4 Endovascular Treatment of Extracranial Disease

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Cervical Carotid Artery Disease

Internal carotid artery arteriosclerosis at its origin is the most important cause of transient ischemic attack (TIA) and stroke of arterial origin. Carotid endarterectomy (CEA) is effective in secondary stroke prevention in patients with symptomatic stenosis measuring >50% in severity. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [1], CEA was superior to medical therapy in patients with >70% stenosis, reducing the ipsilateral stroke rate from 26% to 9% at 2 years. Patients with 50–69% luminal narrowing benefited less from surgery with a decrease in 5-year ipsilateral stroke rates from 22.2% to 15.7% but fared better than those treated medically. This then is the gold standard therapy against which newer therapies must be measured. CEA has limitations, and the margins for benefit in NASCET were dependent on a low 30-day perioperative stroke and death rate of 5.8%. Higher surgical complication rates can reduce the benefit from this surgery. The NASCET results do not accurately reflect the real population of symptomatic patients with ICA arteriosclerosis for two major reasons. First, the low perioperative complication rates attained by the specialized centers involved in the trial are much lower, by as much as a factor of 3, than those obtained in everyday practice**.** Second, the patients enrolled in the trial were highly selected and did not include those with major medical comorbidities (renal, pulmonary, and especially coronary artery disease [CAD]), patients age 80 and older, or those with a history of prior endarterectomy, radical neck dissection, or radiation therapy to the neck. In addition to the risk of stroke and death noted in NASCET, there was a 7.6% incidence of cranial neuropathy and an 8.9% incidence of surgical wound hematoma or infection [1].

Carotid angioplasty and stenting (CAS) is an attractive alternative to CEA for several reasons. It is potentially less risky to perform in patients with medical comorbidities, especially those with CAD since they are performed without general anesthesia**.** CAS is a less invasive procedure and does not carry a risk of cranial nerve palsies or surgical wound hematomas and infection, the frequency and clinical significance of which are not minor. CAS may also be applied to patients at particularly high risk of complications from CEA, including patients who have major medical comorbidities, those who have had prior CEA or neck exploration and neck irradiation, as well as

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individuals who have high carotid bifurcations, contralateral carotid occlusion, or tandem stenoses (Table 4.1). Early investigators performed ICA angioplasty only and later used stents only as a rescue if a dissection developed. As stent technology improved, it became possible to deliver stents into the ICA with a significant improvement in acute outcomes compared with angioplasty alone. Additional experience has shown that carotid artery stenting (CAS) is best performed with an emboli prevention device. Many non-randomized but large series studies (300–400 patients each) have shown that cerebral embolic events are greatly reduced using these "filter devices" with a decrease in stroke rates from approximately 5–8.6% to 2–3% (Fig. 4.1) [2]. A consensus statement of the world experts in CAS states that the use of emboli prevention devices should be standard practice.

Table 4.1 Indications for CAS: high-surgical-risk criteria

Congestive heart failure (class III/IV) and/or known severe left ventricular dysfunction LVEF <30%
Open heart surgery within 6 weeks
Recent MI (>24 h and <4 weeks)
Unstable angina (CCS class III/IV)
Coexistent severe coronary artery disease requiring carotid and coronary revascularization
Severe pulmonary disease (FEV <1.0)
Contralateral carotid occlusion
Contralateral laryngeal nerve palsy
Post-cervical radiation treatment
Previous CEA (i.e., recurrent stenosis)
High cervical ICA lesions (C2 or higher)
CCA lesions below the clavicle
Severe tandem lesions

High-Surgical-Risk Patients

Following the development of stent and then filter technology, a clinical trial comparing CEA and CAS was needed. Protected stenting (i.e., stenting with the use of an embolism prevention device) had not been validated outside of registries [3–6]. Several small trials were initiated [7, 8], but to date the only large randomized trial of protected CAS vs. CEA in high-surgical-risk patients was the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study [9]. This non-inferiority study evaluated the Cordis Precise™ stent and the Angioguard™ filter and was sponsored by the manufacturer, Cordis Endovascular Inc. The primary study combined endpoint of stroke, myocardial infarction, or death at 30 days, and ipsilateral stroke to 1 year was 12.2% with CAS and 20.1% with CEA,

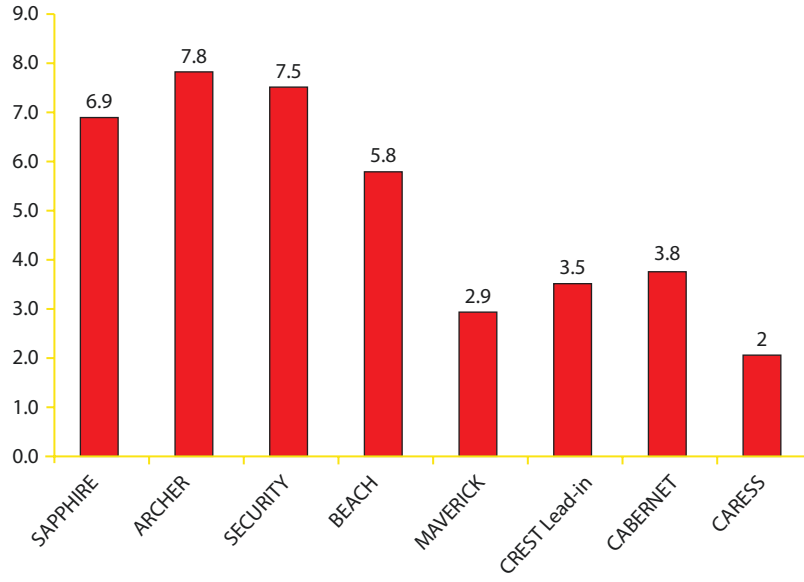

Fig. 4.1 Graph showing 30-day events in studies of CAS

$p = 0.05$ for non-inferiority. The 30-day perioperative stroke/MI/death was lower in the CAS group as compared with the CEA group, 4.4% vs. 9.9%, respectively, but the difference was not statistically significant ($p = 0.06$) in the on-treatment analysis. The CEA complication rates were much higher than those noted in the "low-risk" studies NASCET (5.8%) and ACAS (<3%). The 3-year results continued to show non-inferiority of CAS to CEA with a cumulative major adverse event rate (stroke, death, or MI) of 20.1% in the stenting arm and 30.3% in the CEA arm ($p = 0.231$). Additionally, the need for reoperation at 1 year was significantly lower in the CAS group than in the CEA group, 0.7% vs. 4.6%, respectively, $p = 0.04$.

In addition to the randomized data from SAPPHIRE, two data sets from two large post-marketing studies, CAPTURE [10] and CASES-PMS [11], show continued good outcomes with CAS in high-surgical-risk patients. These registries both consisted of real-world experience with commercially available stent and emboli prevention systems as well as independent neurological adjudication of neurological outcomes and events.

The CAPTURE registry enrolled more than 6000 high-risk patients from 280 sites and 672 operators and the data on the first 6300 patients have been published [12]. Most of the patients were asymptomatic (86.9%), and all received independent pre- and post-procedure neurological evaluation by neurologists. The 30-day results were 0.9% death, 3.1% all stroke, and 0.3% MI. However when the NASCET endpoint was used, the overall 30-day event rate was 3.6%. For symptomatic patients the 30-day event rate was 5.3% (95% CI, 3.6–7.4%) with a major stroke rate of 1.4%. For asymptomatic patients, the 30-day event rate was 2.9% (95% CI, 2.4–3.4%) with a major stroke rate of 0.6%. This trial was one of the first to show that age was associated with a major increase in complications, and in the >80yo symptomatic patients the complication rate was 10.5% (95% CI, 6.3–16.0%) and in asymptomatic >80yo it was 4.4% (95% CI, 3.3–5.7%).

The CASES-PMS registry enrolled more than 4000 patients with the data on the first 1480 high-risk patients published in 2007 [11]. In that cohort the 30-day death/stroke/MI rate was 5% in all patients and 4.7% in the asymptomatic patients. If NASCET/ACAS outcome definitions are used, then the 30-day death/stroke rate was 4% in asymptomatic patients. The much larger follow-up registry of the same device, the SAPPHIRE Worldwide Registry, has enrolled more than 15,000 patients since October 2006 [13]. The peri-procedural results were presented at the TCT conference in October 23, 2012, on the first 15,003 patients, 4569 of whom (30%) were symptomatic and 10,433 (70%) were asymptomatic. The 30-day stroke/MI/death rate was 4.5% (death 1.2%, MI 0.6%, stroke 3.3%). There was a significant difference in the "NASCET" 30-day endpoint (stroke/death) between symptomatic (5.6%) and asymptomatic (3.5%) patients ($p < 0.0001$). This registry also confirmed that patients 75 years of age and older had a higher complication rate (5.6% vs. 2.9%) compared to younger patients ($p < 0.0001$). These results compare favorably with the results of the CEA arm in the SAPPHIRE trial, the only randomized data set to define the outcomes of CEA in this patient population. These results also compare favorably with ACAS and ACST surgical results of approximately 3% 30-day stroke/death in low-surgical-risk patients who are also at lower risk of stroke or death perioperatively. Based on these data, it is clear now that in the high-risk patient who has a symptomatic ICA stenosis, CAS with a filter device is the procedure of choice.

The SAPPHIRE study results clearly showed that CEA carries a markedly elevated risk to asymptomatic high-risk patients, and it should not be offered to them. Although it appears that in asymptomatic high-surgical-risk patients CAS has similar complication rates to low-surgical-risk CEA patients, the overall benefit in the high-surgical-risk population is not clear**,** and therefore a definitive statement cannot be made on the best treatment option for these patients, for some of whom medical therapy may be the best treat-

ment. Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) is currently enrolling to help answer this question. In CREST-2 the patient will be randomized to medical therapy vs. revascularization with CAS or CEA. The patient who is randomized to revascularization therapy will be evaluated to determine which procedure is best for him/her depending on factors mentioned previously in this chapter [14].

Low-Surgical-Risk Patients

Four subsequent studies have greatly clouded the issue of CEA vs. CAS in low-surgical-risk patients. The CaRESS trial was a non-randomized study with "real-world allocation" of 397 primarily asymptomatic patients that found no statistical difference in death/stroke/MI at 30 days (4.4% vs. 2.1%) or 1 year (14.3% vs. 10.9%) with CEA compared to protected CAS, respectively [15]. The SPACE trial was a randomized comparison of CEA vs. CAS in 1183 symptomatic patients. Not surprisingly, since less than 30% of patients were treated with emboli prevention devices contrary to the accepted standard of care, there was no difference in outcomes at 30 days (6.34% vs. 6.84%, $p = 0.09$). This study effectively replicated the results of the earlier CAVATAS trial and adds no new data except to confirm that CAS without emboli prevention devices is not safe [16]. The most problematic study was the EVA-3S study of 527 randomized patients with symptomatic stenosis. This study was conducted with poor standardization of CAS technique including inconsistent use of dual antiplatelet therapy, incomplete use of EPD, no angiographic exclusion criteria for CAS patients but with high-risk exclusion for CEA patients, and most importantly very low CAS operator experience with some operators having performed only five cases prior to randomizing patients. Not surprisingly the complication rates were unacceptably high in the CAS arm compared to the CEA arm 9.6% vs. 3.9%, respectively [17]. The final study was the International Carotid Stenting Study (ICSS), which was a randomized trial of CEA vs. CAS in symptomatic normal-surgical-risk patients. In that trial the use of EPD was the discretion of the operator, and approximately 20% of patients were treated without an EPD. Also, operators did not have to have extensive experience in performing CAS. They could be supervised by an experienced operator and experience was defined having performed 50 stent procedures anywhere in the body, of which a minimum of ten were required to be carotid artery procedures. That trial showed that the 30-day stroke/MI/death rate was 8.5% with CAS and 5.1% with CEA ($p = 0.004$) [18].

The most important trial of CAS, the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), was actually started in 2000 but took 10 years to complete [9, 10]. The initial purpose of CREST was to compare protected CAS vs. CEA in low-surgical-risk, symptomatic patients, but due to slow enrollment, it was expanded to include asymptomatic low-surgical-risk patients in 2005. CREST was sponsored by both the National Institutes of Health (NIH) and Guidant (now Abbott Vascular). It was designed as a 2500-patient superiority trial with equal randomization between CEA and protected CAS using the Accunet™ emboli prevention device ("whenever feasible") and Acculink™ carotid stenting system (Abbott Vascular Inc.). Symptomatic patients with a carotid bifurcation stenosis ≥50% in severity on angiography, ≥70% on ultrasonography, or ≥70% on computed tomographic angiography or magnetic resonance angiography were enrolled. Asymptomatic patients were enrolled with a stenosis ≥60% by angiography, ≥70% on ultrasonography, or ≥80% on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50–69%. In addition to the exclusion of high-surgical-risk patients, the study excluded patients who had contraindications to CAS such as severe tortuosity, extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery, an intraluminal filling defect, ipsilateral intracranial or extracranial arterial stenosis more severe than the lesion to be treated, and occlusion or "string sign" >1 cm of the ipsilateral common or

ICA. Aspirin in the CEA arm and dual antiplatelet therapy (aspirin 325 mg plus clopidogrel 75 mg or ticlopidine) in the CAS arm were mandated for at least 30 days, with aspirin in all patients thereafter.

Importantly the study included a rigorous vetting of interventionalists with a lead-in/credentialing phase of approximately 20 patients per interventionist [19, 20]. In fact only 225 (52%) of 429 interventionists were approved for randomization [21]. Those who were refused outright had a median case experience of 12 (range 1–56); these operators would have qualified for EVA-3S and ICSS.

The study's primary endpoint consisted of the composite of any periprocedural (i.e., within 30 days) stroke, MI, or death and ipsilateral stroke within 4 years of randomization [22]. Patients underwent independent neurological evaluations.

A total of 2522 patients were enrolled (1271 CAS and 1251 CEA) with a median follow-up of 2.5 years [13]. Approximately 5.4% of the CAS patients and 8.8% of the CEA patients were lost to follow-up or withdrawn consent. The patients were very well matched other than a slightly higher preponderance of patients with dyslipidemia in the CEA group (85.8% vs. 82.9%, $p = 0.05$) and more smoking in the CAS group during follow-up (21.8% vs. 13.8%, $p = 0.03$). The median time to treatment from randomization was similar (6 days for CAS and 7 days for CEA). The majority of the CEA were performed under general anesthesia (90%) and most had a patch (62.4%) or shunt (56.7%). The overwhelming majority of CAS were performed with embolic protection (96.1%) and most had predilation before stenting (67.7%). There was a high rate (12.1%) of CAS patients not taking dual antiplatelet agents for the full 4 weeks and a high rate of no aspirin use among CEA patients (8.9%).

CREST showed no difference in the primary study endpoint stroke/MI/death within 30 days (CAS 5.2 ± 0.6 vs. CEA 4.5 ± 0.6, hazard ratio [HR] 1.18 [0.82–1.68], $p = 0.38$) or up to 4 years (CAS 7.2 ± 0.8 vs. CEA 6.8 ± 0.8, HR 1.11 [0.81–1.51], $p = 0.51$). There was no difference in the individual endpoint of periprocedural death (CAS 0.7 ± 0.2 vs. CEA 0.3 ± 0.2, $p = 0.18$), but there was a difference for any periprocedural stroke (CAS 4.1 ± 0.6 vs. CEA 2.3 ± 0.4, HR 1.79 [1.14–2.82], $p = 0.01$) or MI (CAS 1.1 ± 0.3 vs. CEA 2.3 ± 0.4, HR 0.50 [0.26–0.94], $p = 0.03$). Following the periprocedural period, the incidence of ipsilateral stroke was similar (CEA 2.4% vs. CAS 2.0%, $p = 0.85$) as was the risk of fatal stroke (CAS $n = 7$ vs. CEA $n = 6$). There was no difference in the primary endpoint during the perioperative period among symptomatic patients (CAS 6.7% vs. CEA 5.4%, HR 1.26 [0.81–1.96]) or asymptomatic patients (CAS 3.5% vs. CEA 3.6%, HR 1.02 [0.55–1.86]). There was no interaction between sex and symptomatic status and treatment effect although there was an interaction between age and efficacy ($p = 0.02$). The crossover point for age was approximately 70 years with greater efficacy with CAS in younger patients and greater efficacy with CEA for older patients. The risk of cranial neuropathy was significantly higher in the CEA group (0.3% vs. 4.7%).

The CREST trial, the first trial to compare protected CAS vs. CEA in low-surgical-risk symptomatic and asymptomatic patients, has shown that both procedures are relatively equivalent in perioperative morbidity and mortality as well as long-term stroke prevention. There was a clear difference however in the risk of perioperative stroke with an increased risk in the endovascular group; most of these strokes were minor. Conversely there was a higher risk of MI in the surgical group. Importantly the 30-day outcomes were similar for both procedures to the accepted thresholds for clinical benefit compared to medical therapy, i.e., <6% for symptomatic (6% stroke/death with CREST CAS and 3.2% for CREST CEA) and <3% for asymptomatic patients (in CREST the rate of 30-day stroke/death with CAS was 2.3% for ACAS eligible patients). It is important to note that the stroke rate declined over time in the CREST trial, and if the results from the latter half of the study were utilized, there would have been no difference in stroke rate with CEA. This highlights the importance of case experience and improved patient selection [23].

The results of CREST were reinforced in the Asymptomatic Carotid Trial (ACT I) published in 2016. This trial included 1453 subjects 79 years or younger with asymptomatic severe carotid stenosis who were considered not a high surgical risk. Subjects were randomized at a 3:1 ratio to CAS with emboli protection vs. CEA. The primary endpoint was a composite of death, stroke, or MI within 30 days after the procedure or ipsilateral stroke within 1 year. CAS was non-inferior to CEA with regard to the primary composite endpoint (event rate, 3.8% and 3.4%, respectively: $p = 0.01$ *for non-inferiority*). The risk of perioperative stroke was slightly higher in the endovascular group (2.9% vs. 1.7%; $p = 0.33$). Most of these strokes were minor, similar to the results from CREST. The rate of freedom from non-procedure-related ipsilateral stroke through 5 years was 97.8% in the stenting group and 97.3% in the endarterectomy group ($p = 0.51$) [24].

These results contradict the results of the three randomized European trials discussed earlier [16–18]. The EVA-3S, ICSS, and SPACE trial results have greatly reduced the enthusiasm for CAS and initially blocked the expansion of CMS coverage for CAS. Taken at face value, this cooling of enthusiasm is understandable; however all randomized trials are not created equal, and the results of these trials must be reconciled with those of the CREST trial, ACT I trial, and the registries. As with the early trials of CEA, the differences in outcomes have to do with patient and operator selection as well as procedural techniques. Several authorities have highlighted the limitations of these trials, and Table 4.2 highlights the differences and possible explanations for the differing results between trials. Chief among the limitations was the inexperience of the operators performing the stenting and the lack of consistent EPD use. In an observational study of 24,701 Medicare beneficiaries from 2005 to 2007 who underwent CAS by 2339 operators, the median case volume was 3/year [25]. When outcomes were analyzed based on high experience (≥24 cases/year), medium (12–23 cases/year), low (6–11 cases/year), and very low (<6 cases/year), mortality was associated with decreasing experience: adjusted OR 1 in high-experience group (reference), 1.2 (95% CI 0.8–1.7) in medium-experience group, 1.4 (95% CI 1.0–2.0) in low-experience group, and 1.9 (95% CI 1.4–2.7) in the very-low-experience group. Interestingly as a further marker of technical skill the OR for not using an EPD were also greatly increased with decreasing experience: adjusted OR 1 (reference, high experience), 1.6 (95% CI 0.8–3.2, medium experience), 2.9 (95% CI 1.5–5.6, low experience), and 8.1 (95% CI 4.4–14.9). Gray et al. [10] also reviewed the large CAPTURE data set and found a linear relationship between increasing experience and decreased complications. Smout et al. [26] conducted a literature review and meta-analysis and also found a consistent association between experience and outcomes. These outcomes would seem to be self-evident, yet the aforementioned randomized

Table 4.2 Comparison of CAS trial protocols

	SAPPHIRE	CAVATAS	EVA-3S	SPACE	ICS	CREST
Stenting	✓	X	✓	✓	✓	✓
EPD mandatory	✓	X	✓	X	X	✓
Experienced operators	✓	X	X	X	X	✓
Dual antiplatelet Tx	✓	X	X	✓	✓?	✓
Angiographic exclusions	✓	X[a]	X	X	✓	✓
Independent neurologist	✓	✓?[b]	✓	✓	✓?[b]	✓
No general anesthesia	✓?	✓?	X	X	✓?	✓
Symptomatic definition	3 months	>6 months	4 months	6 months	12 months	6 months
Angiography in all patients	X	X	X	X	X	X

[a]Only if known pre-procedure, no crossovers allowed
[b]Neurologist or "physician interested in stroke"

trials seemed to ignore the obvious. To summarize then, the EVA-3S, SPACE, and ICSS trials have confirmed that CAS performed poorly by inexperienced operators is inferior to properly performed CEA.

A meta-analysis of all the trials that had exclusive use of emboli protection devices comparing CAS to CEA was published by Sardar et al. [27]. There was no significant difference in the composite outcome of periprocedural death, stroke, myocardial infarction (MI), or non-periprocedural ipsilateral stroke between CAS and CEA (OR 1.22; 95% CI 0.94–1.59). The risk of any ipsilateral stroke was higher with CAS (OR 1.50; 95% CI 1.22–1.84). This increased stroke risk with CAS was mostly attributed to periprocedural minor stroke (OR 2.43; 95% CI 1.71–3.46). Significantly lower risk of periprocedural MI (OR 0.45; 95% CI 0.27–0.75), cranial nerve palsy (OR 0.07; 95% CI 0.04–0.14), and the composite outcome of death, stroke, MI, or cranial nerve palsy during the periprocedural period (OR 0.75; 95% CI 0.60–0.93) was seen in association with CAS.

Long-term follow-up from CREST over 10 years showed no significant difference between patients who underwent CAS vs. CEA. Post-procedural ipsilateral stroke over the 10 years was 6.9% (95% CI, 4.4–9.7) for CAS group and 5.6% (95% CI, 3.7–7.6) for CEA group [22].

Carotid artery stenting can be performed in nearly all patients (98.6% in SAPPHIRE). The remainder may be better treated medically or surgically (Table 4.3 lists the relative contraindications to CAS). There are two groups of patients for whom the ideal therapy is unknown. The first are patients who have an intraluminal filling defect (i.e., thrombus) within the stenotic segment. In NASCET these patients had an 18–22% risk of perioperative stroke [1]. Such patients have not been enrolled in the trials of CAS, and it is generally agreed that they may also have a high stroke risk with CAS. In these patients, a short period of anticoagulation may be appropriate followed by CEA or CAS when the thrombus resolves. The other and far larger group of patients is those over the age of 80. These patients were mostly excluded from the trials of CEA and are known to have a higher perioperative complication rate than younger patients. With CAS however, the elderly appear to have a higher rate of complications (CREST, CAPTURE). In the CREST trial [22, 28] lead-in phase (N = 1246) octogenarians had a 12.1% 30-day stroke/death rate. At this time, therefore a conclusion cannot be drawn on the optimal treatment for octogenarians, but medical therapy alone should be given strong consideration since CEA also carries a nearly 12% complication rate in those over age 75.

There are several issues that have not yet been addressed by the published results, such as the long-term patency of each procedure has yet to be determined, and given that newer emboli prevention devices and stents are available, might one or several of them be associated with lower stroke rates?

Table 4.3 Contraindications to CAS

Severe vascular tortuosity
Poor arterial access
Coagulation or platelet disorder that precludes adequate antithrombotic agent use
Severe, circumferential target lesion calcification
Target lesion length >15 mm

Other Considerations

There have been debates about the type of stent used with some suggesting that closed cell stents are associated with lower periprocedural stroke [29]. Proximal occlusion EPDs have also been touted to be superior at stroke prevention, but they have some limitations such as larger bore femoral access and increased probability of intolerance to the occlusion of antegrade flow. In a large single-center registry of 1300 patients treated with proximal occlusion, the 30-day stroke/death rate was 1.38% with independent neurological assessment at 24 h and 30 days [30]. In a meta-analysis of 2397 patients from six independent databases, Bersin et al. found that the composite of stroke/MI/death occurred in 2.25% of cases [31]. While these data are tantalizing,

there are no definitive randomized trial data that show one type of EPD device is superior to another. Retrospective analysis of 13,786 CAS procedures using different stent-EPD combinations such as Xact-Emboshield (n = 2438, 17.6%), Precise-Angioguard (n = 1480, 10.7%), Acculink-Accunet (n = 829, 6.01%), and Acculink-Emboshield (n = 660, 4.8%) showed no statistically significant difference in rates of periprocedural stroke/TIA across device combination [32]. Clinicians should, in the author's opinion, become familiar with one or two devices/approaches and use them exclusively until there is definitive data on superiority of one approach or device over another.

Predictors of Complications

A study pooled data on 2104 patients from four Cordis Endovascular Inc.-sponsored registries [33]. In that analysis, the median age was 74 years (24% >80 years), 36% were female, and 24.2% of the patients were symptomatic. Multivariate predictors of the 4.2% neurological deaths or strokes included older age (continuous), African-American race, angiographically visible thrombus in symptomatic patients, procedural use of glycoprotein IIb/IIIa inhibitor, procedural transient ischemic attack, final residual stenosis >30%, and periprocedural use of protamine or vasopressors.

Of particular interest is that in symptomatic patients, the risk of a neurological event declines with increasing time between incident event and CAS [34]. The issue of timing of CAS in symptomatic patients has been a major unanswered question. The vast clinical experience with CEA has clearly shown that earlier intervention is superior to delayed intervention in preventing recurrent ischemic stroke, but comes at the cost of increased intracerebral hemorrhage [35]. The fear of reperfusion/hyperperfusion intracerebral hemorrhage (ICH) is perhaps more justified with CAS since patients are treated with dual antiplatelet agents and are theoretically more likely to have ICH. The available literature has not corroborated those fears. To the contrary with adequate blood pressure control, the risk of the hyperperfusion syndrome can be mitigated [36], and early CAS can also be performed safely in selected patients [37].

To conclude, in high-surgical-risk patients, CAS is at least as safe as CEA and is the preferred treatment option in patients eligible for revascularization. Furthermore, the CREST trial has shown that protected CAS and CEA are both good options for the treatment of low-surgical-risk patients with carotid atherosclerosis with CAS better in younger patients and CEA better in older patients.

General Technique

CAS is usually performed under minimal sedation in order to avoid mental status impairment. This procedure usually involves five stages: embolic protection device placement, pre-stenting angioplasty to facilitate passing the stent, stent delivery and deployment, post-stenting angioplasty, and retrieval of the protection device. Pre-procedural planning is essential for optimal outcome; planning can be based on noninvasive or angiographic imaging.

Procedural Considerations

- *Antiplatelet therapy*:
  Antiplatelet therapy should be started at least 48 h before carotid artery stenting. In CREST, patients received aspirin, at a dose of 325 mg twice daily, and clopidogrel at a dose of 75 mg twice daily at least 48 h prior to CAS. When carotid artery stenting was scheduled for within 48 h, 650 mg of aspirin and 450 mg of clopidogrel were given 4 or more hours before the procedure. After the procedure, patients received one or two 325-mg doses of aspirin daily for 30 days and either clopidogrel, 75 mg daily, or ticlopidine, 250 mg twice daily, for 4 weeks. The continuation of antiplatelet therapy for more than 4 weeks after the procedure was recommended for all patients who had undergone carotid artery stenting [22]. More

recently eptifibatide, a highly selective platelet glycoprotein IIb–IIIa receptor inhibitor, emerged as safe adjunct to CAS [38]. Eptifibatide has a rapid antiplatelet effect and is rapidly reversible with a half-life of 10–15 min. Its IV route of administration made it popular especially in emergent CAS.

- *Sedation:* Overall, sedation should be minimized in CAS. A brief neurological examination should be performed immediately prior to the procedure and after the post-dilatation angioplasty. Patients are asked to repeat a sentence, smile, squeeze with both hands, and wiggle toes. A complete neurological exam should be performed after the procedure.
- *Anticoagulation:* A loading dose of IV heparin should be given after femoral arterial access is obtained to keep the activated clotting time (ACT) between 250 and 300 s.
- *Hemodynamic changes:* Mechanisms of brain injury in CAS include both embolic and hemodynamic events. In a retrospective series of 500 patients who underwent CAS, hemodynamic depression defined as systolic blood pressure of <90 mmHg or bradycardia (heart rate of <60 beats/s) was noted during 42% of all procedures and was persistent in 17% of patients. This was more common when the lesion involved the carotid bulb or was calcified and was less common in patients with prior CEA. Patients who developed persistent HD were at a significantly increased risk of a peri-procedural major adverse clinical event (OR 3.05 [range 1.35–5.23], $p < 0.02$) or stroke (OR 3.34 [95% CI 1.13–9.90], $p < 0.03$) [39]. Close monitoring of blood pressure and heart rate is recommended during and after CAS, and self-expanding stents can continue to expand in the first 24 h after implantation and can result in persistent hypotension and/or bradycardia in some patients. Premedication with atropine may occasionally be needed in patients at risk of hemodynamic depression. Peri-procedural hypertension should also be avoided, especially in patients at risk of hyperperfusion syndrome.
- A three-vessel diagnostic arteriogram is recommended to evaluate the contralateral internal carotid artery and the intracranial anterior and posterior circulation. The diagnostic catheter is then exchanged to a 90-cm shuttle sheath over an exchange length of 300-cm wire without contacting the atherosclerotic plaque. Alternatively, these steps can be achieved using the telescoping technique with a diagnostic 5-French catheter within a 6-French, 90-cm shuttle sheath and a Glidewire. Secure position of the shuttle sheath in the CCA is essential for adequate support during the five stages of the procedure.

Embolic Protection Devices (EPD): Using proximal carotid occlusion or distal protection can decrease the risk of cerebral embolization during CAS. Théron et al. described the first protection device in 1990, and their technique involved temporary occlusion of the cervical ICA distal to the lesion by a nondetachable latex balloon [40].

Many EPDs have been introduced since then, and adequate selection of a protection device requires good knowledge of their functions and shortfalls. In the updated review of the global carotid artery stent registry, the rate of strokes and procedural-related deaths was 5.29% in the 6753 cases done without protection and 2.23% in the 4221 cases with cerebral protection [41]. Embolic protection can be achieved by distal balloon occlusion, distal filter devices, or proximal balloon occlusion with or without flow reversal.

- Distal balloon occlusion: This technique is not commonly used in the USA. The best known off-label distal balloon occlusion system is the GuardWire Temporary Occlusion and Aspiration System (Medtronic AVE, Santa Rosa, CA).
- Filter devices: The most commonly used EPDs, they are filtration membranes placed beyond the ICA lesion in a straight segment and can capture medium to large (>100 μm) debris. Their performance depends on their "crossing profile" or delivery system and "capturing profile" which depends on filter wall opposition and the size of pores. Table 4.4

Table 4.4 Filter devices

	Delivery system	Crossing profile	Pore size (μm)	Trials	FDA approved
Accunet	Wire mounted	3.5–3.7 Fr	120	ARCHeR, CREST, CAPTURE	Yes
SpideRX	Bare wire	2.9 Fr	50–300	CREATE II	No
Angioguard	Wire mounted	3.2–3.9 Fr	100	SAPPHIRE, CASES	No
Emboshield	Bare wire	3.7–3.9 Fr	120	EXACT, SECURITY	No
FilterWireEX	Wire mounted	3.2 Fr	110	BEACH, CABERNET	No
Rubicon	Wire mounted	2.1 Fr	100		No
Interceptor Plus	Wire mounted	2.7 Fr	1400	MAVERIC III	No

summarizes the main features of the currently available filter devices.

The limitations of filter devices include crossing the lesion prior to protection which can result in distal embolization, generating spasm in the ICA if the device cannot be advanced to petrous ICA segment, dislodging emboli from the filter during filter retrieval, and letting micreoemboli pass through the device due to poor wall opposition or through the pores of the device.

- Proximal Balloon Occlusion: This technique involves inflation of a balloon in the CCA and a balloon in the ECA with the advantage of providing protection before crossing the lesion. It does not require a distal landing zone for the EPD and could potentially minimize the risk of ICA dissection and retrieval complications. The MO.MA device (Invatec, Roncadelle, Italy) requires a minimum sheath size of 8 French and a 0.035″ guidewire. The balloon occlusion range is up to 13 mm in the CCA balloon and 6 mm in the ECA balloon with the goal of providing a static blood column at the carotid bifurcation. At the end of procedure, aspiration with at least three 20 cc syringes is performed before deflating the balloons.

  The Parodi Anti-Emboli System (W.L. Gore & Associates, Flagstaff, AZ) requires an 11-French sheath. This technique cannot be used in patients with severe ECA disease and can be limited sometimes by occlusion intolerance.

  Pre-dilatation: The aim of this step is to allow the passage of the stent; a low profile coronary balloon is usually used. Oversize should be avoided as it can increase the risk of embolic events.

  Stents: The majority of stents in use for CAS are self-expanding. Balloon-expandable stents have fallen out of favor due to their propensity to deform and their difficult delivery. The stent should be sized appropriately to allow complete opposition to the CCA lumen. Stents can have an open-cell or closed-cell design and can be tapered to accommodate the difference in size between the CCA and the ICA if the stent is intended to extend between the two vessels. All stents are made of nitinol except for Wallstents, which are made of stainless steel. Slow stent deployment is essential to optimize the stent position; nitinol stents can store energy and slide forward during deployment. The following stents are the most commonly used in the USA:

  Open-cell design:
  - Acculink (Abbott Laboratories, Abbott Park, IL): tapered
  - Precise (Cordis Neurovascular, Miami Lakes, FL): auto-taper
  - Protégé (Covidien, Irvine, CA): tapered

  Closed-cell design:
  - Xact (Abbott Laboratories, Abbott Park, IL): tapered
  - Wallstent (Boston Scientific Scimed, Maple Grove, MN): tapered

  The stent diameter is usually selected based on the diameter of the ICA; the distal end of the stent is usually oversized by 1–2 mm. High frame rate cine is usually used to deploy the stent with the vertebral anatomy used for landmarks after a cine run is obtained.

Post-dilatation: This is usually performed using monorail peripheral balloons sized at 1.5 mm less than the diameter of the stent used. A residual stenosis of 20% is acceptable in most cases.

Management of Complications During CAS

Complications of carotid artery stenting are largely preventable [42].

Secure shuttle sheath access to the distal CCA and adequate selection of EPD can minimize the risk of embolic complications. Hemodynamic monitoring during and after the procedure can also minimize the risk of hemodynamic depression and reperfusion injury.

Hemodynamic Depression: Timely administration of atropine or glycopyrrolate prior to balloon dilatation helps prevent baroreceptor stimulation leading to severe bradycardia and hypotension in patients at risk of hemodynamic depression. Mild hypotension is commonly seen after the procedure and should only be treated if symptomatic.

In-Stent Filling Defect: This can be due to thrombus formation or plaque prolapse.

A thrombus can result in diffuse haziness or a filling defect inside or at the edge of the stent. Incidence of this complication ranges from 0.04% to 2% [43, 44]. This can be treated with intra-arterial administration of abciximab or recombinant tissue plasminogen activator (r-tPA). This can theoretically increase the risk of intracranial hemorrhage especially in patients with recent cerebral infarcts. Thrombus formation is more frequently seen in patients who were not adequately treated with dual antiplatelet therapy prior to the procedure but can also indicate resistance to clopidogrel or aspirin.

Plaque prolapse can be treated with in-stent balloon inflation or implantation of a second stent.

Emboli: Cerebral emboli can occur despite meticulous CAS technique, and a rapid neurological evaluation should be performed if this complication is suspected. Symptomatic large emboli should be treated with mechanical thrombectomy if the MCA or the ACA is occluded. Small symptomatic emboli to distal ACA or MCA branches can be treated with intra-arterial recombinant tissue plasminogen activator or a bolus of glycoprotein IIb/IIIa inhibitors.

Inadequate Stent Placement: This can be due to inadvertent stent migration or technical error. Placement of a second stent is usually necessary for adequate plaque coverage.

Carotid Dissection: This is more common in the ICA and usually occurs during EPD placement or retrieval. A flow-limiting or spiral dissection should be treated with stent placement. A non-flow-limiting dissection can be monitored with a follow-up carotid ultrasound or CT angiography.

Filter-Related Complications: EPD-induced spasm can occur in up to 3.8% of patients when a filter device is used [45]. This is usually self-limited but can be treated with intra-arterial spasmolytic administration if it persisted or thought to be symptomatic. Filter occlusion was seen in 4.9% of patients in one series; it is usually due to entrapment of a large load of embolic material in the basket and does not seem to correlate to the type of the filter used. As long as it is managed appropriately, most patients with this complication do not suffer any neurological complications. This is usually managed by aspiration with special catheters at the filter site and retrieval of the device into the aspiration catheter or EPD recovery without full withdrawal into the retrieval catheter to avoid migration of the debris.

Filter retrieval can sometimes be difficult due to tortuous anatomy or altered configuration of the ICA after stent placement. This must be managed carefully to avoid filter disruption; forceful pulling of the EPD should be avoided as it can lodge into the stent struts. Neck rotation and swallowing can sometimes facilitate advancing the retrieval sheath. Adequate shuttle sheath or guide catheter support is necessary to pass the retrieval sheath through the stent. A diagnostic

5-Fr. with a mild-shape catheter can also be used to retrieve the EPD.

Hyperperfusion Syndrome: This was first described by Sundt as a combination of increased arterial blood pressure with the clinical triad of ipsilateral migraine-like headache, seizure, and transient focal neurological deficits in the absence of cerebral ischemia after a successful CEA in 1981 [46].

Cerebral hyperperfusion is defined as cerebral blood flow that exceeds the metabolic requirements of brain tissue and/or an increase in cerebral perfusion of more than 100% compared to pretreatment values. This syndrome usually occurs in the first week after carotid revascularization and typically results in headache, seizures, and focal neurological deficits. Intracerebral or subarachnoid hemorrhage commonly occurs in those patients and can result in a high rate of mortality. The following risk factors have been identified as predictors of hyperperfusion syndrome after carotid revascularization: DM, chronic hypertension, increased age, recent contralateral carotid revascularization, high-grade stenosis with poor collateral flow, incomplete circle of Willis, and post-procedural hypertension. Post-procedural intensive treatment of hypertension seems to decrease the risk of this syndrome in patients who underwent CAS [40].

Contrast Encephalopathy: This usually occurs in the first 24 h after CAS and can be attributed to contrast toxicity to the brain. Patients usually present with symptoms that mimic a stroke with transient visual loss or obscuration being the most common symptom. This benign and self-limited complication has to be differentiated from thromboembolic events to avoid additional invasive therapies.

Illustrative Case 1

A 70-year-old man presented with sudden-onset right arm weakness and speech impairment. His symptoms improved after several days of hospitalization, but a small middle cerebral artery territory stroke was seen on MRI. MR angiography showed high-grade left internal carotid artery stenosis and occlusion of the right internal carotid artery. Given this high-risk feature (contralateral carotid occlusion), the patient was loaded with clopidogrel (300 mg) and started on aspirin in preparation for carotid artery stenting.

The procedure was performed under monitored anesthesia care. Central venous access was obtained to facilitate the use of vasopressor agents post-procedurally as needed. An arterial line was placed for continuous hemodynamic monitoring. An aortic arch angiogram was performed utilizing a 5-Fr. 100-cm pigtail catheter. A 7-Fr. 90-cm Flexor Shuttle Guiding Sheath (Cook Medical, Bloomington, IN) and 6-Fr. 125-cm Simmons II Slip Cath (Cook Medical, Bloomington, IN) along with a stiff 0.035-in. Glidewire (Terumo, Somerset, NJ) were used to select the left common carotid artery. Once arterial access was obtained, 100 U/kg of unfractionated heparin was administered to achieve an activated clotting time (ACT) of ≥250 s. The Glidewire and Slip Cath were removed, and a baseline cervical and cerebral angiogram was performed (Fig. 4.2a). A 0.014-in. Transend Floppy (Stryker, Kalamazoo, MI) wire was used to cross the stenosis and was positioned within the petrous carotid segment. A 6-mm SpideRX (Covidien, Irvine, CA) EPD was navigated across the stenosis and deployed within the distal cervical carotid artery. Over the filter wire a 2-mm × 20-mm Maverick (Boston Scientific, Natick, MA), monorail, angioplasty balloon was navigated and inflated to nominal pressure within the stenosis. The balloon was removed and an 8-mm to 6-mm × 40-cm Xact (Abbott, Chicago, IL) carotid stent was deployed. The patient's heart rate was in the 50 s, and 0.6 mg of atropine was administered intravenously prior to post-stent angioplasty. A 5-mm × 20-mm, monorail AVIATOR balloon catheter was positioned with the residual stenotic lesion and inflated to nominal pressure. A post-angioplasty angiogram of the neck and head was performed (Fig. 4.2b).

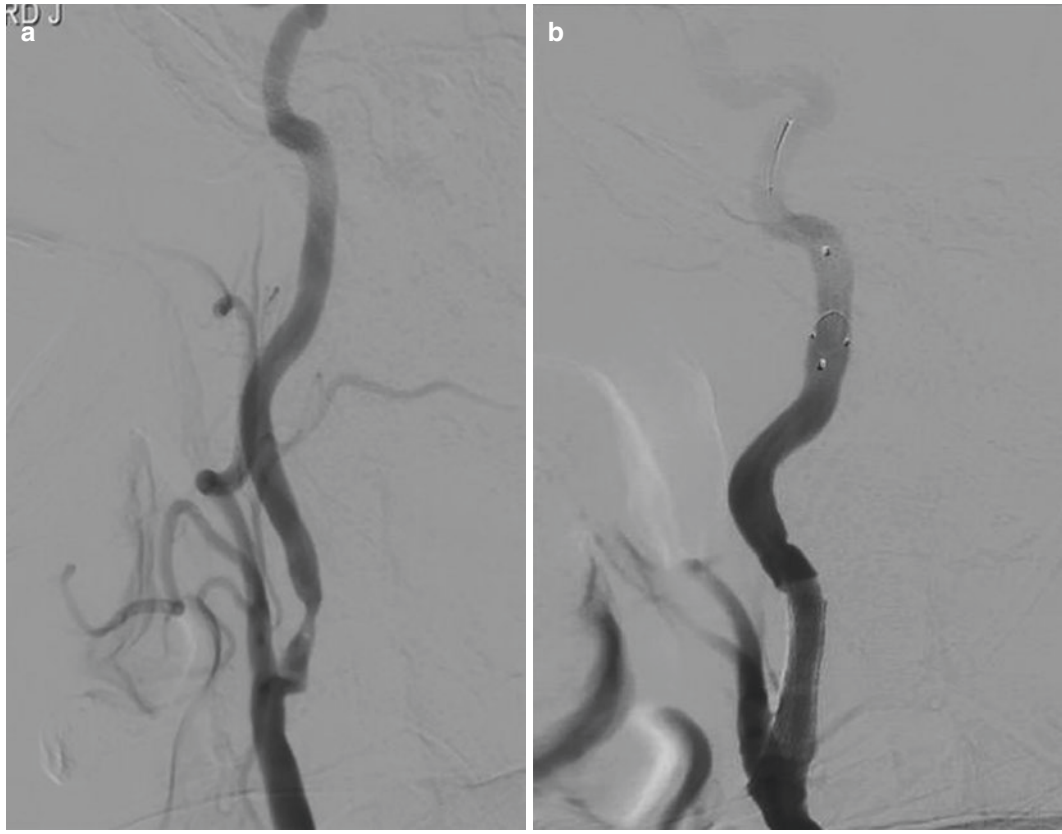

Fig. 4.2 Lateral projection angiogram showing high-grade carotid bulb stenosis (**a**) and resolution post-stenting with EPD (**b**)

Extracranial Vertebral Artery Stenosis

Extracranial vertebral artery (VA) stenosis and great vessel (i.e., ostial common carotid, innominate and subclavian arteries) stenosis are less common but important causes of stroke that are often overlooked in the evaluation of patients with stroke. Of vertebrobasilar territory strokes, VA origin (ostial) disease accounts for approximately 20%. Most often VA stenosis is a source of emboli to the basilar and posterior artery territories; however, in cases of bilateral severe VA stenoses or in situations in which one VA is hypoplastic and the other severely stenotic, symptoms of true vertebrobasilar insufficiency (VBI) may occur. The clinical presence of true VBI associated with extracranial VA stenosis mimics intracranial basilar artery stenosis both in symptomatology and the high risk of stroke as noted in the WASID trial [47]. Much like cervical ICA stenosis, VA stenosis can be treated with endarterectomy, angioplasty, and stenting, as well as surgical bypass. The former is uncommonly performed because of the high surgical morbidity associated with the surgical exposure. Angioplasty and stenting can be generally easily performed with extremely low complication rates of approximately 1–2% in experienced hands [48, 49]. The drawback to VA ostial intervention is a high rate of restenosis of 30–50%. This can be overcome with the use of drug-eluting coronary stents used off-label. In fact, all VA ostial stenting is off-label as there are no FDA-approved devices for this location.

General Technique

- *Preoperative preparation:* As with all neurovascular stenting, patients must be pretreated with dual antiplatelet therapy. Aspirin 325 mg for 3 days and clopidogrel 75 mg daily for 5 days is one effective regimen.
- *Anesthesia:* These brief, minimally stimulating procedures are done under local anesthesia with light sedation.
- *Procedural steps:* VA origin stenting is usually performed through 6-Fr. guiding catheter placed in the subclavian artery. A buddy wire can be place into the brachial artery to provide support in patients with tortuous anatomy. A microcatheter can facilitate passing a 0.014-in. wire through the lesion but is usually unnecessary. An EPD can be used although the retrieval process can be challenging at times. Once the microwire tip is positioned at the v2/V3 junction, a monorail, balloon-mounted stent is positioned across the lesion and deployed at nominal or supra-nominal pressures. The ideal stent position allows for 1–2-mm overhang into the subclavian artery.
- *Post-procedural considerations:* Dual antiplatelet agents must be continued for a minimum of 6 weeks post-stenting. When drug-eluting stents are utilized, aspirin and clopidogrel should be continued for a minimum of 12 months. Close angiographic follow-up at 6 months, 12 months, and 24 months should be performed to detect in-stent stenosis.

Illustrative Case 2

A 58-year-old man with a history of multiple coronary artery stents was admitted with sudden-onset dizziness, nausea, and visual impairment. MRI revealed several punctate acute infarcts affecting the left cerebellar hemisphere and left occipital lobe. A CT angiogram showed a hypoplastic right vertebral artery ending in PICA and a focal stenosis at the left V1 segment. The patient was started on dual antiplatelet therapy in preparation for catheter angiography and possible stenting.

The procedure was performed under conscious sedation under the supervision of the interventionalist. Right femoral access was obtained with a 6-Fr. 35-cm BRITE TIP introducer sheath (Cordis, Bridgewater, NJ). Heparin is administered to obtain an activated clotting time 1.5–2.0 times the baseline value. A 6-Fr. MPC ENVOY (Codman Neurovascular, Raynham, MA) guiding catheter is then positioned in the subclavian artery in proximity to the vertebral artery origin (Fig. 4.3a). A 0.014-in. Transend Floppy microwire was used to cross the stenotic lesion under roadmap guidance. A 3.5-mm × 23-mm, monorail, balloon-mounted XIENCE everolimus-eluting stent (Abbott, Chicago, IL) was used to navigate across the stenosis. The stent was deployed across the stenosis allowing for 2 mm of stent overhang into the subclavian artery to ensure coverage of the ostium of the vertebral artery (Fig. 4.3b). Dual antiplatelet therapy was continued for 12 months and aspirin was continued for life.

Great Vessel Stenosis

It is not clear what percent of stroke is due to great vessel stenosis, but it is thought to be <5% (Fig. 4.4a). Common carotid artery ostial stenoses may cause cerebral ischemia via embolization or more often hemodynamic compromise. Subclavian stenosis is well recognized as a cause of the subclavian steal syndrome, but innominate disease may also cause arm ischemia, TIA, and embolic stroke. Since stenoses in these locations may be treatable, it is important to search for them as potential causes. Ultrasonography is a poor modality for imaging these vessels, and they are best evaluated with computerized tomography angiography (CTA) or contrast-enhanced magnetic resonance angiography (MRA). Surgery on the great vessels typically consists of arterial bypasses but is associated with significant morbidity.

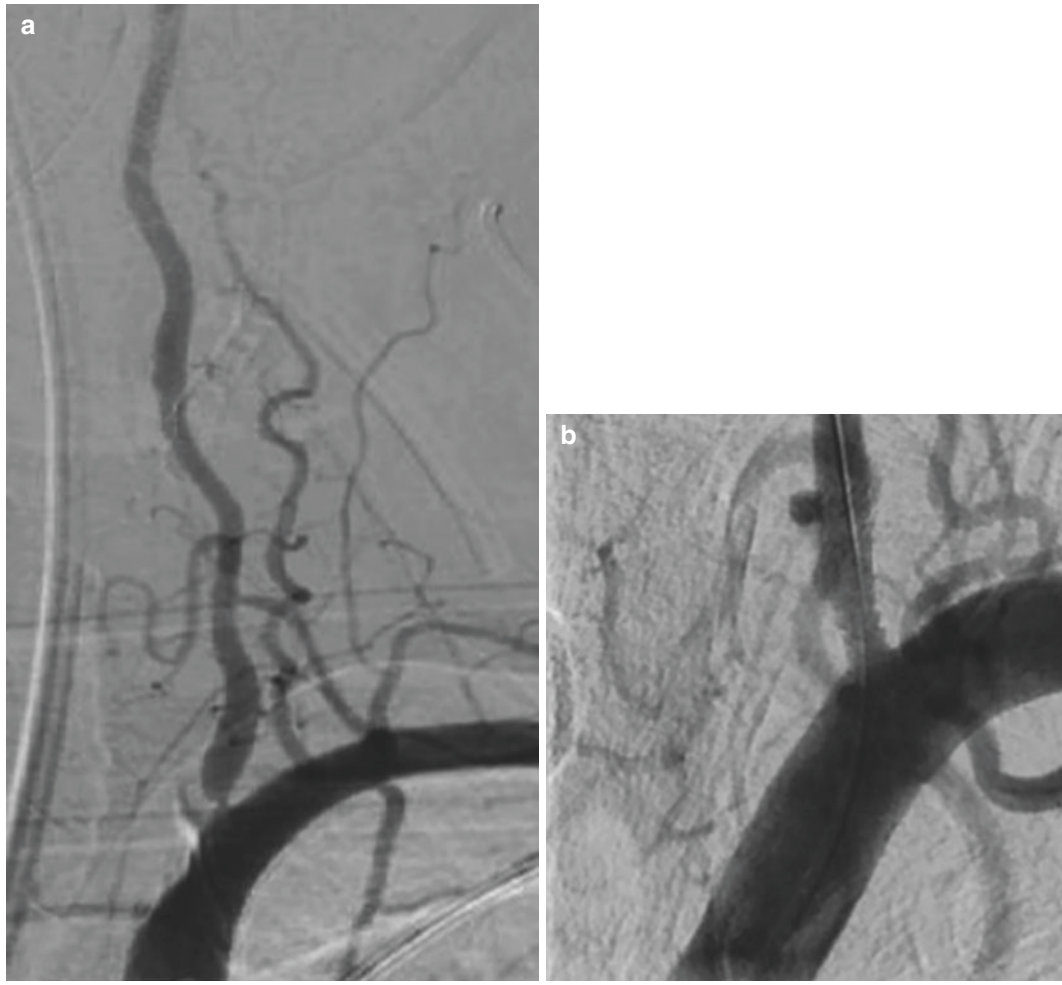

Fig. 4.3 Left anterior oblique angiogram showing high-grade vertebral artery origin stenosis (**a**) with resolution post-stenting (**b**)

General Technique

Angioplasty and stenting of great vessel stenosis can be performed with low morbidity and mortality:

- *Preoperative considerations:* Once again, dual antiplatelet therapy is essential to safe neurovascular stenting. Pre-procedural planning with a separate catheter angiogram should be considered to allow selection of the optimal approach and equipment.
- *Anesthesia:* Most procedures are performed under conscious sedation. However, general anesthesia may facilitate treatment through mechanically induced apneic periods and enhanced imaging clarity.
- *Procedural steps*: All procedures are done under therapeutic heparinization with a goal activated clotting time of ≥250 s. Selection of a large, stable base system is essential to great vessel stenting. The guiding catheter or sheath will remain in the aortic arch and lacks the buttress of a vessel wall to support its position. An angled tip or headhunter tip 8-Fr. guide catheter is often suitable. The use of a "buddy" wire creates additional stability and can be positioned within the external carotid

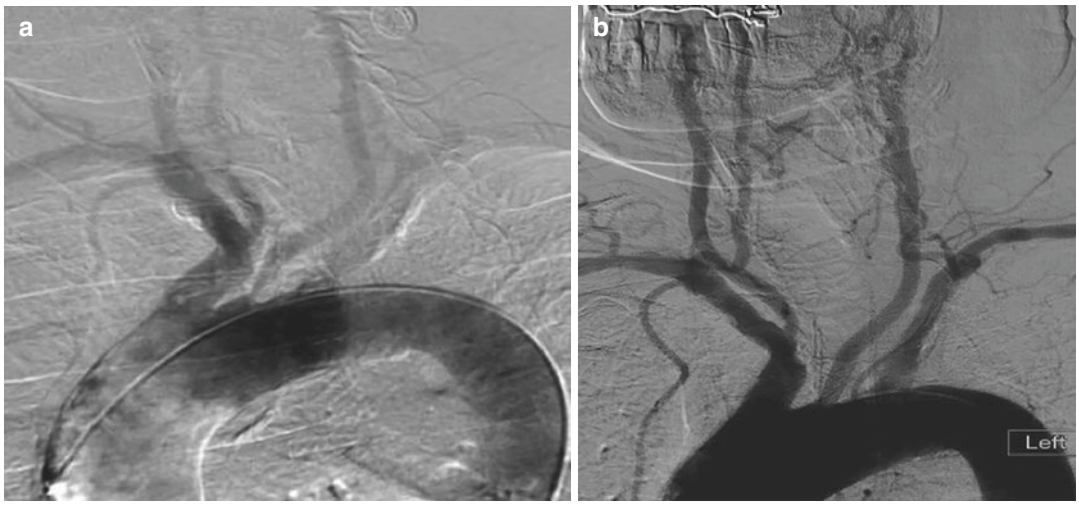

Fig. 4.4 Left anterior oblique angiogram showing severe proximal left common carotid artery stenosis (**a**) with resolution post-stenting (**b**)

artery (common carotid stenosis) or brachial artery (innominate or subclavian stenosis). The use of an EPD within the internal carotid artery is recommended in CCA stenting procedures, but these devices may not be compatible with the 0.035-in. peripheral balloon-expandable stents most commonly required (Fig. 4.4b).

- *Post-procedural care*: Dual antiplatelet therapy is maintained for a minimum of 6 weeks. Perioperative cardiac events are less common than post-carotid bulb stenting, but perioperative stroke and hemorrhage remain a concern.

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