

# Durability of eversion carotid endarterectomy

Enzo Ballotta, MD,<sup>a</sup> Antonio Toniato, MD,<sup>a</sup> Giuseppe Da Giau, MD,<sup>a</sup> Renata Lorenzetti, MD,<sup>a</sup>  
Anna Da Roit, MD,<sup>a</sup> and Claudio Baracchini, MD,<sup>b</sup> *Padova, Italy*

**Objective:** Carotid endarterectomy (CEA) remains the gold standard for treating carotid disease in selected symptomatic and asymptomatic patients, though carotid angioplasty and stenting has emerged as a safe alternative. The aim of this study was to assess the durability of CEA in a large series of patients followed up according to a strict clinical and ultrasonographic protocol.

**Methods:** Over a 23-year period (1990-2012) a total of 1773 patients (1251 men and 522 women) with a mean age of 75.2 years (range, 31 to 96 years) who underwent 2007 consecutive primary eversion CEAs performed by the same surgeon under general anesthesia with electroencephalographic monitoring and selective shunting were prospectively followed up with ultrasonography at 1, 6, and 12 months, then yearly. A long-term follow-up (median, 11.2 years; mean, 12.9 years) was obtained for 1680 patients (94.8%). End points were perioperative (30-day) stroke and death and late carotid restenosis/occlusion rates.

**Results:** More than two in three of the lesions (1446 of 2007, 72.1%) were symptomatic at the time of surgery, with a 25% rate of preoperative stroke. Preoperative antiplatelet or anticoagulant therapy was used by 1675 patients (94.4%), whereas 918 (51.8%) were receiving statin treatment. Overall, there were eight (0.4%) perioperative strokes and no deaths. During the follow-up, there were nine (0.47%) asymptomatic late carotid restenoses (six moderate [50%-69%] and three severe [ $\geq 70\%$ ]) and one (0.05%) carotid occlusion. Nine patients (0.47%) had late ipsilateral strokes, none of them related to restenosis/occlusion. Overall, there were 159 late deaths (9.4%).

**Conclusions:** The results of this study show that eversion CEA can be performed in symptomatic and asymptomatic patients with an extremely low perioperative stroke/death risk and a negligible incidence of late restenosis/occlusion, thus assuring a persistently good protection against the risk of cerebral ischemia. (*J Vasc Surg* 2014;59:1274-81.)

Randomized controlled trials (RCTs)<sup>1-4</sup> have validated the efficacy of carotid endarterectomy (CEA) for stroke prevention in selected patients with symptomatic internal carotid artery stenosis and, to a lesser extent, in cases of asymptomatic carotid disease, with acceptably low perioperative (30-day) stroke and death risks.<sup>5</sup> Large RCTs have also recently addressed the question of the relative safety of carotid artery stenting (CAS) vs CEA in symptomatic and asymptomatic patients,<sup>6,7</sup> and CAS has emerged as a good alternative to surgery in selected patients. CEA nonetheless remains the first choice for revascularization treatment for symptomatic and asymptomatic carotid lesions at most centers.<sup>8</sup> A >50% restenosis rate at the surgical site, detected by ultrasound according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria,<sup>9</sup> represents a noteworthy drawback of CEA, however, which can limit the long-term benefit of revascularization for the purpose of preventing stroke. The reported occurrence of post-

CEA restenosis differs considerably, and a review of the literature discloses a variability relating to the length of follow-up, the criteria for defining restenosis, and the method used to close the arteriotomy, which appears to strongly influence recurrence. The risk of restenosis is reportedly highest in the first 2 to 3 years after CEA (10% in the first year, 3% in the second, and 2% in the third),<sup>10</sup> and it is attributable to intimal hyperplasia, whereas any later development of restenosis (>5 years) is consistent with progression of the underlying atherosclerotic disease,<sup>10</sup> so it is not different from the primary carotid lesion.<sup>11</sup> The purported tendency of restenosis to cause stroke also appears to be highly variable. The relative risk of stroke reported in patients with restenosis as compared with those without restenosis ranges from 0.1 to 10, with a mean of 1.88, but it is generally lower than the stroke rate associated with a primary lesion.<sup>10</sup> Despite the reportedly low though not insignificant incidence of restenosis after CEA, redo surgery is infrequent and is related mainly to symptomatic severe restenosis or lesions rapidly progressing toward occlusion.<sup>12,13</sup>

The present observational study was designed to establish the incidence of post-CEA restenosis/occlusion in a series of patients consecutively undergoing primary CEA followed up according to a strict clinical and ultrasonographic protocol.

## METHODS

The local institutional review board approved this study. Between January 1, 1990, and May 31, 2012, there were 2007 consecutive primary CEAs performed in 1773 patients at our tertiary referral vascular surgical center. The

From the Vascular Surgery Group, 2nd Surgical Clinic, Department of Surgical, Oncological, and Gastroenterological Sciences<sup>a</sup> and Department of Neurosciences<sup>b</sup> at the University of Padua, School of Medicine.

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Reprint requests: Enzo Ballotta, MD, Vascular Surgery Group, 2nd Surgical Clinic, Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua, School of Medicine, Via N. Giustiniani, 2, 35128 Padova, Italy (e-mail: [enzo.ballotta@unipd.it](mailto:enzo.ballotta@unipd.it)).

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criteria for performing CEA were based on the NASCET recommendations<sup>1</sup> for symptomatic patients and on the Asymptomatic Carotid Atherosclerosis Study (ACAS)<sup>3</sup> for asymptomatic patients. Patients were prospectively enrolled in the present study. Patients scheduled for CEA with concomitant coronary artery bypass grafting or concurrent surgery for associated supra-aortic trunk lesions and patients needing procedures for recurrent disease were excluded from the present analysis. The patients' demographic and clinical data were recorded on a standardized form, including potential atherosclerotic risk factors, anatomical and clinical variables, preoperative medication, details of surgery, and all perioperative outcomes. For most patients, the diagnosis of carotid disease was based on preoperative duplex ultrasound scans combined with magnetic resonance (MR) angiography, computed tomography (CT) angiography, or digital subtraction angiography in selected patients (ie, those who had either a pseudo-occlusion on duplex ultrasound or a stenosis of the carotid intracranial segment detected by transcranial Doppler sonography). For most of the symptomatic patients and all those without symptoms, the velocity criteria were taken into account for CEA decision-making purposes, as explained elsewhere.<sup>14</sup> All patients underwent neurological assessment by the consultant neurologist before surgery, on awakening from the anesthesia, before discharge from the hospital, and during the follow-up. All patients with diabetes, hyperlipidemia, and/or hypoechoic plaques were receiving statin therapy. Since 2005, all patients with transient ischemic attack (TIA) were routinely started on clopidogrel before surgery. Preoperative patient preparation was standardized. Preoperative cardiac work-up was tailored to each individual on the basis of his or her clinical history, electrocardiographic (ECG) findings, and symptoms. Patients with evidence of clinically important coronary artery disease underwent echocardiography or dipyridamole-thallium stress tests followed by coronary arteriography, as indicated.

All surgical procedures were eversion CEAs (eCEAs) performed by the same surgeon in patients under general anesthesia and with routine intraoperative electroencephalographic monitoring for a selective use of intraluminal shunting. The technical details of the eCEA have been described elsewhere.<sup>15</sup> Shunting depended exclusively on electroencephalographic changes consistent with cerebral ischemia occurring during carotid cross-clamping, unrelated to any bradycardia or arterial hypotension.<sup>16</sup> Patients were administered intravenous unfractionated heparin (5000 U) before carotid clamping. No completion angiography or imaging studies were performed.

Patients were usually monitored in the recovery room for 2 hours until their blood pressure and neurological status were judged acceptable; they were then transferred to a nursing unit specialized in vascular care and monitored for the next 12 to 24 hours after surgery. All patients with severe headache were observed for hyperperfusion syndrome, and hypertension was treated

aggressively. Most patients were discharged 36 to 48 hours after their CEA.

**Surveillance protocol.** After discharge, visiting nurses monitored the patients' blood pressure and neurological status. All surviving patients systematically underwent physical and neurological assessment by a consultant neurologist, and concomitant duplex ultrasound scan performed by two experienced neurosonographers at 1, 6, and 12 months, then yearly after surgery. All examinations were performed with a high-resolution, color-coded duplex sonography scanner (the Acuson Sequoia 512 ultrasound system up until 2008, and Philips iU 22 from 2008 onward) with the use of a high-frequency (5-10 MHz) linear probe. The ultrasound follow-up schedule was modified if any progressing or severe lesions were detected or if patients became symptomatic. A peak systolic velocity of  $>130$  cm/s with spectral broadening throughout the systole and an increased peak diastolic velocity were consistent with a stenosis  $\geq 50\%$  diameter reduction, whereas a peak systolic velocity  $>240$  cm/s was consistent with  $\geq 70\%$  stenosis. Any stenosis  $\geq 70\%$  identified on duplex ultrasound scanning was confirmed by CT angiography or MR angiography. Neurological events were always classified by the consultant neurologist as TIA, defined as temporary hemispheric symptoms lasting no more than 24 hours, with complete recovery; amaurosis fugax, a transient monocular visual loss; minor stroke, a clinical syndrome of rapidly developing signs or symptoms of focal loss of cerebral function of vascular origin, lasting more than 24 hours but not leading to any handicap or significant impairment in activities of daily living, rated as  $<3$  on the modified Rankin scale<sup>17</sup>; or major stroke, defined as a focal neurological deficit lasting  $>30$  days and inducing a change in lifestyle, assessed as 3 to 5 on the modified Rankin scale. Brain imaging (CT or MR imaging) was performed in all patients presenting a new neurological deficit after CEA. Cardiac complications were classified by a single cardiologist and included (1) myocardial infarction with a diagnosis on the basis of creatine kinase-MB levels and ECG findings; (2) pulmonary edema confirmed by chest radiography; (3) documented ventricular fibrillation or primary cardiac arrest; and (4) new congestive heart failure, requiring a pacemaker. A postoperative ECG was routinely obtained in all patients with a history of coronary artery disease, congestive heart failure, or arrhythmia (rhythm other than sinus), and cardiac isoenzymes were surveyed in all patients who had new findings at postoperative ECG. Other complications and events observed during the follow-up were recorded in accordance with the guidelines of the Ad Hoc Committee on Reporting Standards for Cerebrovascular Disease, Society for Vascular Surgery/North American Chapter of the International Society of Cardiovascular Surgery.<sup>18</sup>

Primary end points were perioperative stroke and death and late carotid restenosis/occlusion rate.

**Statistical analysis.** The statistical analysis was performed with the SPSS statistical software (SPSS version 12.0.1; SPSS Inc, Chicago, Ill). Patients' demographic data are given as medians, means, and ranges and baseline clinical and diagnostic findings in terms of incidence rates. Stroke-free survival and survival rates were calculated by means of the Kaplan-Meier method and are reported as "life-table" analyses. Significance was assumed at  $P < .05$ . Several data items were analyzed vis-à-vis surgical procedures rather than patients because each perioperative outcome was correlated with the surgical procedure and because patients who underwent bilateral CEAs were exposed to twice the risk of stroke, death, or other complications.

## RESULTS

**Descriptive analysis.** Patients' demographic details, risk factors, and indications for CEA are summarized in Table I. Among the 1773 patients who underwent 2007 CEAs (234 were staged bilateral CEA procedures), there were 522 women (29.4%) and 1251 men (70.6%), with a mean age of 75.2 years (range, 31 to 96 years). More than two in three of the lesions (72.1%; 1446 of 2007) were symptomatic, with a 25% rate of preoperative strokes. The interval from presentation to operation for TIA/minor stroke patients was <1 month, whereas asymptomatic cases or patients with major stroke were treated within 6 months from diagnosis/event, respectively. No adverse ischemic events occurred during the waiting period. It is noteworthy that the ipsilateral carotid artery had a stenosis between 75% and 99% in more than half of the cases, whereas the contralateral carotid artery was occluded in 287 cases (16.2%). More than 90% of patients (1675 of 1773) were receiving antiplatelet or anticoagulant treatment at presentation, that is, 478 patients (26.8%) were taking clopidogrel (75 mg/d), 526 (29.7%) aspirin (100 mg/d), 255 (14.4%) ticlopidine (500 mg/d), 71 (4.0%) dipyridamole (400 mg/d), 222 (12.3%) clopidogrel plus aspirin, and 123 (6.9%) warfarin. Statin medication was being used by 918 patients (51.8%; Table II).

### Perioperative (30-day) stroke and mortality rates.

Overall, there were eight (0.39%) perioperative strokes (five major and three minor) and no deaths (Table III). In all eight cases, the stroke occurred in symptomatic patients within the first 24 hours of surgery, while they were still in the recovery room, and prompt duplex ultrasound scan showed that the endarterectomized artery was patent. Four major strokes occurred in patients (one of them was shunted) who had a mildly diseased contralateral carotid artery and, judging from the cerebral CT scans, they produced a cortical infarction in the territory of the middle cerebral artery; because they could not be caused by technical errors, we assumed that they were probably embolic (from the aortic arch or the heart). The other major stroke was ipsilateral to an occluded contralateral carotid artery. All minor strokes were most likely hemodynamic in nature because they were identified as border zone infarcts on CT imaging: two of them developed in the hemisphere contralateral to the revascularized carotid artery and ipsilateral to an occluded

**Table I.** Demographics and clinical data

Preoperative characteristics	No. (%)
Patients	1773 (100)
CEA procedures	2007 (100)
Mean age $\pm$ SD, years	75.2 $\pm$ 5.3
<70	558 (31.5)
70-80	912 (51.4)
>80	303 (17.1)
Male sex	1251 (70.6)
Risk factors	
Hypertension <sup>a</sup>	1053 (59.4)
Smoking <sup>b</sup>	1223 (68.9)
Diabetes	574 (32.4)
Hyperlipidemia <sup>c</sup>	803 (45.3)
Cardiac disease	766 (43.2)
CKD	141 (7.9)
Pulmonary disease	285 (16.1)
PAD	977 (55.1)
Qualifying event	1446 (72.1)
Hemispheric stroke	504 (25.1)
TIA	675 (33.6)
Retinal ischemia	267 (13.3)
No symptoms	561 (27.9)

CEA, Carotid endarterectomy; CKD, chronic kidney disease; PAD, peripheral atherosclerotic disease; SD, standard deviation; TIA, transient ischemic attack.

<sup>a</sup>Arterial pressure >140/90 mm Hg or blood pressure treated with medication.

<sup>b</sup>Current use or cessation within the past 5 years.

<sup>c</sup>Serum concentration of cholesterol >6.5 mmol/L or triglycerides >2.0 mmol/L.

**Table II.** Degree of carotid lesions, concomitant medication, and intraoperative variables

	No. (%)
Degree of ipsilateral stenosis	
<50%	69 (3.4)
50%-59%	23 (1.1)
60%-69%	148 (7.3)
70%-79%	857 (42.7)
80%-89%	665 (33.1)
90%-99%	245 (12.2)
Contralateral carotid disease	
<60%	1292 (72.9)
$\geq$ 60%	194 (10.9)
Occlusion	287 (16.2)
Concomitant medication	
Antiplatelet treatment	1552 (87.5)
Clopidogrel	478 (26.8)
Clopidogrel plus aspirin	222 (12.5)
Aspirin	526 (29.7)
Ticlopidine	255 (14.4)
Dipyridamole	71 (4.0)
Anticoagulant (warfarin)	123 (6.9)
Lipid-lowering drug	918 (51.8)
Intraoperative variables	
Left side of operation	1107 (55.1)
Shunt placement	318 (15.8)

internal carotid artery. Among the 504 patients (25.1%) with a preoperative stroke, we observed three perioperative strokes, with no clear correlation between preoperative cerebral imaging and outcome ( $P = .42$ ).

**Table III.** Perioperative (30-day) outcomes

Outcomes	2007 CEAs (1773 patients), No. (%)
Stroke	8 (0.39)
Major	5 (0.24)
Ipsilateral	4
Shunting	1
No shunting	3
CCO	0
Contralateral	1
Shunting	0
No shunting	1
Carotid occlusion	1
Minor	3 (0.14)
Ipsilateral	1
Shunting	0
No shunting	1
CCO	0
Contralateral	2
Shunting	0
No shunting	2
Carotid occlusion	2
TIA	40 (1.99)
Ipsilateral	23 (1.14)
Contralateral	17 (0.84)
Stroke plus TIA	48 (2.39)
Death	0
Cerebral hemorrhage	0
Hyperperfusion syndrome	0
Nonfatal myocardial infarction	1 (0.04)
Nerve injury	91 (4.53)
Cervical re-exploration for bleeding	86 (4.28)

CCO, Contralateral carotid occlusion; CEA, carotid endarterectomy; TIA, transient ischemic attack.

**Minor perioperative neurological events.** Of the 40 (1.99%) perioperative TIAs observed in all, 17 (0.84%) occurred in the middle cerebral artery territory contralateral to the operated side. In all cases, duplex ultrasound scanning immediately after the onset of neurological signs showed that the revascularized carotid artery was patent, and cerebral CT/MR images were negative for any new ischemic events (Table III).

**Other complications.** Overall, there was only one perioperative cardiac complication (0.04%) in a male patient, which was managed conservatively. None of the patients had any cerebral hemorrhage or hyperperfusion syndrome. Overall, postoperative arterial hypertension needing medication in the recovery room was recorded in 271 eCEA procedures (13.5%), and, to reduce the risk of hyperperfusion syndrome, these patients were treated by means of an intravenous infusion of the medication (mainly urapidil). There were 91 nerve injuries (4.5%) altogether, 62 (3.1%) involving the cranial nerves and 29 (1.4%) the cervical nerves. Other surgical morbidities included 86 (4.28%) neck hematomas requiring surgical evacuation but causing no further complications (Table III). This prompted a change in practice during the study period: intraoperative heparinization was never reversed with protamine up until 2009, but from January 2010 onward, all patients had partial (half-dose) heparin

**Table IV.** Long-term results

Outcomes	1905 CEAs (1680 patients), No. (%)
Stroke	9 (0.47)
Ipsilateral	4 (0.21)
Contralateral	5 (0.26)
Death	159 (9.46)
Stroke-related	2 (0.10)
Restenoses	9 (0.47)
50%-69%	6 (0.31)
$\geq 70\%$	3 (0.15)
Carotid occlusion	1 (0.05)
All restenoses plus occlusions	10 (0.52)

CEA, Carotid endarterectomy.

reversal. Our decision to arbitrarily use a partial heparin reversal was based on the amount of residual heparin thought to be still in circulation at the moment of neutralization, given its relatively short half-life and the limited carotid cross-clamping time during eCEA, which was averaged <25 minutes in our hands. This meant that CEA was always performed with the certainty of a complete systemic anticoagulation, but its effects were not prolonged after declamping. After this change was introduced, there were no further postoperative neck hematomas needing re-exploration.

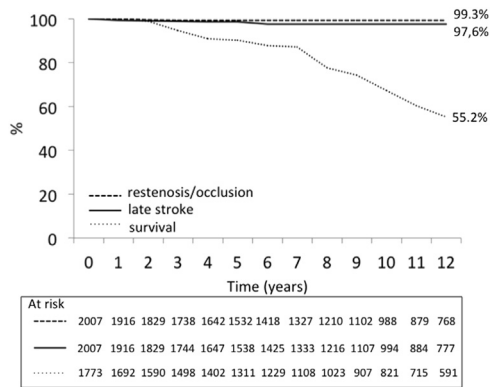
**Long-term results.** Among the 1773 patients alive 30 days after their CEA, 93 (5.2%; 102 CEAs) were lost to follow-up. A complete follow-up (median, 11.2 years; mean, 12.9  $\pm$  0.8 years; range, 1-20 years) was thus obtained for 1680 patients (94.8%) and an overall 1905 CEA procedures (94.9%).

Overall, only one carotid occlusion was detected (0.05%): this occurred in a male patient without symptoms within the first postoperative year and involved a carotid artery that had not been shunted and that had been patent at the first two duplex ultrasound scans (Table IV).

Altogether, nine restenoses (0.47%) were  $\geq 50\%$ , involving vessels that had not been shunted and occurring without symptoms, mainly within 24 months of surgery; only three of them (0.15%) were  $\geq 70\%$  (Table IV). The first of these three  $\geq 70\%$  restenoses remained stable at subsequent duplex ultrasound scans and was treated conservatively, whereas the other two rapidly progressed, becoming severe enough to require a second CEA and a CAS procedure, respectively, 19 and 33 months after the first revascularization. Kaplan-Meier analysis showed that the rates of freedom from restenosis/occlusion at 1, 5, 10, and 12 years were 99.9  $\pm$  0.1%, 99.3  $\pm$  0.2%, 99.3  $\pm$  0.2%, and 99.3  $\pm$  0.2%, respectively (Fig).

Overall, there were nine late strokes (0.47%), none of which occurred in patients with recurrent stenosis. Three were cardioembolic and four were lacunar (two contralateral to the operated side) whereas two (ipsilateral to the operated side and contralateral to a carotid occlusion) were probably hemodynamic in nature, judging from the CT images (Table IV). Kaplan-Meier analysis showed that the rates of freedom from stroke at 1, 5, 10, and





**Fig.** Kaplan-Meier analysis curves show the freedom from >50% restenosis/occlusion (dotted line), late stroke risk (line), and late survival (bulleted line). Percentages on the right represent the rates at 12 years. The standard error is <10% at each time point for all curves, ranging from 0% to 0.2% for restenosis/occlusion, from 0% to 1.7% for stroke risk, and from 0% to 8.4% for late survival. Raw numbers of eversion carotid endarterectomy (eCEA) procedures (restenosis/occlusion and stroke) and patients (survival) at risk analyzed at each time point are provided below the figure.

12 years were  $99.4 \pm 0.2\%$ ,  $98.6 \pm 0.4\%$ ,  $97.6 \pm 1.7\%$ , and  $97.6 \pm 1.7\%$ , respectively (Fig).

There were 159 late deaths (9.4%) in the series as a whole. The cause was primarily cardiac-related ( $n = 88$ ; 55.3%), whereas two deaths were stroke-related, one involving a female patient with atrial fibrillation of recent onset, and the other contralateral to the revascularized side and ipsilateral to a carotid occlusion. The survival rates at 1, 5, 10, and 12 years were  $99.6 \pm 0.2\%$ ,  $90.2 \pm 0.9\%$ ,  $67.3 \pm 7.7\%$ , and  $55.2 \pm 8.4\%$ , respectively (Fig).

## DISCUSSION

Large RCTs have shown that CEA is superior to the best medical therapy in the prevention of stroke in symptomatic patients with severe carotid stenosis<sup>1,2</sup> and in selected cases of asymptomatic carotid disease.<sup>3,4</sup> For CEA to be meaningful, however, the long-term benefit (in terms of stroke prevention) must balance the perioperative risk (stroke and death).<sup>5</sup> Although the perioperative stroke and mortality rates after CEA reported in the RCTs are still considered acceptable, they are 15 to 20 years old, and the literature has demonstrated that these rates have dropped drastically over time, thus setting a high standard of care for comparison with evolving stenting procedures. As well as the often-emphasized perioperative results, the durability of CEA is intuitively important too, with a view to avoiding the risk of secondary procedures being needed for any significant progression of restenoses, even without counting the fact that they can trigger adverse clinical events such as TIA and stroke.

The results of the present study correlate well with other large, contemporary surgical series, going to show that eCEA has an extremely low perioperative risk and is

an excellent treatment for selected symptomatic and asymptomatic carotid lesions (Table V).<sup>19-32</sup> Because late carotid occlusions and recurrent stenoses are the real indicators of CEA durability, our combined occlusion and >70% restenosis rate of 0.21% over a mean follow-up of 12.9 years clearly demonstrates that eCEA is a durable procedure, against which other interventional treatment options should be matched.

Because the occurrence of post-CEA restenosis is mainly related to how the arteriotomy is closed, a number of technical variations have been introduced to minimize its incidence.

Two CEA techniques are currently used: conventional CEA with patching and eCEA, because CEA with primary closure is not to be recommended and has been virtually abandoned because of inferior early outcomes and a high incidence of late restenosis.<sup>33</sup> eCEA involves the oblique transection of the internal carotid artery from the common carotid artery at the bulb, with an incision almost longitudinal, making a long hole on the lateral wall of the common carotid artery. The adventitia of the internal carotid artery is then everted over its atherosclerotic core to the end of the plaque, thus enabling to close and direct visualization of the end point for its entire circumference, simplifying the careful debridement of all circular fibers and the complete removal of loose fragments, with no need for end point tacking sutures. After completion of the internal carotid artery endarterectomy, the eversion is reduced. The arteriotomy can be extended into the common carotid artery to facilitate the removal of the common and external carotid arteries' plaque, so that the suture line is in the adventitia and nowhere in the plaque area. The reanastomosis of the internal carotid artery with the common carotid artery allows widening of both lumens, preserving the original carotid configuration, with the internal and common carotid arteries ultimately patching each other. In a recent Cochrane Collaboration Systematic Review comparing the above two CEA methods, the authors concluded that there is currently no evidence of the superiority of one over the other in terms of perioperative stroke.<sup>34</sup> The optimal surgical technique for CEA therefore has yet to be ascertained, and the choice of one or other continues to depend on the personal experience and preferences of the surgeons involved, although eCEA has commonly been identified as an independent factor contributing to better long-term results.<sup>19,21,29,35</sup>

Since 1990, when eCEA was first introduced at our institution, this technique has gradually replaced conventional CEA with routine patching in our daily surgical practice as the treatment of choice for patients with carotid occlusive disease. We have used exclusively eCEA to treat all primary carotid lesions since 1998. Although the numerous advantages of eCEA include short clamping and operating times, no need for prosthetic material, an easier correction of concomitant redundant carotid artery, and a lower incidence of restenosis, the few concerns raised regarding this method relate to the potential incomplete visualization of the distal endarterectomy end point and the reported

**Table V.** Early and late outcomes in large series adopting preferably conventional CEA with patching and/or eCEA

Author <sup>Ref</sup>	Method of closure (%)	Mean follow-up, years	CEA/patients	Symptoms, %	30-day death/stroke, %	RS, %	Late CO +RS, %
Shah <sup>19</sup>	Patching (3)	1.5	474/410	44	4.5	>60	1
	Eversion (82)	1.5	2249/1855	34	2.3		0.3
Archie <sup>20</sup>	Patching (99.6)	4.6	1289	62	2.1	>50	2.1
	Primary (0.4)	4.6	51		0		
Cao <sup>21</sup>	Patching (19)	2.7	256	N/A	N/A	>50	1.5
	Primary (31)	2.7	419	60	1.3		7.9
	Eversion (50)	2.7	678	57	1.3		2.8
Scavee <sup>22</sup>	Patching (100)	4.1	600	46	0.9	>50	5.8
Trisal <sup>23</sup>	Patching (62)	N/A	1648	N/A	N/A	>70	3.8
	Primary (38)						5.8
LaMuraglia <sup>24</sup>	Selective patching	6.1	2127/1853	36	1.4	>70	9.8
Crawford <sup>25</sup>	Patching (53)	5.5	155/155	30	1.1	>70	5.2
	Eversion (47)	3.5	135/135	31	0		5.9
Black <sup>26</sup>	Eversion (100)	8.86	534/485	44	3.8	>60	4.1
Goodney <sup>27</sup>	Patching (88)	1.1	2611	52	Overall, 1.2	>80	2
	Eversion (12)	1.1	370			6	
	Selective patching	1	1203/1203	85		N/A	>50
Radak <sup>29</sup>	Eversion (100)	N/A	9897/9181	98	1.9	>50	4.3
Demirel <sup>30</sup>	Patching (40)	2	310	100	3	>70	3.2
	Eversion (60)	2	206	100	9		2.4
Babu <sup>31</sup>	Patching (100)	15.8	1492/1335	60	0.9	>70	0.4
Hertzer <sup>32</sup>	Patching (66)	5-10	1301/1129	32	Overall, 2.7	>60	10.3
	Primary (34)	5-10	658/559	42		30	
Present series	Eversion (100)	15.9	2007/1773	72.1	0.39	>50	0.52

CEA, Carotid endarterectomy; CO, carotid occlusion; eCEA, eversion CEA; N/A, not available; RS, recurrent stenosis.

technical difficulty in the presence of a shunt. None of the CEA procedures considered in this series were aborted or incomplete, however, and none of the patients were refused eCEA for technical issues arising during surgery.

The reported rates of recurrent stenosis after CEA vary, but any comparison of the results between the different series is bound to be methodologically flawed, given the differences in its definition, the length of patient follow-up, and the technique used to perform the CEA. In a recently-published series of 1492 CEAs with patching performed in 1335 patients followed up for a mean 15.8 years, the rate of >70% recurrence was 0.4% (much the same as ours).<sup>31</sup> Similarly, an analysis on 2723 CEA procedures (2249 eCEAs and 474 CEAs with patching, performed in 1855 and 410 patients, respectively) identified an incidence of >60% restenosis of 0.3% for eCEAs and 1% for conventional CEAs over a mean follow-up of 1.5 years.<sup>19</sup> Further studies, including an RCT comparing CEA with patching and eCEA,<sup>21</sup> and other large single-center series (≥500 CEA procedures) adopting only one type of surgical technique<sup>22,24,26,28,29,31</sup> or combinations of conventional CEA and eCEA,<sup>19,25,27,30</sup> reported recurrence rates ranging from 1.5% to 14.7% for conventional CEA and from 2.4% to 6% for eCEA, with an overall mean follow-up ranging from 1.1 to 8.9 years (Table V).

In recent years, CAS has emerged worldwide as a potential alternative to CEA for the treatment of carotid disease. Our indications for CAS are restricted to a small

subset of patients, such as individuals with severe or symptomatic recurrent stenosis after CEA or with radiation-induced stenosis. Although data from centers with high-volume experience have demonstrated the technical feasibility and safety of CAS, a recent meta-analysis of pooled individual patient data from three RCTs comparing CAS with CEA (mainly in symptomatic patients),<sup>6</sup> and the latest randomized evidence from a large RCT comparing CAS with CEA in both symptomatic and asymptomatic patients<sup>7</sup> clearly indicate that more periprocedural strokes and deaths occur with CAS than with CEA. Currently emerging long-term results demonstrate the durability of CAS, but there are limited data to support the claim of the noninferiority of CAS to CEA. Only a few nonrandomized studies have focused on the incidence of restenosis after CAS, through the use of very different follow-up protocols. Although several thousand CAS procedures have been described in the literature, the real incidence of in-stent restenosis remains unknown because different studies report quite different rates, ranging from <5%<sup>36</sup> to >21%.<sup>37</sup> A secondary analysis of the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST)<sup>38</sup>—a large RCT comparing outcomes of CAS vs CEA in 2502 patients enrolled at 117 centers in the United States and Canada—reported a >70% restenosis rate of 6% after CAS at 2 years, which was comparable with the 6.2% restenosis rate after CEA. In previous RCTs on CAS vs CEA, the incidence of restenosis after CAS varied

from 3% at 3 years (in a sample of 143 patients) to 11.1% at 2 years (among 541 patients) and to 16.6% at 5 years (considering 50 patients).<sup>38</sup>

As in other institutional series demonstrating that restenosis is rarely responsible for neurological symptoms,<sup>10,31</sup> no late adverse ischemic events occurred in our patients with post-CEA restenosis; considering the relatively short interval before its onset after surgery, this might be related to the nonembolic nature of the new carotid lesion (intimal hyperplasia). On the other hand, other studies have found that restenosis increases the risk of ipsilateral stroke. A recently-published single-center series on 361 patients who had CEA between 1970 and 2002 showed that recurrent stenosis in the ipsilateral carotid artery occurred at a rate of 5.2% at 5 years and 37% at 20 years and found that the likelihood of further ipsilateral adverse ischemic events in a substrate of recurrence was 10% after 5 years and 50% after 20 years.<sup>39</sup> More than 88% of the conventional CEA procedures in this series were completed with primary closure, however. Similarly, post hoc analysis of the CREST proved that individuals who had development of restenosis/occlusion within 2 years were at greater risk of ipsilateral stroke after the perioperative period and up until the end of their follow-up than those who did not have development of restenosis/occlusion within 2 years.<sup>38</sup> The investigators admitted, however, that they were unable to state whether restenosis developed before or after stroke.

Although a late TIA or stroke occurring on the same side as a CEA is not necessarily correlated with carotid disease, our 0.39% risk of ipsilateral stroke goes to show that the eCEA procedure offers a good protection against the risk of late cerebral ischemia.

**Limitations of the study.** Some limitations of our study warrant consideration. First, all our nonrandomized, observational data were collected prospectively but analyzed retrospectively. Second, the study represents a single surgeon's experience with eCEA at a single institution, and, although this ensures that the surgical technique was the same for every operation, it does not mean that the results are reproducible; to make these findings more generalizable, a wider, more representative sample of surgeons and institutions must be considered. Third, this is a case series, not a comparative study of recurrent stenosis, exploring the differences between eCEA and conventional CEA with patching or CAS. Our analysis was undertaken to demonstrate that eCEA affords perioperative mortality and morbidity rates and a durability that makes it worthy of consideration when advising patients on how best to manage their carotid occlusive disease.

## CONCLUSIONS

The results of this observational study show that eCEA can be performed in symptomatic and asymptomatic patients with an extremely low perioperative stroke/death risk and a negligible incidence of late restenosis/occlusion, affording good long-term protection against the risk of cerebral ischemia.

## AUTHOR CONTRIBUTIONS

Conception and design: EB, AT, CB

Analysis and interpretation: EB, AT, CB

Data collection: RL, ADR

Writing the article: EB, CB

Critical revision of the article: EB, AT, GDG, CB

Final approval of the article: EB, AT, GDG, RL, ADR, CB

Statistical analysis: GDG

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