Further, CAS may be performed with a low incidence of recurrent stenosis. In fact, CAS may be the intervention of choice under certain circumstances such as a hostile neck. Although patients who have had previous neck cancer are at slightly increased risk for restenosis, no neurologic events developed in patients with in-stent restenosis in this study. Thus, CAS should still be the procedure of choice in this patient population. This study would suggest, however, that this patient population may need to be monitored more closely.

We acknowledge Dingcai Cao, PhD, Department of Health Sciences at The University of Chicago, for statistical analysis.

**AUTHOR CONTRIBUTIONS**

Conception and design: CS, EW

Analysis and interpretation: CS, EW

Data collection: CS, KG, RF, JC, OV, SP, EW

Writing the article: CS, KG, EW

Critical revision of the article: CS, KG, RF, JC, OV, SP, EW

Final approval of the article: CS, KG, RF, JC, OV, SP, EW

Statistical analysis: CS

Obtained funding: N/A

Overall responsibility: CS

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Submitted Mar 6, 2006; accepted Jul 26, 2006.