Appropriateness of learning curve for carotid artery stenting: An analysis of periprocedural complications

Fabio Verzini, MD, Piergiorgio Cao, MD, FRCS, Paola De Rango, MD, Gianbattista Parlani, MD, Agostino Maselli, MD, Lydia Romano, MD, Lucia Norgiolini, MD, and **Giuseppe Giordano, MD,** *Perugia, Italy*

Objectives: **Cerebral embolism is the first cause of neurologic complications of carotid artery stenting (CAS). A large debate has been raised to identify the caseload necessary for an appropriate learning curve before systematic use of CAS. This study examined (1) the timing of periprocedural complications during CAS and how these complications vary over time to identify factors that contribute to neurologic morbidity and (2) a sufficient number of procedures for adequate training.**

Methods: **During 2001 to 2006, 627 CAS procedures with cerebral protection devices (CPD) were performed in a single vascular surgery center by a team including a vascular surgeon and an interventional radiologist. These represented 38% of a total of 1598 carotid revascularizations performed in the same interval. CAS procedures were divided into two groups according to time interval: the first period, 2001 to 2003, included 195 CAS procedures, and the second period, 2004 to 2006, included 432 CAS procedures. During each CAS procedure, five major steps were considered: phase 1, or the catheterization phase, included the passage of the aortic arch, catheterization of the target vessel, and introduction of a guiding catheter or sheath. Phase 2, or the crossing stenosis phase, included the placement of a CPD. Phase 3, or the stent ballooning phase, included predilation (when indicated), stent implantation, postdilation, and recovery of the protection system. Phase 4, or the early postinterventional phase, included the first 24 hours after leaving the catheterization table. Phase 5, or the late postinterventional phase, included the interval from the first postoperative day to 30 days.**

Results: **At 30 days, 10 major strokes (2 of which were fatal) and 1 cardiac death occurred, for an overall major stroke/death rate of 1.75%. Furthermore, 18 minor strokes (2.9%) were recorded. By analyzing the occurrence of major strokes according to the three intraprocedural phases, four occurred in phase 1 and six in phase 3. All strokes but one were ischemic; six were ipsilateral, three were contralateral, and one was posterior. Minor strokes occurred prevalently after the procedure (11 in phase 4, 5 in phase 5, and 1 for phases 1 and 3). Comparing the first with the second interval of the study period, the 30-day major stroke and death rate decreased from 3.1% to 0.9% ($P = .047$), and the 30-day any stroke and death rate decreased from 8.2% to 2.7% ($P = .005$). According to multivariate analysis, study interval (hazard ratio, 3.68; 95% confidence interval, 1.49-9.01; $P = .005$) and age (hazard ratio, 1.06; 95% confidence interval, 1.00-1.12; $P = .05$) were significant predictors of stroke.**

Conclusions: **A large proportion of major strokes (4/10) from CAS cannot be prevented by using CPD, because these strokes occur during catheterization (phase 1). This finding, together with the significant decrease in the overall stroke/death rate between the first and the last interval of the study period, enhances the importance of an appropriate learning curve that involves a caseload larger than that generally accepted for credentialing. The noticeable number of postprocedural cerebral embolizations leading to minor strokes and occurring in the early and late postinterventional phases (16/18) is likely due to factors less strictly related to the learning-curve effect, such as stent design and medical therapy. Moreover, expertise in selecting material and design of the stents according to different vessel morphology, in association with correct medical treatment, may be useful in reducing the number of minor strokes that occur in the later postinterventional phases of CAS. (J Vasc Surg 2006;44:1205-12.)**

Carotid artery stenting (CAS) is becoming increasingly common for the treatment of carotid stenosis because accumulating (but not randomized) data suggest that CAS has promising efficacy in preventing stroke, with an acceptable rate of procedure-related complications when compared with carotid endarterectomy (CEA). However, CAS procedures can carry a risk of nonnegligible complications; the most frequently encountered are generally due to brain embolism during catheter, wire, or sheath manipulation in the aortic arch and through the carotid artery.[1] These strokes, occurring before or after cerebral protection device (CPD) placement, depend on multiple factors such as patient selection, material choices, and, ultimately, the operator's skills. All these data enhance the importance of an appropriate learning curve, but there is still debate to identify the caseload necessary before systematic use of CAS. The aim of this study was to evaluate the extent of experience required to ensure the safety of CAS procedures

From the Division of Vascular and Endovascular Surgery, University of Perugia.

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Reprint requests: Piergiorgio Cao, MD, FRCS, Division of Vascular and Endovascular Surgery, Ospedale S. Maria della Misericordia, S. Andrea delle Fratte, 06132 Perugia, Italy (e-mail: pcao@unipg.it).

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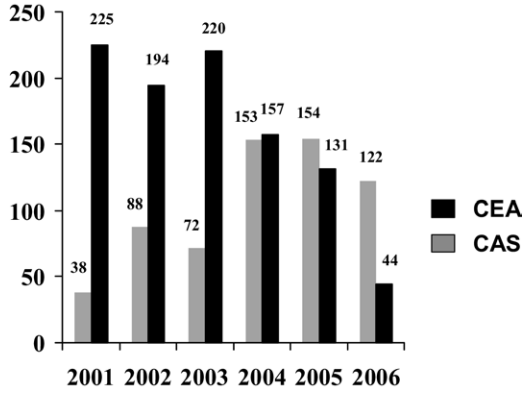

Fig 1. A total of 1598 carotid procedures: carotid artery stenting *(CAS)* and carotid endarterectomy *(CEA)*.

through the analysis of the timing of occurrence and factors affecting neurologic morbidity.

SUBJECTS AND METHODS

From May 2001 to April 2006, a total of 627 CAS procedures were performed in 570 patients (57 staged and bilateral) in a single vascular surgery center. These represented an overall rate of 39% of 1598 carotid revascularizations performed in the same interval (Fig 1). By using the same 2% threshold rate for major stroke achieved with CEA,[2,3] CAS procedures were divided into two groups based on time interval. The first period, 2001 to 2003, included 195 CAS procedures, and the second period, 2004 to 2006, included 432 CAS procedures, in which the major stroke risk remained stable (<2%). All patient data were systematically collected in a prospective database including preprocedural, intraprocedural, and follow-up information. The primary criterion for treatment was either symptomatic (≥60%) or asymptomatic (>70%) internal carotid artery stenosis.

Preoperative evaluation. All patients underwent diagnostic carotid duplex ultrasonography (US) within 1 month before carotid revascularization. Duplex US scanning was performed by experienced vascular surgeons, who defined the site, degree and length of stenosis, plaque characteristics, and vessel measurements to select the proper size of the balloon and stent. On the basis of duplex examination, plaques were divided into three groups: echolucent, echogenic, and mixed (including a similar amount of echolucency and echogenicity). Preoperative diagnostic digital arch aortography, cerebral computed tomography (CT) scan, and supra-aortic vessel spiral CT scan were used selectively. Patients scheduled for CAS received full antiplatelet therapy consisting of clopidogrel (loading dose of 300 mg within 12 hours before the procedure and then 75 mg/d) in addition to aspirin (mean dose of 125 mg/d).

Operative techniques. All CAS procedures were performed with patients under local anesthesia in an operating room equipped with a digitalized portable C arm or a fixed angiographic facility (for the last 150 cases) by a team consisting of 1 vascular surgeon and 1 interventional radiologist, who had much experience in aortic arch diagnostic and endovascular procedures before beginning to perform carotid stenting. However, most of the procedures (76%) were conducted by the senior vascular surgeon (P.C.).

Arterial access was transfemoral for all but nine procedures, for which left brachial artery was used because of severe obstruction in the iliac/femoral vessels. During CAS, the patient's neurologic status was checked continuously by having the patient squeeze a toy in the appropriate hand and by talking to the patient. Transcranial Doppler monitoring (4040 Pyoneer Eme; Nicolet/EME, Weinheim, Germany) was applied when possible (330/627; 53%).

Procedures started with a diagnostic angiogram of the aortic arch followed by selective catheterization of aortic arch vessels in double projection. Intravenous heparin 100 U/kg was given before selective catheterization of the common carotid artery. Intracranial images were routinely obtained before and after the intervention to confirm patency of intracranial vessels.

CAS was performed after proper placing of CPD under roadmap guidance. Seven different protection systems were used: FilterWire EZ system (n = 470, 75%; Boston Scientific, Natick, Mass), TRAP Filter (n = 30, 5.6%; Microvena, White Bear Lake, Minn), EV3 SpideRX Filter (n = 5, 0.9%; Plymouth, Minn), Angioguard RX Filter (n = 103, 17.3%; Johnson and Johnson–Cordis, Warren, NJ), Rubicon Filter (n = 3, 0.5%; Rubicon Medical Inc, Salt Lake City, Utah), MO.MA system (n = 7, 1%; Invatec, Brescia, Italy), and Rx Accunet Guidant Filter (n = 1, 0.17%; Guidant, Santa Clara, Calif). The stenosis was crossed with a 0.014-inch guidewire (either a CPD distal filter guidewire or an exchange guidewire) over which the stent and angioplasty balloon were advanced. Predilation (balloon dilation before delivery of the stent) was performed at the discretion of the operator in 64 (10.2%) cases.

In all patients, self-expandable stents were used: 430 (73%) carotid Wallstents (Boston Scientific), 155 (25%) Precise stents (Johnson and Johnson-Cordis), 3 (0.5%) Acculink stents (Guidant), 3 (0.5%) NexStents (Boston Scientific), 2 (0.3%) Conformexx stents (Bard, Murray Hill, NJ), and 2 (0.3%) Exponent stents (Medtronic AVE, Santa Rosa, Calif). The selection of the stent depended on operator preference, lesion characteristics, and commercial availability.

Stent size conformed to the largest diameter of the artery to be treated according to the preoperative measurements of the artery by US examination. Intravenous atropine (mean dose, 1 mg intravenously) was used in 444 procedures (70.8%) just before balloon inflation, at the discretion of the anesthesiologist. After retrieval, CPDs were visually checked for debris.

Procedural success for CAS was defined as stent deployment with resolution of stenosis or with residual stenosis less than 30% at the completion angiogram in double projection. Arterial access hemostasis was obtained by using

Table I. Risk factors in the two study periods

Variable	*Overall (n = 627)*	*2001-2003 (n = 195)*	*%*	*2004-2006 (n = 432)*	*%*	P *value*
Mean age (y)	72.1	72.17		72.23		NS
Sex (male)	439 (70%)	138	71%	301	70%	NS
Symptomatic stenosis	139 (22%)	53	27%	86	20%	.05
Hypertension	545 (87%)	165	85%	380	88%	NS
Diabetes	192 (31%)	58	30%	134	31%	NS
Cardiac disease	320 (51%)	118	60%	202	47%	.02
Peripheral arterial disease	120 (19%)	49	25%	71	16%	.01
Echolucent plaque	50 (8%)	4	2%	46	11%	.0001
Contralateral occlusion	52 (8%)	21	11%	31	7%	NS
Restenosis	93 (15%)	31	16%	62	14%	NS

NS, Not significant.

a closure device in 289 procedures, including 261 Perclose (Abbott Laboratories, Abbott Park, Ill) and 28 Angioseal (St Jude Medical, Inc, St Paul, Minn) devices.

Patients were evaluated at the end of the procedure, monitored, and routinely discharged the following day, with the exception of those with complications. Clinical and US examinations were performed before discharge, at 1 month, and every 6 months after the procedure. In the case of symptoms or uncertainty, all patients were examined by a neurologist, and the necessary diagnostic imaging was performed (CT scan or magnetic resonance imaging). The same team of stroke neurologists evaluated patients with clear or suspected symptoms before and after the procedure. Patients continued taking aspirin and clopidogrel (75 mg/d) for 30 days after the procedure, and aspirin was continued for life.

Definition of outcome and complications. Outcome measures were stroke, death, cardiac events, and local complications. Perioperative stroke was defined as any new neurologic event persisting for longer than 24 hours and occurring within 30 days from the procedure.[4] Strokes were classified as fatal, major (requiring a significant modification of lifestyle for >1 month after onset), or minor (symptoms without significant modification of lifestyle as evaluated by a neurologist). Transient ischemic attack (TIA) was defined as any new retinal or hemispheric focal event with complete recovery within 24 hours. TIAs were recorded but not considered as primary end points of the study.

Myocardial infarction was diagnosed with the occurrence of a new Q wave in two or more leads and/or the presence of increased enzymes (including creatine phosphokinases and troponins) routinely tested. To precisely define the timing of occurrence of complications, five major steps were identified for each procedure. Phase 1, or the catheterization phase, included the passage of the aortic arch, catheterization of the target vessel, and introduction of a guiding catheter or sheath. Phase 2 included crossing the stenosis and placement of CPD. Phase 3 included predilation (when indicated), stent implantation, postdilation, and recovery of the protection system. Phase 4, or the early postinterventional phase, included the first 24 hours after leaving the operating table. Phase 5, or the late postinterventional phase, included the interval from the first postoperative day to 30 days.

Statistical analysis. For univariate comparisons of risk factors and preoperative findings, statistical significance was assessed by two-tailed χ^2 test with Yates corrections or the Fisher exact test. Odds ratios and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by standard methods. Continuous data are expressed as mean ± SD. To control for potential confounding variables regarding the risk of stroke, multivariate analysis with conditional logistic-regression models was used. The following variables were included in the model: age, sex, diabetes, cardiac disease, history of ipsilateral symptoms, contralateral occlusion, echolucent plaque, restenosis after CEA, stent configuration (open cell vs closed cell), hemodynamic instability during CAS, and study interval (years 2001-2003 vs 2004-2006). Significant values were considered with $P < .05$. SPSS (SPSS Inc, Chicago, Ill) was used for all analyses. Study outcomes were analyzed on an intention-to-treat basis.

RESULTS

Characteristics of patients per study period are shown in Table I. A total of 139 stenoses (22%) were symptomatic. The mean age was 72.1 years (range, 49-91 years), and 438 patients (69.4%) were male.

Inability to complete CAS occurred in 32 procedures (5.1%); 24 were converted, during the same admission (n = 6) or later (n = 18), to CEA. Reasons for failure included 24 inabilities to cross the stenosis and 8 inabilities to reach the target vessel because of excessive tortuosities or calcification in the aortic arch.

Procedures were conducted by the vascular surgeon in charge: in detail, 76% of CAS procedures, embracing a similar rate of neurologic complications (75%), were managed by the same operator (P.C.). At 30 days, 10 major strokes (2 of which were fatal) and 1 cardiac death occurred, for an overall major stroke/death rate of 1.75%. All strokes but one were ischemic; six were ipsilateral, three were contralateral, and one was posterior. Four occurred in phase 1 and six in phase 3, whereas no major stroke oc-

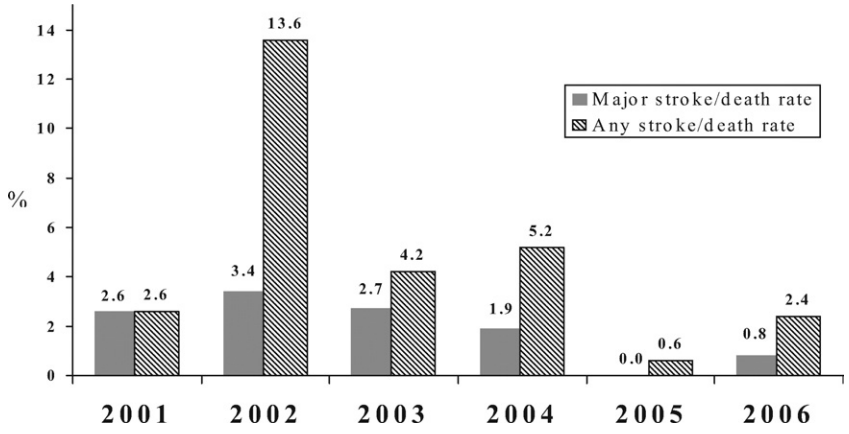

Fig 2. Perioperative stroke and death rate per year in 627 carotid artery stenting procedures.

Table II. Results of univariate analysis on perioperative stroke

Risk factor	*Strokes with risk factor (n)*	*%*	*Strokes without risk factor (n)*	*%*	P *value*
Age >80 y	7/90	7.7	21/537	3.9	.09
Sex (male)	19/439	4.4	9/188	4.7	.47
Diabetes	10/192	5.2	18/435	4.1	.34
Cardiac disease	11/320	3.4	17/307	5.5	.14
Symptomatic stenosis	9/139	6.4	19/488	3.9	.14
Echolucent plaque	3/50	6	25/577	4.3	.39
Contralateral occlusion	3/52	5.8	25/575	4.3	.41
Restenosis	4/93	4.3	24/534	4.5	.59
Open-cell stent	5/162	3.1	23/433	5.3	.13
Hemodynamic instability	9/160	5.6	19/467	4.1	.55
2001-2003 study period	16/195	8.2	12/432	2.8	.003

curred after leaving the operating room. In addition, 18 (2.9%) minor strokes were recorded.

Of 18 minor strokes, all ipsilateral, 1 occurred during phase 1, 1 during phase 3, 11 within 24 hours (phase 4), and 5 after 24 hours from treatment. Most TIAs (22/23), all ipsilateral, occurred in the protected phase (phase 3).

Visible debris was collected in the CPD in 233 (37%) CAS procedures and in 72% of those with stroke. A marked hemodynamic response (bradycardia, hypotension, or both) was recorded with a similar rate in CAS patients with (32%; 9/28) and without (25%; 151/599) stroke complications ($P = .4$). Three myocardial infarctions occurred at 30 days (0.5%), one of which was fatal in a patient converted to CEA. There were no neurologic events in patients converted to CEA or left on medical treatment after a failed CAS.

Vascular-access complications occurred in 13 patients (2.1%); 12 were due to false aneurysm formation at the femoral puncture site. All required surgical correction. The other was due to median nerve injury after percutaneous left brachial access in a patient with iliac obstruction.

We specifically analyzed how the stroke rate varied over the study period. The major and any stroke/death incidence for each year is shown in Fig 2. Comparing the first with the second interval, 30-day major stroke and death rates significantly decreased from 3.1% to 0.9% ($P = .047$; odds ratio, 3.2; 95% CI, 1.1-12.1), and any stroke and death rates decreased from 8.2% to 2.7% ($P = .005$; odds ratio, 3.1; 95% CI, 1.45-6.74).

Furthermore, the timing of occurrence of major strokes varied from the first to the last 3 years: four of the six major strokes occurring during the first study interval (years 2001-2003) were in phase 1, whereas all four major strokes in the years 2004 to 2006 occurred in phase 3. Results of the univariate analysis on perioperative stroke are displayed in Table II. According to multivariate analysis, study interval (HR, 3.68; 95% CI, 1.49-9.01; $P = .005$), and age (HR, 1.06; 95% CI, 1.00-1.12; $P = .05$) were significant predictors of stroke.

DISCUSSION

It is evident by the recent increase in the number of studies on CAS that CEA as the gold standard of treatment for carotid stenosis is under challenge. Although current evidence is generally considered to be of lower scientific value than randomized trials, systematic reviews of observational studies are providing a source of persuasive data to support CAS.[5] Using the best and most recent literature,

Burton and Lindsay[6] found CAS to be associated with an adverse event rate of 2.4% ± 0.3 in 2992 patients (3091 CAS) from 26 studies published between 2002 and 2004. Among the different studies, the minor stroke rate was 0% to 6%, the major stroke rate was 0% to 3%, and the death rate was 0% to 7%. The present single-center study showed an overall periprocedural CAS stroke/death rate of 4.6% that decreased to 2.7% during the second study interval. These event rates are comparable to those of current CEA.[6-11]

As with any new procedure, safety is of paramount importance, and this is especially true for CAS when compared with a well-established, safe, and effective technique, such as that used in carotid surgery. We recently analyzed outcomes in a matched case-control study in which CAS was compared with CEA.[2] Although the difference in major strokes was not statistically significant, the overall risk of any periprocedural stroke was higher for CAS; stroke incidence markedly decreased over the study period. Considering a learning-curve effect for the first 100 CAS procedures, 30-day any stroke rates decreased from 13% to 5.4%, and 30-day disabling stroke rates decreased from 4% to 2.5%. In this study, we attempted to better define the caseload necessary before performing safe CAS, assuming the same 2% threshold rate for major stroke achieved for CEA in previous studies conducted by our center.[2,3] Indeed, it was only after the first 195 CAS procedures that the yearly major stroke risk remained stable at less than 2%.

Multivariate analysis including common stroke risk factors found that the most significant predictor of stroke was the study interval (2001-2003 vs 2004-2006), with the first period carrying a higher risk (HR, 3.68; 95% CI, 1.49-9.01; $P = .005$). Other studies recently agreed on the importance of a larger number of CAS interventions to overcome the negative effects of the initial learning phase. Ahmadi et al[10] showed a significant reduction in the frequency of neurologic complications ($P < .03$) and in the mean duration of intervention ($P < .0001$) with increased carotid experience in 320 CAS procedures performed by 1 operator at a single center.

In our study, a team consisting of one vascular surgeon and one interventional radiologist performed every CAS procedure. Since not everyone achieves the same level of expertise with the same learning curve, and given that each member of the team can learn from the experience of the others, we found it more realistic to analyze the learning curve of the team rather than that of the individual. We believe, therefore, that the results are more generalized because they are not related to the particular skills of a single operator. Indeed, the senior operator's results (in 76% of the CAS procedures included in this study), are identical to those of the remaining 24%, thus proving a similar performance among different team members. Other studies have reported on a CAS learning curve with a team approach: Lin et al,[11] analyzing the effect of learning curve on a series of 200 CAS procedures conducted by a team and dividing the entire series into 4 groups of 50 consecutive interventions, reached similar conclusions, with a significant reduction in the stroke/death rate from 8% to 0% ($P < .05$) between the first and the last 50 procedures.

According to this experience, besides the study period, only older age increased the stroke risk during CAS (HR, 1.06; 95% CI, 1.00-1.12; $P = .05$). Other risk factors previously identified as significant predictors of periprocedural stroke, such as symptomatic lesions and plaque morphology, did not seem to influence the outcome.[12-14] Regarding plaque analysis, we did not consider the gray-scale median classification[14] because this methodology is still debated and because its reproducibility is not fully accepted.

The low incidence of cerebral hemorrhage and cardiac complications compares favorably with other results of CAS in the literature.[15-17] The careful pressure monitoring during and shortly after the procedure may explain these findings.

In-depth analysis of the timing of complications showed that phase 1 (catheterization or diagnostic phase) and phase 3 (stent-ballooning phase) seemed to be the most hazardous steps for CAS; all major strokes occurred during these two phases. However, the 4 major strokes occurring before CPD placement (phase 1) were recorded during the first 195 procedures, whereas no major event occurred during phase 1 in the last study interval.

Hammer et al[12] specifically analyzed the embolism risk in 53 CAS patients by systematic application of cerebral diffusion-weighted magnetic resonance imaging 24 hours before and 5 to 30 hours after the procedure. The authors found new ischemic lesions in approximately 40% (n = 21) of the patients, although these were symptomatic only in 4% (n = 2). It is interesting to note that in 62% (13/21) of the positive diffusion-weighted magnetic resonance imaging cases, embolic lesions were found outside the vascular territory of the treated internal carotid artery, thus suggesting embolization from the aortic arch. These findings showed that embolization originating from sources proximal to the treated lesion is a relatively frequent and not completely avoidable event, but the significance of such clinically silent embolization should be of concern, especially in an elderly population and in patients with impaired brain function or previous cerebral infarction. Conversely, embolic events originating from the catheter, wire, or sheath manipulation in the aortic arch and the common carotid artery cannot be excluded.

In our study, six major strokes occurred during the ballooning/stent phase. Visible debris was recovered in the CPD in 72% of patients with major strokes vs 37% of the overall study group. The presence of CPD could not prevent all the embolic risks of CAS, and it is obvious that placement of CPD may add complexity and additional instrumentation to the angioplasty and stent-placement procedure. Crossing a high-grade stenosis may be very challenging and may increase the risk of dissection or other damage to the vessel wall. However, CPDs have been largely recommended for CAS because their benefits could greatly outweigh the risks inherent to the use.[12] Technological improvement, including filters with a better crossing

profile and the use of flow-reversal systems, when appropriate, may increase the appropriateness of these devices in preventing intraprocedural embolization. In this study, in all but seven procedures, distal filters were used as CPDs, and in most cases (82% in the first period and 72% in the second) a single brand was used (FilterWire EZ). This technical approach did not allow us to make any meaningful comparison between different types of filters.

The sharp decline of all neurologic complications during the study period and its different occurrence according to the different phases of the procedure may be due to multiple factors, but certainly a learning-curve effect cannot be ignored, both in terms of better selection of the patients (eg, avoiding severely diseased aortic arches) and of a more careful manipulation of wires and catheters in approaching the target lesion. According to the steady decline of major neurologic complications, we extended indications for CAS to low-risk patients with carotid stenosis, as can be deduced from the relative reduction of symptomatic and noncoronary patients treated. Similarly, the higher incidence of patients with echolucent plaque shows an attitude toward generalizing the indications (Table I).

Finally, most of the 18 minor strokes recorded occurred in the last phases: 16 occurred after the end of the procedure, and 5 occurred after 24 hours. The frequent late occurrence of these minor events is difficult to explain: probably selection of stent material and design and appropriate antiaggregation may play a role.[18-20] Although we cannot completely exclude that in few cases subtle symptoms indicating mild neurologic events may be overlooked during the procedure and recognized later, further studies assessing the specific role of technology improvements, stent adaptability (stiffness vs flexible material), or plaque scaffolding (open-cell vs close-cell design) and coverage will be most helpful. Furthermore, the adjunctive benefit of medical therapy is far from being clarified.

Our study presents some limitations: it was a nonrandomized study, and the progressive extension of the indications due to the declining complication rate may have produced selection biases between the populations of the two periods. The role of chance may have affected the yearly occurrence of complications. This study was a single-center experience, and we should be cautious in extending these results to other centers.

CONCLUSIONS

The effect of the learning curve related to technical expertise and patient selection may influence the results of CAS. Our data show that the CAS caseload should be large enough to ensure a major complication rate of less than 2%. This experience attempts to reduce strokes that may occur during the unprotected phase of catheterization and the approach to the target vessel. Moreover, expertise in selecting the material and design of the stent according to different vessel morphology, in association with correct medical treatment, may be useful in reducing the number of minor strokes that occur in the later postinterventional phases of CAS. Team experience, knowledge of endovascular materials and medications, and the ability to navigate through a difficult aortic arch and to cross and treat challenging lesions can ensure CAS safety. Until results of randomized trials are available, CAS may be considered an alternative treatment option for carotid revascularization in experienced centers.

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AUTHOR CONTRIBUTIONS

Conception and design: PC, PDR, GP, LR
Analysis and interpretation: FV, PC, PDR, GP, AM, LR, LN, GG
Data collection: FV, PDR, GP, LR, LN, GG
Writing the article: FV, PC, PDR, GP
Critical revision of the article: FV, PC, PDR, GP, LR, LN, GG
Final approval of the article: FV, PC, PDR, GP, AM, LR, LN, GG
Statistical analysis: FV, PDR, GP
Overall responsibility: PC

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DISCUSSION

Dr Richard Powell *(Lebanon, NH)*. The Guidant 2500 data were recently presented, and one of the conclusions of that study was that the low-volume operators had equivalent results with the high-volume operators following their prescribed training course. I was just wondering if you would comment on that, especially in light of your study, which shows that, if anything, more cases may be required.

Dr Cao. I have no real comment on that. This is a single-center with independent results. It's striking to see how the first interval carries a higher risk with a protective device. In our experience, the learning curve was still a crucial aspect of our results.

Dr Marc Bosiers *(Dendermonde, Belgium)*. All 18 observed minor strokes occurred in the postprocedural phase. Was any correlation observed between the selected stent types and the number of observed events? What could be the reasoning?

In the EVA-3S study, the controlled randomized trial comparing CAS vs CEA in France, which is going to be published, CEA turns out to be superior over CAS. Taking into account this publication, I would like to hear your comment on the required study credentials: an experience of minimally 50 to 100 CEA procedures is required, while participating centers only need 10 to 15 documented CAS cases.

Dr Cao. Regarding the stent configuration, we have not enough numbers to evaluate the difference; also, many events occurred during the unprotected phase. Consequently, we would need a very large sample size.

As to the learning curve, I completely agree with you. The main problem of all randomized trials, including the technical aspect, is that centers with an incomplete learning curve can be recruited. So, probably, to fully evaluate the results of different techniques in randomized trials, we should be careful to select centers with adequate track records.

Dr Munier Nazzal *(Toledo, Ohio)*. I have one question regarding the catheter experience. Did you look at catheter experience in other vessels? Because the operators might be new in the carotid, but they do other procedures, like renal, which might be more difficult even sometimes than carotid.

Dr Cao. Let me first specify that our cases were done in the operating room with a fixed imaging system during the last 6 months. Previously a digitalized mobile system was used, with a team made of a radiologist with a large experience of catheterization and a vascular surgeon. I think that the background of the team was adequate.

Dr Robert Hobson *(Newark, NJ)*. Dr Cao, I appreciated your presentation. It's what we have come to expect from the University of Perugia.

My question has to do with your calculation of a learning curve. The CREST investigators here in North America and our biostatistical associates have been working on a similar project. It's particularly difficult to perform these analyses when you have a low number of end points, as you do, and the excellence of your work confirms that.

However, I noticed that you did not recommend a number of cases that you think is appropriate for a vascular surgeon to then proceed independently with carotid artery stenting. The Interventional Management Committee of CREST has put this figure at about 30 cases. But if you look at the biostatistics of this question, it may be as low as 15 cases, which reinforces Dr Powell's comments about Guidant's ARCHeR data in that "experienced" interventionalists did as well as more experienced clinicians. If you could please review your method of analysis on the learning curve, perhaps you can then recommend an appropriate number of cases.

Finally, like Dr Bosiers, do you have any insight on the results of the EVA-3S trial, which apparently demonstrated a benefit for endarterectomy over stenting.

Dr Cao. In our study we included all the cases of carotid stenting, trying to localize the time of occurrence of the complication. I think this is quite crucial, because many other reports, in my opinion, didn't focus on this topic.

With regard to the caseload, I think we cannot generalize our results. A person can be trained in different ways, with a proctor, going to other centers, and so on. For sure, according to our experience, the previously suggested number seems quite low to assure safety of carotid stenting.

Dr John Ricotta *(Stony Brook, NY)*. Dr Cao, excellent presentation, and I want to thank you for starting me on my learning curve several months ago. I have two questions for you.

It seemed to me that in the second period, you liberalized your indications for stenting. You were stenting people with less peripheral vascular disease and less coronary disease. I wonder if you would comment on whether you think that influenced the outcome of your patients. Do you think that the patient groups were similar, or do you think that as you liberalized your indication for stenting, you were actually doing stenting on a safer group of patients?

I also have a comment, similar to what other people have said: if we're going to start on a learning curve, somehow you have to get to 200 cases. What suggestions do you have for us to select patients between number 10 and number 200?

Dr Cao. I was aware that by presenting 200 cases as a learning curve, most of the vascular surgeons would shoot me, because it makes the starting experience very difficult. I would say, again, that these results are not intended to be guidelines. I would suggest to start with patients with easy-access vessels, low-risk patients, possibly with a team approach including different specialties.

Regarding the possible selection bias of the results, we have pointed out that this is not a randomized study. With multivariable analysis, we showed that patient characteristics were not predictors of complications.

Dr Marc Schermerhorn *(Boston, Mass)*. In your analysis, age was a weak predictor of outcome, but it looked like you were analyzing it as a continuous variable. Did you look at it as a dichotomous variable? What were the stroke rates above and below 80?