Carotid Artery Stenting—Historical Context, Trends, and Innovations

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Abstract

Keywords

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Surgical carotid endarterectomy (CEA) has been proven effective in both primary and secondary stroke prevention and, until recently, has been considered the standard treatment approach for patients with severe carotid artery disease. Because of its technical limitations and less favorable outcomes, carotid artery stenting (CAS) has been offered preferably to patients considered to be too comorbid to undergo surgical treatment. However, CAS has evolved over time into a reliable method and is currently considered an alternative to CEA. The aim of this review was to discuss the historical aspects, trends, and innovations in CAS.

Up to 20% of ischemic strokes are attributable to severe extracranial carotid artery disease (CAD) and its manifestation poses a significant burden on patients, their families, and society.^{1,2} For several decades, carotid endarterectomy (CEA) has been used extensively as a primary option to eliminate both hemodynamic stenosis as well as carotid plaques as a source of cerebral atheroemboli. With the introduction of minimally invasive percutaneous transluminal techniques, carotid artery stenting (CAS) has emerged as a therapeutic alternative to CEA and has evolved dynamically, particularly during the last decade (► **Fig. 1**). Because it has been shown that the outcomes of both CAS and CEA are comparable beyond 30 days of follow-up, the efficacy and safety of both procedures are highly dependent on the extent of periprocedural adverse events, largely influenced by procedural technique, patient selection, and operator experience.^{3,4} The aim of this review article was to discuss the historical context, trends, and innovations in CAS.

Historical Aspects of Carotid Revascularization

It was back in the early 1950s when DeBakey and Eastcott et al pioneered first surgical attempts to alleviate symptoms in patients with severe obstructive CAD.^{5,6} Since then, CEA has been largely accepted by surgical community and early

matured into a stable and fine-tuned method. Furthermore, several large multicenter randomized controlled trials proved its superiority over the best available medical therapy in both primary and secondary stroke prevention.^{7–10} On the basis of the results of these trials, carotid revascularization is indicated in patients with symptomatic carotid stenosis of > 50% and asymptomatic carotid stenosis of > 70% severity based on the NASCET criteria.⁷ One should, however, keep in mind, that these studies were performed at times when optimal medical treatment of vascular risk factors was not available.

More than two decades later, in 1981, Klaus Mathias performed first percutaneous transluminal balloon angioplasty for CAD.¹¹ Although showing favorable results, simple balloon dilatations were associated with several complications such as vessel wall recoil, angiographically evident intimal dissection, and plaque dislodgement with particulate embolization. On the basis of favorable reports in coronary interventions, stent-supported carotid procedures soon replaced simple balloon angioplasties and, since 1994, CAS has been investigated as an alternative to CEA in multiple randomized trials.

The CAVATAS trial, performed in the late 1990s, randomized symptomatic patients at low-to-moderate risk for surgery to either CEA or carotid angioplasty (stents not available until late in the trial). Emboli protection devices (EPDs) were not available at the time. Despite that, no difference in

Fig. 1 Carotid angiography in a patient undergoing carotid artery stenting for severe internal carotid artery stenosis (area of stenosis marked by arrow): (A) preprocedural and (B) postprocedural image.

ipsilateral stroke, ipsilateral stroke or transient ischemic attack, or any stroke between the two arms was observed.¹² The incidence of major adverse events was 10% in the endovascular and 9.9% in the surgical group. The SAPHIRE study randomized patients (71% asymptomatic) at high risk for surgery to CEA or CAS with systematic use of EPDs.¹³ The primary end point, a composite of death, stroke, or myocardial infarction (MI) within 30 days after intervention or death or ipsilateral stroke between 31 days and 1 year favored CAS predominantly based on the lower rate of periprocedural MI. Nevertheless, the results of this trial established the indication for CAS in patients at high risk for surgery. The SPACE study included 1,200 symptomatic patients, but was terminated ahead of time due to slow enrollment and lack of funding.^{3,4} The study was designed to prove noninferiority of CAS (EPDs used in a minority of patients) and found no difference in the incidence of ipsilateral stroke or death at 30 days between patients allocated to CAS or CEA (6.8 and 6.3%, respectively). The EVA-3S trial⁴ was again designed as a noninferiority trial, but it was stopped early because of significantly higher rate of adverse events in the CAS arm (death or stroke 9.6% in CAS vs. 3.9% in CEA). The study was largely criticized for the participation of centers with insufficient experience in CAS procedure. Indeed, the evidence of only 12 CAS or 35 stenting procedures in any other vessel was considered sufficient for participation.

The ICSS study randomized 1,713 symptomatic patients to CAS or CEA with the primary end point of long-term rate of any fatal or disabling stroke. The final results of the study were published recently (2014) and showed that the 5-year incidence of fatal or non disabling stroke did not differ between CAS (6.4%) and CEA (6.5%). However, the rate of non disabling strokes favored CEA.¹⁴

The CREST study,¹⁵ published in 2010, was designed to avoid the major pitfalls of the previously published trials with mandatory use of EPDs and participation of experienced centers only, thereby being considered the most informative CAS study published so far.¹⁵ The primary end point was a

composite of stroke, MI, or death from any cause during the periprocedural period (30 days) or any ipsilateral stroke within 4 years after randomization. The total of 2,502 symptomatic and asymptomatic patients were randomized and observed over the mean period of 2.5 years. There was no significant difference in the estimated 4-year rates of primary end point between the stenting and endarterectomy group (7.2 vs. 6.8%, respectively), with a slightly more frequent stroke in CAS (4.1 vs. 2.3%, $p = 0.01$), and MI in CEA (2.3 vs. 1.1%, $p = 0.03$). Although the absolute rates of either component events were low, it was proposed that the quality of life was more impacted by stroke compared with MI. On the basis of the results of the CREST trial, current guidelines recommend that CAS may be considered an alternative to CEA in average surgical risk patients.¹⁶

Finally, despite the results of SAPHIRE and CREST, the evidence suggesting optimal treatment method in asymptomatic patients on optimal medical therapy is still limited. Currently, several randomized trials in standard surgical risk asymptomatic patients are in progress (ACT-1, ACST-2, SPACE-2, and CREST-2). Unfortunately, the enrollment (as in most CAS/CEA trials) is very slow and meaningful results will probably not be available for several years to come.

Patient Selection

Apart from operator training, it is equally essential to carefully select patients to reach favorable outcomes in both CEA and CAS. In general, the modifying factors can be divided into “patient-related” and “lesion-related,” and while some guide the approach from the earliest experiences with invasive treatment, others have not emerged until recently.

Regarding the “patient-related” characteristics, only few restrictions used to be applied in CAS because of its minimal invasiveness, mostly comprising severe renal insufficiency, contraindications to dual antiplatelet therapy, and/or history of bleeding complications. Therefore, CAS has notoriously been preferred over CEA in patients with multiple medical comorbidities. Nevertheless, the results of several trials such as BEACH, SPACE, and CREST have doubted this long-established concept and proved that patients with cumulation of comorbidities and particularly older patients (> 75 years) had superior outcomes with CEA as opposed to younger less comorbid patients.^{3,15,17} Interestingly, in the BEACH trial, 30-day outcomes of patients enrolled for CAS because of their medical comorbidities were worse compared with those enrolled because of unfavorable CEA anatomy. The explanation may be the more complicated endovascular approach to the target artery underscoring the increased risk of complication because of the prolonged manipulation within “vulnerable” terrain. Indeed, difficult arch anatomy such as type III aortic arch with acute angulation into carotid artery, severe calcification of the lesion, or presence of advanced atherosclerotic changes alongside the access route, all more commonly present in elderly patients, have been proven to excessively increase the risk of CAS.¹⁸

Apart from atherosclerotic complications, bovine aortic arch may also favor surgical approach.¹⁹ On the contrary,

extensive accumulation of scar tissue following previous neck surgery (including CEA) or irradiation as well as high carotid bifurcation (especially lesions located above second cervical vertebra) or lesions below the clavicle clearly represent surgical challenge.^{20–23}

Procedural and Technological Improvements

CAS arbitrarily can be divided into several phases including wiring, predilation, EPD placement, stent deployment, stent postdilation, and device withdrawal. Nowadays, there is a clear trend toward minimizing the forces applied on the atherosclerotic plaque (particularly if not protected by EPDs).^{24–31} Therefore, it is currently a routine practice to avoid, if possible, the predilation of the stenosis (direct stenting), compared with vigorously recommended predilation in the early reports suggesting less scissoring effect of the stent during implantation.²⁴ In addition, omitting postdilation in highly selected patients with soft plaques has also been proven safe with low risk of restenosis.²⁵ However, most of the procedural improvements can be attributed to the introduction and fine tuning of EPDs and stents.

Despite thorough patient selection and operator experience may significantly increase the safety and efficacy of CAS, there is always a risk of mobilizing atherothrombotic material during endovascular manipulation. To decrease such a risk, EPDs have been developed and are consistently improving to provide the best possible protection during CAS. Moreover, the concept that the structure of a stent may play a role in protecting from delayed embolization has recently been revived. By far most commonly used EPDs have been distal filter-type protections. These systems are low profile and typically can be advanced across a carotid stenosis without previous predilation. They allow to capture large particles (macroemboli) that are likely further disintegrated into small ones that can pass through the filter micropores. The advantages of these EPDs are the ease of delivery and deployment and the ability to visualize the carotid artery during the procedure without interrupting the antegrade intracranial flow. Limitations of these devices include the potential for distal embolization during initial lesion crossing, the possibility of incomplete seal, the inability to capture microparticles that may in high loads enter distal circulation, and the risk of carotid artery spasm or dissection at the site of filter deployment.

Proximal protection systems address some of the drawbacks of filter-type EPDs. By inflating distal balloon in external carotid artery and proximal balloon in common carotid artery, flow arrest (or even reversal) in internal carotid artery may be induced similarly to a surgical clamp. If properly deployed, these systems may significantly reduce embolization during the most hazardous phases of stent implantation and postdilation.^{26,27} The disadvantages of these systems are larger arterial sheath (commonly 9F) requiring “more straightforward” vascular-to-carotid access, inability to angiographically control stent deployment, longer duration of the procedure and, particularly, the dependence of the ipsilateral hemisphere on collateral cerebral circulation. Al-

though not suitable for all patients, the superiority in embolic protection seems to outweigh the limitations and, in experienced hands, improve the safety of CAS.^{28–30}

Recently, a direct carotid access EPD was developed and is in early stages of clinical evaluation. This system, introduced through a surgical cut down, is based on arteriovenous shunting into femoral vein induced after the occlusion of common carotid artery just proximal to the arterial sheath. A limited experience with this EPD published so far suggests lower incidence of new lesions on the postprocedural magnetic resonance imaging scan.³¹

Carotid Stents

Inspired in coronary interventions, the early stent supported CAS procedures were performed using balloon expandable stents. This practice, however, must have been abandoned because of higher risk of stent deformation (external crushing) because of its relatively superficial location, and has been largely replaced by self-expanding stents. In general, the latter can be further divided into two overlapping groups based on the stent structure. Simply put, stents are formed by sequentially aligned annular rings interconnected by bridges. Depending on the density of the bridges, the design of the stent may be either open cell (lower numbers of bridges with larger free cell areas) or closed cell. While either design has its advantage, such as increased conformability of the open cell design stent or presumed better plaque coverage of the closed cell design stent, neither has been proven superior and the choice of stent is currently based on the operator experience. It seems logical, that the optimal stent should be both flexible and able to support the plaque preventing the atherosclerotic particles from being squeezed into vasculature. Indeed, examples of both stent malposition and through stent plaque prolapse, both well-known risk factors of delayed adverse events, are nowadays more commonly observed with improvement of intravascular imaging.³² Furthermore, it has been proven that delayed embolization (albeit mostly asymptomatic) occurs in a substantial proportion of patients.³³ Therefore, the concept of “optimal stent” is again discussed and searched for. While hybrid-type stents (closed cell design in the midportion with open cells in proximal and distal segment) aspired to be an appealing concept, most of the current attention is focused on a novel carotid stent design—a double layer mesh stent. Its structure is characterized by micromesh layer for plaque coverage mounted over self-expanding nitinol layer for scaffolding, offering the flexibility comparable to the open cell design stent. It is to be shown whether such a concept will result in further improvement of the safety of CAS.

Conclusion

Both CEA and CAS are likely the most studied procedures in the vascular medicine. CEA, optimized and fine-tuned decades ago, has been considered the standard approach for the majority of patients with CAD. Conversely, CAS was introduced as an alternative for surgically high-risk patients and its

wide acceptance has been mitigated by inferior outcomes compared with CEA, mostly driven by technical and operator-dependent limitations. Particularly over the last decade, CAS has improved substantially and matured into a reliable method. When performed in experienced centers, it may be considered equivalent and in selected (particularly younger) patients even preferable to CEA.

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