Bangladesh Journal of Neuroscience 2022; Vol. 38 (1): 43-54

REVIEW ARTICLE

Carotid artery Stenting: Review of Technique and Randomized Studies

DEY SK[1], BAKSHI L[2], SHAHIDULLAH M[3],HABIB A[4],AHMED A[5]

Abstract:

Stroke is one of the leading causes of death and the number one cause of long-term disability in the Bangladesh. Carotid stenosis is an important cause of ischemic strokes, accounting for 20 to 25%. Both symptomatic and asymptomatic carotid stenosis, carotid endarterectomy are established as a standard care of treatment. Symptomatic patients with carotid stenosis > 50% and asymptomatic patients with carotid stenosis > 70% are candidates for endarterectomy. Recently, carotid artery stenting has emerged as an alternative treatment for carotid stenosis. Several studies have been published comparing endarterectomy with carotid artery stenting. In this article, the authors discuss carotid artery stenting technique, the results from the most recent trials, comparison with endarterectomy and future directions.

Keywords: *Carotid artery stenting, carotid endarterectomy, ischemic stroke.*

Introduction:

In 1950s, C Miller Fisher first recognized carotid artery stenosis to be a major cause of stroke.[1] When carotid endarterectomy (CEA) was done in selected patients, recurrence of ischemic stroke was reduced than medical therapy alone. [2-4]. Recently judicious use of medical devices (carotid stent) in endovascular techniques created a good alternative to carotid endarterectomy for carotid revascularization. Carotid stenting (CAS) is now a widely accepted alternative to endarterectomy in specific situations.[5,6,7,8] The authors describe here the current state of carotid revascularization devices and the evidence to support them. Elective carotid stenting will be focused in this article. The carotid artery is unique because it is end-organ. Whereas the primary concern during revascularization in peripheral vessels is restoration of flow and hemodynamic balance, even minor distal embolization in the carotid artery can be associated with devastating neurological injury. Carotid arteries lack significant muscularity and have lower resistance bed, so it remains a concern during instrumenting and manipulating intracranial vasculature. To achieve adequate endoluminal recanalization against a centripetal muscular force, carotid device technology is used, while minimizing distal embolic events. Carotid technologies divided into three groups: stent, balloon angioplasty, and embolization prevention devices. Other miscellaneous technologies are also presented.

Patient Selection: Success of the procedure depends upon the appropriate patient selection. Before selection of carotid stenting, proper history, examinations and relevant investigations of the patients should be evaluated. Stroke risk stratification should be performed and will determine the appropriate treatment plan. After stroke, carotid revascularization should be done within 2nd day to 15 days after stroke. Stroke patients who have >50% stenosis and asymptomatic patients who have > 70% of carotid stenosis are candidates for carotid

1. Dr Subash kanti Dey, Professor, Department of Neurology, BSMMU.
2. Dr Lipy Bakshi, Assistant Professor, Dept of Obs &Gynae, Dhaka National Medical College.
3. Dr Md Shahidullah, professor, Department of Neurology, BSMMU.
4. Dr Ahsan Habib ,Professor, Department of Neurology, BSMMU.
5. Dr Anis Ahmed, Assistant professor, Department of Neurology, BSMMU.

revascularization. Choice between CEA and CAS will depend on patient factors, operator preference.

Patient Preparation: Before Carotid artery stenting (CAS) informed written consent should be obtained. Those who are taking double antiplatelet do not need extra medications. But those who are not taking antiplatelets before, oral antiplatelet therapy with clopidogrel and aspirin should be initiated 5 days prior to treatment date. In case of emergency CAS a loading dose of 300 mg of clopidogrel and 300 mg of aspirin should be given 4 to 5 hours prior to the procedure. Bilateral inguinal regions should be prepared for access.

The right common femoral artery (CFA) is the preferred access for CAS. The left CFA and the brachial artery are alternative accesses if the right CFA is not optimal. Once access is gained, a short 5-F vascular sheath should be placed, 2500 iu of heparin is infused through short sheath. Cervical arch aortography obtained at approximately 35 degrees left anterior oblique projection should visualize the origins of the great vessels. This step may be skipped if recent, high-quality, noninvasive imaging of the cervical aortic arch is available for reference. Catheter selection for common carotid artery (CCA) catheterization will depend on the aortic arch anatomy. The aortic arch may be classified based on the origins of the great vessels in reference to the convexity of the aortic arch: Type I—great vessel origins are level with upper convexity; Type II—great vessel origins are between the upper and lower convexity; and Type III—great vessel origins are caudal to lower convexity. Selection of great vessels in the setting of Type III arch can present a challenge and typically requires a reverse curve catheter (e.g., Simmons 2 or 3). The CCA is selected and anterior-posterior and lateral projections of the cervical carotid artery should be obtained . Baseline neurological examination should be performed and documented.

Oblique/ lateral projections of carotid bifurcation may be necessary to optimally visualize the stenosis. The authors prefer, North American Symptomatic Carotid Endarterectomy Trial (NASCET) technique to measure the carotid stenosis. If the stenosis measurement does not meet the criteria for stenting, then the procedure is terminated. The patient should be followed-up clinically and managed with best medical therapy.

Carotid Artery Stenting: Short sheath is replaced by long 8F sheath (90 cm length). Under guidance of a wire; a diagnostic catheter was used to place the long sheath into common carotid artery at least

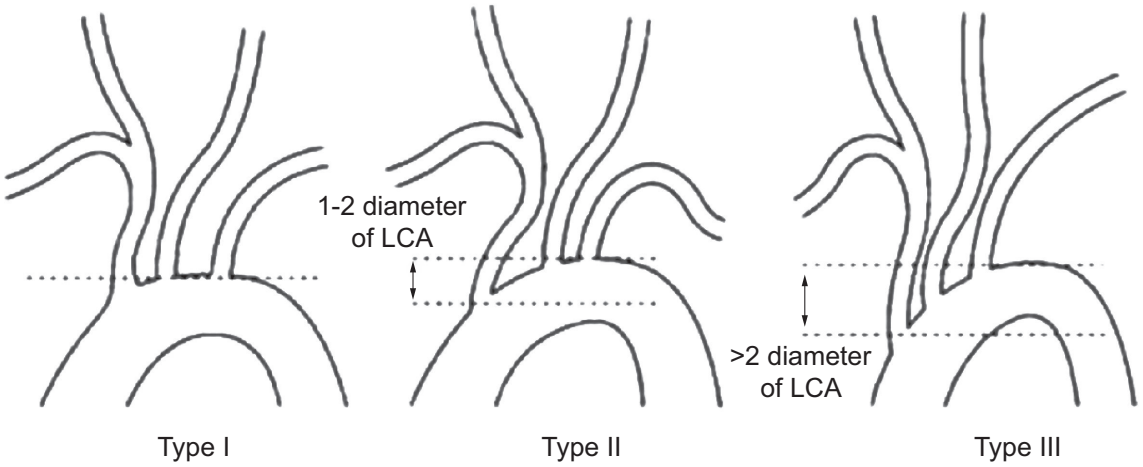

Fig.-1: *Different types of aortic arch*

5 cm below the lesion. An exchange length guide-wire is placed distal part of carotid artery crossing the stenotic part. Attention is needed to avoid inadvertent wire contact with the stenosis. When using the long sheath extra attention should be paid once the tip has reached the CCA. The Shuttle is equipped with a Tuohy-Borst (Y-adapter). Intravenous anticoagulation is required and most operators prefer unfractionated heparin. A bolus dose of 100 unit/ kg is administered and titrated to reach an activated clotting time (ACT) of 250 to 300 seconds. Once the sheath is in place and the desired ACT level is reached, stent, angioplasty balloon is introduced. After deployment of carotid stent whole system are removed. Long sheath is replaced by 8/9F short sheath.

Types of stent:

Basics of stent types & design: Carotid artery stents come in various configurations and are made of several materials. Generally, these stents are self-expanding bare-metal stents. The two common metals used to construct these stents are nickel–titanium alloy (Nitinol) and cobalt–chromium alloy. Nitinol, at present, is more commonly used in the construction of carotid stents. Carotid stents are further categorized as 'open cell' or 'closed cell' based on the free-cell area between the stent lattices [9]. These stents have important mechanical and structural differences that are unique [10-12]. Each stent has a set of properties that make their utilization advantageous in distinct scenarios. Thoughtful device selection based on preprocedural symptomatic status, specific stent characteristics, anatomic challenges and plaque morphology is crucial to optimizing the results of CAS.

Characteristics of open- & closed-cell stents: Classifying a stent as either open cell or closed cell is based on the free-cell area of a given stent. The free-cell area is a measure of the amount of space between stent lattices[10]. Closed-cell stents have a smaller free-cell area between the stent lattices. As a consequence, closed-cell stents are more rigid, and therefore, less conformable in tortuous vessels. These characteristics can make advancing a closed-cell stent more challenging in serpentine vessels. Excessive device manipulation should be avoided when possible, and therefore, closed cell stents should be avoided in these situations. Furthermore, an inflexible stent placed in a compliant, but coiled vessel may create kinks due to forced straightening of a curved structure. The theoretical advantage of a closed-cell stent is in its ability to better scaffold labile carotid plaques that are at an increased risk of generating particulate debris. These high-risk plaques are more commonly seen in symptomatic individuals[13,14]. This enhanced scaffolding effect may decrease distal embolization [10]. An added benefit, observed by Gurbel et al. in a porcine model, is that closed-cell stents may result in less platelet aggregation[15]. This observation is theorized to result from less intimal prolapse and a smoother stent–arterial wall interface seen with closed-cell stents. Alternatively, the larger free-cell area between the stent struts in an open-cell stent creates a more malleable structure. Therefore, open-cell stents readily navigate through tortuous vessels allowing smooth device delivery in unfavorable anatomy. By reducing the manipulation necessary to traverse a target lesion with a stent, embolic potential may be reduced. In addition, the flexible nature of open-cell stents helps avoid arterial kinking due to unnecessary vessel straightening. Arterial kinking may increase the risk of cerebrovascular insufficiency and sustained hypertension [16]. However, due to the increased area between the stent lattices, these stents do not exclude the plaque as well as their tightly woven counterparts. It is important to realize that the free-cell area of a given stent, whether open cell or closed cell, is variable. This changeability is dependent on several factors. For example, when implanted, the stent's free-cell area of a constrained stent will differ from when it is freely expanded[17]. Stent oversizing will result in a reduced free-cell area when constrained within an arterial lumen. Similarly, due to the natural taper that occurs from the CCA to the ICA, free-cell area will vary along the length of the stent. Distally, these stents will have less space between the stent interstices. This has resulted in the production and availability of tapered stents to accommodate the caliber difference between the CCA and ICA. Auricchio et al. demonstrated, in a carotid model, that after stenting, free-cell area variability is most pronounced with open-cell stents[17]. This inconsistency is most prominent at the carotid bifurcation due to observed caliber changes and the presence of diverging vessels. Muller Hulsbeck et al. also created a model to assess the impact of various forces on carotid stents[11]. In their in vitro

model, carotid stents were subjected to 20 and 30° of bend, and 10 and 15° of twist. These investigators demonstrated that closed-cell stents generate a higher force when contorted. Therefore, deploying these tighter and more rigid structures in unfavorable vessels will result in a counter effect. Simply, if the forces generated by

Table-I

Various carotid stents, stent materials and associated free cell areas.[9]

Carotid stent	Metal	Free cell area mm^2
Closed cell		
Wallstent	Cobalt chromium	1.1
Xact	Nitinol	2.7
Nexstent	Nitinol	4.7
Open Cell		
Precise	Nitinol	5.9
Protege	Nitinol	10.7
Acculink	Nitinol	11.5

the stent exceed that of the recipient artery, the treated vessel will inherently accommodate the unyielding structure. As described above, the extreme manifestation of this effect is arterial kinking due to the straightening of a previously meandering vessel. An ideal stent will conform to a winding vessel without generating excess force. Importantly, this model also established that free-cell area will vary along the proximal, middle and distal portions of the stent. This unevenness appeared most pronounced in open-cell stent configurations corroborating the study performed by Auricchio et al [11,17]. Free-cell area will vary along the length of a stent, and therefore, will offer different degrees of scaffolding along its course. Normally, extracranial carotid disease is localized to the carotid bifurcation and extends into the ostium of the ICA. An ideal stent must scaffold this area to prevent distal embolization. A small free cell area is less important proximal and distal to this high-risk zone. These observations are being utilized to optimize the design of newer generation carotid stents. For example, the Cristallo Ideale stent implements a hybrid design [17]. The midportion of this stent has a closed-cell configuration, while the proximal and distal ends are open cell. The theoretical benefit of such a design is an optimal balance of conformability and scaffolding.

Stent selection: Selecting the ideal stent for specific carotid anatomy and plaque morphology becomes applicable once the long vascular sheath is in proper place (5 cm distal to CCA). At this stage, selecting the best stent possible can impact procedural outcomes. When choosing a stent, the embolic potential of the plaque and carotid tortuosity should be considered. Preprocedural assessment of the target carotid stenosis or an individual's presentation can identify friable plaques. These high-risk lesions will benefit most from the increased scaffolding seen with closed-cell stents. In particular, duplex ultrasound is the most helpful tool used to categorize these plaques. Lesions that appear more echolucent are more prone to distal embolization and stroke[13,14]. Furthermore, calculating the gray scale median (GSM) can be a useful adjunct [20]. GSM uses plaque imaging and an assessment of the number of white and black pixels within a plaque. More black pixels results in a lower GSM score and represents a more echolucent plaque. Malik et al. demonstrated a propensity to generate more embolic debris and particulates of larger calibers in patients undergoing CAS with a calculated GSM <20. Symptomatic patients often demonstrate high-risk plaque morphology[13,14]. The degree of carotid tortuosity can be determined by assessing intraprocedural angiogram. In patients with grade I (<30°) or grade II (30–60°) ICA tortuosity, both open- and closed-cell stents are conformable enough to allow safe positioning. In this scenario, the plaque morphology should influence the stent utilized. However, in patients with very serpentine carotid arteries (grade III, >60°), open-cell stents are ideal due to their malleable properties. In addition to choosing the appropriate stent configuration, it is important to choose the correct diameter and length of the device. The stent should be of an adequate caliber to appose the vessel wall. Therefore, carotid stents are usually oversized. To achieve a better size match given the incongruent CCA and ICA diameters, a tapered stent configuration is preferred. The use of a radiopaque ruler can help determine the best length. The extent of the stent should be long enough to cover the target stenosis without excess intrusion into the relatively normal proximal and distal vessel. If possible, landing the stent in a straight arterial segment will achieve the best result.

Impact of stent design on outcomes: There was few large prospective, randomized control data comparing stent configurations. Therefore, definitive data are lacking. Several retrospective studies of varying size and one randomized control trial with insufficient power have been executed. Despite the theoretical advantage of plaque stabilization when closed-cell stents are used, comparisons of outcomes have produced varying results. Closed-cell stents have not uniformly resulted in decreased periprocedural neurological events when compared with open-cell stents. These results may be confounded by selection bias as operators may inherently use specific stents in vulnerable situations. Furthermore, a disparity exists when evaluating the impact of stent design on outcomes in symptomatic and asymptomatic treatment groups. A clear and consistent improvement in outcomes due to stent configuration has not been demonstrated. These observations are due to the multiple confounding factors that influence the results of CAS. Furthermore, the process of stent selection encompasses complex decision-making that is difficult to capture without a well-structured and adequately powered randomized trial. Therefore, an agreement on an ideal stent design has not been reached. Bosiers et al. and Hart et al. independently showed improved outcomes when using closed-cell stents [9,19]. Further analysis of their data, however, demonstrated that these benefits were not observed in asymptomatic patients. Bosiers et al. investigated the impact of carotid stent design in 3179 patients [9]. Their end points included 30-day and overall transient ischemic attack (TIA), stroke and death rates. Although the use of closed-cell stents resulted in a lower event rate at 30 days and overall in the entire study population, these benefits were mainly observed due to differences seen in the 1317 patients treated for symptomatic carotid disease. Similarly, the study by Hart et al. assessed the influence of stent type on 30-day TIA, stroke or death rates [19]. In their total cohort of 701 patients, stent design did not alter outcomes. However, in a subgroup analysis of symptomatic patients, open-cell stent use resulted in a higher likelihood of an adverse event (odds ratio: 4.1; 95% CI: 1.4–12; p = 0.014). Labile plaques are more commonly seen in symptomatic patients [13,14]. Therefore, the benefits of scaffolding observed with closed-cell stents may account for the improved TIA, stroke and death rate seen exclusively in symptomatic patients treated with this configuration. Conversely, in retrospective studies by Tadros et al., Schillinger et al., Jim et al. and Maleux et al. comparing stent designs in mixed populations of symptomatic and asymptomatic patients, no differences in outcomes were observed [18,21–22] In an effort to clarify the utility of closedcell stents, data from four studies were pooled (Figure 5) [9,19]. Closed-cell stents are thought to reinforce labile plaques. These high-risk stenoses are more common in symptomatic patients [13,14]. Furthermore, the studies that demonstrated an advantage with closed-cell stents recognized these benefits strictly in symptomatic populations. Of the available retrospective studies, results specifically for symptomatic patients were reported by four investigators, Bosiers et al., Hart et al., Schillinger et al. and Jim et al.[9,21,22]. Moreover, these researchers uniformly detailed 30-day TIA, stroke and death rates as an end point in patients receiving either open- or closed-cell stents. Cumulatively, 4352 symptomatic patients were pooled, 1892 received a closed-cell stent and 2460 were stented with an open-cell device. Adverse events at 30-days were observed in 67 patients (3.5%) in the closed-cell group and in 116 individuals (4.7%) in the open-cell group. Overall, the combined odds ratio when comparing open-cell stents with closed-cell stents in symptomatic patients was 1.35 (95% CI: 0.99–1.83; p = 0.057) for the end point of 30-day TIA, stroke or death. The CREST trial, which demonstrated the lowest stroke rate of all of the CAS trials, utilized an open-cell t stent. Therefore, stent design and selection is an modifiable variable that may impact upon procedural outcomes. However, more than any other variable, operator experience has the most impact on improving outcomes. This observation is further exemplified by the authors' own low adverse event rate [18,21–23].

Predilatation: Predilatation of the stenosis before stent deployment is not always necessary. The authors prefer it when stenosis is >90%. The theoretical benefits include less traumatic stent delivery and reduced need for postdelivery dilation. The potential disadvantages include the risk of distal embolization, potential for plaque rupture without stent protection, and additional time requirements. If predilatation is desired, a 2.5- or 3-mm diameter balloon should suffice. In a native carotid artery (i.e., no previous CEA), prior to

predilatation 0.5 to 1 mg of atropine may be ready for administration if bradycardia ensues.

Self-expanding stents are used for CAS. The stent length has to be sufficiently long enough to completely cover the stenosis, which in most cases necessitates extending from it from the CCA to the ICA. To achieve optimal wall apposition in all carotid segments, the stent diameter needs to match that of the CCA. The stent should be advanced slightly beyond the desired location distal to the stenosis and retracted prior to deployment to reduce any slack or redundancy that may cause the stent to jump forward. If there is incomplete coverage of the stenosis, a second stent may need to be placed. Atropine should be given or be ready to give immediately in the event of bradycardia.

Postdilatation: After the stent is placed, post dilation is a controversial issue. As carotid stent is

Self-expanding, post dilatation is not preferred by author.

Postprocedural Care: After CAS is completed, the patient should be observed for 48 hours. Serial neurological examinations should be performed and documented. Routine evaluation of the access site is appropriate. Serial hemodynamic monitoring is recommended; if postprocedural hypotension is noted, volume resuscitation is typically adequate. Rarely, pharmacological pressure support and critical care monitoring are required. If hypertension is present, it is advised to lower the blood pressure to below 150 mm Hg systolic. At the authors' institution, most patients are admitted to a neurology unit. Most patients are discharged the next day with longitudinal follow-up. Clopidogrel and Aspirin should be continued for 45 days, after which aspirin should be taken for life. Ultrasound follow-up is recommended at 3 months, 6 months, and then yearly.

Embolic Protection Device Placement: It is a controversial issue. The author does not recommend for Embolic protection device.

Carotid stenting done in BSMMU

RICA stenosis | After stenting | Carotid stent

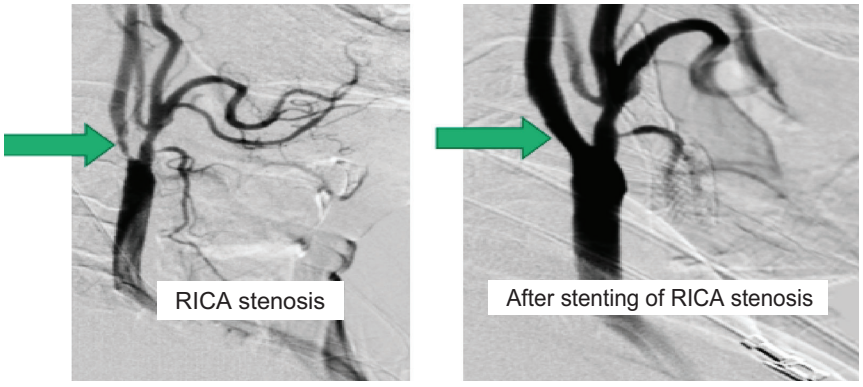

Fig.-2:

Outcomes of CAS & CEA : Several randomized controlled trials have compared CAS with CEA in the recent literature. Because of the heterogeneity of patient populations, study endpoints, operator experience levels, treatment technique, etc., consensus has been difficult to reach. On the other end, more questions have been raised than answered. the authors of the article will attempt to highlight these in a practical manner.

Overall, the data for CAS are encouraging. Over the past 10 to 15 years, the CAS data have shown progressive improvements in terms of 30-day mortality and stroke rates, as illustrated by Silver et al.[24] which enrolled symptomatic patients with > 60% stenosis and was terminated early, and Carotid and Vertebral Artery Transluminal Angioplasty Study, a trial of average risk and mostly symptomatic patients, produced combined 30-day stroke and death rates of 12.1 and 10%, respectively.[25,26] Subsequently, Stent-Protected Angioplasty versus Carotid Endarterectomy, Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis , International Carotid Stent Study, and Carotid Revascularization Endarterectomy versus Stenting Trial have shown 7.7, 9.6, 7.4, and 6% combined 30-day stroke and death rates, respectively, for symptomatic and average risk patients.[27–30] SAPPHIRE trial was done to compare between CAS and CEA. CAS was indicated for highly surgical risk patients. Using a composite of stroke, myocardial infarction, and death as the primary endpoint, CAS was shown not to be inferior to CEA.[31] Within the eligible group, symptomatic patients with 51 to 70% and asymptomatic patients with > 80% CS are eligible for CAS Medicare coverage only if enrolled in an approved research trial. Following SAPPHIRE, several studies have compared CAS with CEA for average surgical risk patients. The results have been mixed. No significant difference between CAS and CEA was shown in the most recent randomized trial, CREST. This was a study of 2,502 patients with symptomatic or asymptomatic CS with average surgical risk randomized to either CAS or CEA. The combined rates of stroke, myocardial infarction, or death were not significantly different between CAS and CEA (7.2 vs. 6.8%, respectively).[29] In contrast, EVA-3S, a randomized study of 60% symptomatic stenosis, was terminated early due to excessively higher rate of death and stroke in the CAS treatment arm at 30 days (9.6 vs. 3.9%; p ¼ 0.01).[28] In the SPACE trial, another comparison of CAS versus CEA, similar results to CREST, was reported in 1,200 symptomatic patients. The primary endpoints (ipsilateral stroke and death) were not significantly different between CAS (6.8%) and CEA (6.3%). However, due to the design of the study, the investigators concluded that CAS had failed to demonstrate noninferiority, as CAS did not meet the prespecified 2.5% margin difference.[27]CAS compared with endarterectomy in patients with symptomatic CS (International Carotid Stenting Study) randomized 1,713 patients; at 120 days, the rates of disabling strokes and death were 4.0 versus 3.2% for CAS and CEA, respectively; and combined stroke, death, and myocardial infarction rates were higher for CAS compared with CEA (8.5 vs. 5.2%, respectively).[30] As CAS is a relatively newer procedure compared with CEA, operator inexperience may be a factor contributing to higher complication rates. In a review of Medicare beneficiaries treated with CAS, a correlation between lower annual case volumes and early experience with increased 30-day mortality rates was observed.[32] Both SPACE and EVA-3S have been criticized for inclusion of inexperienced operators. On the contrary, CREST applied much more rigorous criteria to select its CAS operators, which may partially explain the improved outcomes of this study. EPD utilizations may also have contributed to mixed outcomes. While no conclusive data exist on the absolute benefits of EPD, its use is widely adopted. In addition, future refinements will hopefully lead to reductions in perioperative stroke rates. A Cochrane database meta-analysis of 16 trials, totaling 7,572 patients, has provided several insights regarding the efficacy of CAS. For non–high-risk patients with symptomatic CS in the perioperative period (randomization to 30 days): (1) CAS and CEA did not show significant difference in death and disabling stroke rates, (2) CAS had higher total stroke rate, and (3) CAS had lower myocardial

infarction, cranial nerve palsy, and access site hematoma rates compared with CEA.[34] In the follow-up period after 30 days from the procedure, CAS and CEA had no significant difference in stroke rates.[34] CREST, which was included in the meta-analysis, showed that, in the periprocedural period, CAS had a higher death rate (0.7 vs. 0.3%, respectively; not significant (ns), CAS had a higher overall stroke rate (4.1 vs. 2.3%, respectively; p ¼ 0.01), and CEA had a higher myocardial infarction rate (2.3 vs. 1.1%, respectively; p ¼ 0.03). It is clear that if CAS is to make further gains, reduction in perioperative stroke rate may hold the key. Investigators have performed secondary analyses in an attempt to identify factors that may have potential effects on CAS outcomes. Advanced patient age appears to have a negative effect on CAS outcomes. Despite the exclusion of > 80-year-old patients in the earlier CEA trials as high risk, recent comparative studies have indicated that CAS had worse outcomes than CEA in older patients.[27–29] Meta-analysis of EVA-3S, SPACE, ICSS, and Cochrane meta-analysis have shown that patients older than 70 years have higher incidence of negative events with CAS compared with CEA.[34,35] Conversely, patients younger than 70 years tended to do slightly better with CAS.[29] The negative CAS outcome correlation with advanced age is likely due to difficult anatomy more commonly found in the elderly who may pose a technical challenge, especially for the less experienced operators. With experience and proper patient selection, researchers have shown that CAS can be performed with low complication rates in the elderly. Grant et al[36] and Setacci et al[37] have published their experience of CAS in octogenarians with low complication rates; not surprisingly, difficult anatomies including aortic and great vessel calcification and tortuosity, as well as Type III aortic arch configuration, were statistically more common in the elderly.[37] The true effect of age on CAS and CEA outcomes is critical[38] as the proportion of the elderly population increases. Moreover, in general practice, the majority (59%) of carotid revascularization is performed on patients older than 70 years.[39] The effect of operator experience has been proposed to influence CAS outcomes. It makes sense that lack of experience and expertise in any procedure may lead to higher complication rates during the learning curve. The comparison of study centers in SPACE showed that the complications rates were directly correlated with lower numbers of study patients.[33] Nallamothu et al stratified Medicaid beneficiaries who had CAS from 2005 to 2007 by operator case volume levels, and early and late results during new operators' experience. The study showed statistically significant relationship between 30-day mortality rates and low operator volume and early experience.[32] Analysis of the Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2) revealed that to achieve a combined death and stroke rate below 3%, a minimum of 72 cases was necessary, a strikingly high number. In another study, more adverse events were also found in hospitals with low patient volumes and for individual operators with low volumes.[40] Despite these reports, large meta-analyses have not shown significant differences in outcomes related to CAS operator experience Outcomes based on patient gender, symptomatic/asymptomatic status are less compelling and did not show a significant difference.[24,29,,41,42] In CREST, gender had no significant effect on primary endpoints; however, women tended to have higher perioperative event rates (mostly stroke) with CAS than with CEA.[29,42] SPACE and meta-analyses have failed to show any gender predilection for differences in outcomes.[27,34,41] The current data for EPD use is also inconclusive. Kastrup et al reported a significantly lower perioperative stroke rate with EPD utilization (1.8 vs. 5.5%; $p < 0.001$),[43] but recent analyses have not supported this finding.[34,41] The literature suggests that both CAS and CEA can provide durable treatments for CS. In the CREST trial, CAS had a slightly lower restenosis rate, which was not statistically significant. Female gender, diabetes, and dyslipidemia significantly increased the risk of restenosis for both CAS and CEA groups in CREST, while smoking was correlated to restenosis for the CAS group only.[44] Similarly, EVA-3S did not show a significant difference in restenosis rates between CAS and CEA.[28] In

contrast, SPACE showed a significantly higher rate of restenosis for CAS compared with CEA (11.1 vs. 4.6% at 2 years; p ¼ 0.0007).[27] Although trying to decipher these conflicting reports is challenging, CREST data may be the most reliable due to more uniform and updated ultrasound criteria for restenosis as well as core ultrasound reading laboratory. Future Directions Asymptomatic Patients In previous studies, CEA has been shown to be superior to BMT for asymptomatic patients with CS > 60%. While these trials provided favorable data for CEA, high surgical risk patients were not included. Moreover, the comparison may not be applicable today, as significant improvements in BMT have been made in terms of antiplatelet and antilipid agents. As a result, the optimal treatment for asymptomatic patients with CS has been the subject of debate.[45,46] Recent epidemiological studies have shown that with BMT advances, the annual risk of stroke has been reduced to approximately 0.5% [47–48] compared with 2 to 3% described in aforementioned older studies. Given the low annual risk of stroke, CAS would have to be performed with an extremely low rate of negative outcomes. The current data, including CREST, is underpowered and insufficient to provide any conclusions for the asymptomatic patient population. Going forward, CREST-2 (proposed to compare BMT, CEA, and CAS in asymptomatic patients) and Against Carotid Artery Disease I (ACT I) trial may add additional information regarding the best therapy for asymptomatic patients. Improvements in Perioperative Stroke CAS outcomes continue to improve as worldwide operator experience grows and refinements/innovations in equipment occur. This evolution is not dissimilar to the maturation process of CEA. To further improve the safety of the procedure and gain wider acceptance, CAS must be reliably performed with a lower perioperative stroke rate. Improvements in operator experience, identification of the “high risk” CAS patient, and better EPD design may help to decrease CAS perioperative stroke rates. Proximal EPDs appear promising as they allow embolic protection throughout the entire CAS procedure. Distal EPDs, in contrast, offer protection only after the stenosis has been traversed. In a meta-analysis of 2,397 patients treated with two proximal occlusion devices (Gore Flow Reversal System) and Mo.Ma Proximal Cerebral Protection Device, the 30-day stroke, myocardial infarction, and death rates were 1.71, 0.02, and 0.40%, respectively, to yield a composite primary endpoint of 2.25%.[49] In a recent small study of 62 patients randomized to distal filter device (Embolic Protection System)) or proximal balloon occlusion (PBO), the PBO group had significantly fewer new ischemic lesions on MR imaging. The 30-day rate of major adverse cardiovascular and cerebral events for the PBO was 0% compared with 3.2% for filter protection group.

Conclusion: CAS has undergone tremendous evolution over the past 20 years; however, it continues to be the subject of much debate and scrutiny. Large studies performed over the past decade have shown that CAS, when performed by skilled operators, can provide a safe and durable option for revascularization of CS.

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