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Review Article

Recommendations for Management of Patients with Carotid Stenosis

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Stroke is a one of the leading causes of morbidity and mortality in the world. Carotid atherosclerosis is recognized as an important factor in stroke pathophysiology and represents a key target in stroke prevention; multiple treatment modalities have been developed to battle this disease. Multiple randomized trials have shown the efficacy of carotid endarterectomy in secondary stroke prevention. Carotid stenting, a newer treatment option, presents a less invasive alternative to the surgical intervention on carotid arteries. Advances in medical therapy have also enabled further risk reduction in the overall incidence of stroke. Despite numerous trials and decades of clinical research, the optimal management of symptomatic and asymptomatic carotid disease remains controversial. We will attempt to highlight some of the pivotal trials already completed, discuss the current controversies and complexities in the treatment decision-making, and postulate on what likely lies ahead. This paper will highlight the complexities of decision-making optimal treatment recommendations for patients with symptomatic and asymptomatic carotid stenosis.

1. Introduction

Stroke is a major, well-recognized cause of morbidity and mortality around the world. Extracranial carotid atherosclerosis with the resulting atherothromboembolism may account for up to 20% of ischemic strokes [1]. Carotid stenosis may manifest itself in many different clinical stroke syndromes, from asymptomatic carotid disease to a TIA affecting the eye (amarousis fugax) or the brain to an ischemic stroke in the cerebral territory supplied by the vessel. Recently, cognitive impairment as a result of carotid stenosis has also been proposed [2].

Multiple treatments have been shown efficacious in treating carotid disease. Carotid endarterectomy (CEA) has been shown to be effective in significantly reducing the risk of recurrent stroke emanating from that pathological nidus [3, 4]. Angioplasty and stenting of the carotid origin have developed and evolved as a less invasive alternative to surgery, initially employed in patients with high surgical comorbidities. Multiple trials have been conducted comparing the two techniques in various subpopulations with often conflicting results. The importance of the best medical treatment cannot be overstated, as more advanced pharmacological agents and more stringent management of various risk factors of atherosclerosis have led to an overall decline in the incidence of stroke. This has altered the risk-benefit analysis of any invasive procedures which carry a nontrivial complication rate of their own. Despite numerous trials and decades of clinical research, the optimal management of symptomatic and asymptomatic carotid disease remains controversial. We will attempt to highlight some of the pivotal trials already completed, discuss the current controversies and complexities in the treatment decision-making, and postulate on what likely lies ahead.

2. Risk Factors

Risk factors for the risk of stroke in the presence of carotid stenosis are age, hypertension, coronary heart disease, irregular and ulcerated plaque morphology, absence of collateral flow, impaired cerebral reactivity, previous stroke or TIA, and microembolic signals observed on Transcranial Doppler (TCD) [5, 6].

Meta-analysis including 23,706 participants [7] of four population-based studies (Malmö Diet and Cancer Study, Tromsø, Carotid Atherosclerosis Progression Study, and Cardiovascular Health Study) showed the prevalence of severe asymptomatic carotid stenosis in the general population to be up to 3.1%. It has been shown that the risk of stroke increases with the degree of stenosis (from less than 1% per year for a <80% stenosis to 4.8% per year for a >90% stenosis).

The risk of stroke in the target vascular territory also rises with higher degree of symptomatic carotid stenosis (Hazard ratio (HR) 1.18 per 10% increase in stenosis; 95% confidence interval (CI) 1.10–1.25) [3, 4, 8]. Paradoxically, patients with ICAs severely narrowed or nearly collapsed due to markedly reduced poststenotic blood flow (pseudo-occlusion, near occlusion) have a relatively lower risk of stroke on best medical treatment alone (HR = 0.49; CI 0.19–1.24) compared to vessels with moderate degree of stenosis [9, 10]. It has been shown that the risk of stroke ipsilateral to ICA stenosis is greater in patients with recent neurological symptoms of ischemia in that vascular target artery [11, 12]. These preceding neurological symptoms have been stratified in the likelihood of subsequent ipsilateral stroke: major stroke (HR = 2.54; 95% CI 1.48–4.35), multiple TIAs (HR = 2.05; 95% CI 0.16–3.60), minor stroke (HR = 1.82; 95% CI 0.99–3.34), single TIA (HR = 1.41; 95% CI 0.75–2.66), and ocular events (HR = 1.0) [8].

Plaque instability, another important risk factor, is characterized by a thin fibrous cap, large lipid core, reduced smooth muscle content, and a high macrophage density. Studies have shown that the irregular morphology or ulceration of the plaque carries an increased risk of a clinical event (HR = 2.03; CI 1.31–3.14) [8]. A thrombotic cascade occurs primarily when the thrombogenic center of the plaque is exposed to the bloodstream carrying clotting factors. The spike in the risk of stroke recurrence in the days and weeks after an ischemic event is likely the consequence of an unstable atherosclerotic plaque, and the rapid decline in risk over the subsequent months likely reflects the healing and stabilization of the said lesion and improved collateral blood flow to the ipsilateral cerebral hemisphere [10].

3. Transient Ischemic Attacks

Transient ischemic attack (TIA) is a brief episode of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction [13]. Among patients who present with stroke, the prevalence of prior TIA has been reported to range from 7% to 40%, depending on factors such as how a TIA is defined, which stroke subtypes are evaluated, and whether the study is hospital or population based [14, 15]. In the population-based Northern Manhattan Stroke Study, the prevalence of preceding TIAs among those with first ischemic stroke was 8.7% [16], with the majority of TIA occurring within 30 days of the patient's first ischemic stroke.

It has long been recognized that TIA can portend stroke [17], with short-term stroke risk being particularly high, exceeding 10% in 90 days [14, 18–22] and studies confirm the elevation of that risk into the long term [23–25]. The timing of a TIA before stroke is highly time dependent, with studies showing 17% occurring on the day of the stroke, 9% within the previous day, and another 43% within the previous week of the index event [18, 26–28].

Several score systems based on clinical characteristics, like California score and the ABCD score, help to stratify patients into differing risk tiers [29]. The newer $ABCD_2$ score was derived to provide a more robust prediction standard and incorporates elements from both prior scores [29]. In addition, patients with severe extra- or intracranial stenosis carry a particularly high risk of disease recurrence [30].

Observational studies showed that urgent evaluation at a TIA clinic and immediate initiation of treatment reduces stroke risk after TIA [31, 32]. It has been shown that early management of TIA patients in a stroke unit leads to specific treatments in a significant proportion of cases [33].

4. Diagnostic Evaluation

Imaging of the brain and its supplying vessels is crucial in the treatment of patients with stroke or TIA. During the initial assessment, radiological studies distinguish ischemic stroke from intracranial hemorrhage and stroke mimics and are used to identify the penumbra and vessel occlusion, thus guiding emergent stroke care. In the acute setting, radiological studies often point to the subtype and etiology of stroke and can be utilized to predict outcome. Presence of a diffusion-weighted imaging (DWI) lesion and a vessel occlusion on a magnetic resonance image (MRI) among patients presenting acutely with a transient clinical symptoms or a minor stroke is predictive of an increased risk for future stroke and functional dependence [34]. For example, in the North Dublin TIA Study [35] of 445 confirmed TIA cases, carotid stenosis predicted 90-day stroke (HR = 2.56; CI 1.27–5.15, $P = 0.003$). Risk of stroke rose with increasing grade of carotid stenosis, ranging from 5.4% (CI 3.3%–8.7%) with <50% stenosis to 17.2% (CI 9.7%–29.7%) with severe stenosis/occlusion (HR = 3.3; CI 1.5–7.4, $P = 0.002$). Thus, prompt advanced vascular imaging is important for effective treatment in secondary stroke prevention. It has been shown that vascular evaluation assessment does identify the site and cause of arterial obstruction, and the patients at high risk of stroke or stroke recurrence [36–40].

Carotid ultrasound provides reliable assessment of the carotid bifurcation with high sensitivity and specificity [41, 42]. It is fast, inexpensive, and widely available. In TIA patients, carotid duplex and TCD performed within 24 hours of symptoms revealed a threefold greater risk for stroke in the next 90 days in those with moderate to severe extra- or

intracranial carotid stenosis compared to patients with no such findings [43].

TCD provides noninvasive monitoring of intracranial stenosis [37], with a positive predictive value (PPV) of 36% and, negative predictive value (NPV) of 86% [44]. The high NPV and the lower PPV reflect the low prevalence of intracranial stenosis in Caucasians [6], with higher rates in other ethnic groups.

TCD can also detect microembolic signals (MESs) seen with extracranial or cardiac sources of emboli. A large number of MESs on TCD is a marker of risk in patients with emboli from the carotid origin, prompting research into optimal strategies for medical treatment and the timing of endarterectomy in those with an extracranial carotid disease [6]. In a cohort of patients unselected for stroke mechanism, MESs were more common in patients with large-artery occlusive disease and were more prevalent in patients treated with anticoagulation rather than antiplatelet agents [5].

The advancement and refinement of computed tomography over the past quarter century has made it powerful tool for the visualization of the vascular system. It can provide highly detailed images of the carotid artery, with higher sensitivity and specificity than ultrasound, but does require patients to undergo radiation and contrast exposure, fares poorly with heavily calcified lesions, and involves some post acquisition image processing. Magnetic resonance imaging (MRA) has also seen an evolution in image resolution and specialized sequencing, and the modality can distinguish not only the anatomy of the vessel but also the composition of the atherosclerotic plaque with remarkable detail. MRI scanners are less widespread, and the study can overestimate the degree and morphology of high-grade stenosis. MRA with contrast provides a more accurate assessment of the vasculature image, but does involve gadolinium, which carries additional risks. Moreover, certain patients have metal implants or pacemakers, making them ineligible for scanning by this technique. Cerebral angiography is still considered "the gold standard" for evaluating the cerebrovascular system and its collaterals. However, it is expensive and has a significant radiation exposure and a discrete chance of retroperitoneal hematoma, vessel perforation, or distal emboli.

A sensible and stepwise nonemergent diagnostic work-up would usually entail an initial carotid duplex for screening purposes. If the stenosis is less than 50%, no further imaging is likely needed. If the carotid duplex comes back as >50% (and certainly >70%), CTA or MRA should be considered for more detailed plaque characterization. At that point and based on patient's presenting symptomatology, cerebrovascular and overall health and available resources, diagnostic/therapeutic cerebral angiogram, surgical intervention, or continued medical management can be undertaken.

5. Carotid Endarterectomy

Carotid endarterectomy is a surgical procedure of removing the plaque from the carotid artery, thus reducing the risk of stroke by enlarging the lumen and by removing a possible nidus of emboli. The anticipated benefit of treatment in asymptomatic patients with carotid stenosis is derived from several clinical trials.

6. Asymptomatic Carotid Stenosis

In Asymptomatic Carotid Atherosclerosis Study (ACAS) [45], patients with asymptomatic carotid artery stenosis of 60% or greater, defined by angiography or Doppler evaluation using local laboratory diagnostic criteria, were randomized to CEA or best medical management. After a median followup of 2.7 years, the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.1% for surgical patients and 11.0% for patients treated medically (aggregate risk reduction of 53%; absolute risk reduction of approximately 1% per year). This net benefit was dependent upon carotid endarterectomy being performed with less than 3% perioperative morbidity and mortality.

The Asymptomatic Carotid Surgery Trial (ACST) [46] randomized asymptomatic patients with significant carotid stenosis according to Doppler criteria, to immediate CEA or indefinite deferral of surgical intervention. The mean followup was 3.4 years. The cumulative 5-year risks of surgical versus medical treatment were 6% versus 12% for all strokes, 4% versus 6% for fatal or disabling strokes, and 2% versus 4% for only fatal strokes, respectively. Subgroup-specific analyses found no significant heterogeneity in the perioperative risk or in the long-term postoperative benefits. A meta-analysis of three trials [47] reported that despite about a 3% perioperative stroke or death rate, carotid endarterectomy for asymptomatic carotid stenosis reduces the risk of ipsilateral stroke, and any stroke, by approximately 30% over 3 years. For the outcome of any stroke or death, there was a nonsignificant trend toward fewer events in the CEA group. In subgroup analysis, CEA appeared more beneficial in men than in women and more in younger patients than in older patients, although the data for age effect was less convincing. There was no statistically significant difference between the treatment effect estimates in patients with different grades of significant stenosis, but the analysis may not have been sufficiently powered.

In Asymptomatic Carotid Emboli Study (ACES), a prospective observational study in patients with asymptomatic carotid stenosis of at least 70%, followed up for 2 years, and monitored for 1 hour at 6, 12, and 18 months, HR for the risk of ipsilateral stroke, or TIA in patients with embolic signals compared with those without was 2.54 (CI 1.20–5.36; $P = 0.015$) [48]. For ipsilateral stroke, alone, HR was 5.57 (CI 1.61–19.32; $P = 0.007$). Therefore, detection of embolization on TCD may be used to help stratify patients with asymptomatic carotid stenosis in a higher and lower vascular event risk groups.

Trials of carotid surgery for asymptomatic carotid stenosis have concluded that although surgery reduces the incidence of ipsilateral stroke (RR 0.47–0.54) and any stroke, the absolute benefit is small (approximately 1% per annum) [45, 46, 49], whereas the perioperative stroke or death

rate is 3%. Medical management is the most appropriate option for most asymptomatic subjects; only centers with a perioperative complication rate of 3% or less should contemplate surgery. Patients with a high risk of stroke (men with stenosis of more than 80% and a life expectancy of more than 5 years) may derive some benefit from surgery in appropriate centers [46, 47].

7. Symptomatic Carotid Stenosis

For symptomatic carotids, the ECSCT and NASCET [9, 28] results established CEA as the treatment of choice for moderate and severe carotid artery stenosis as a secondary stroke prevention measure. The most important periprocedural risks of CEA are death (about 1%) and stroke (about 5%) [9, 28]. From a pooled analysis of data from the three largest RCTs of surgery for symptomatic carotid stenosis [50], CEA reduced the 5-year absolute risk of any stroke or death in patients with 50–69% stenosis, according to angiographic NASCET criteria (which consist of measuring the lumen at the point of the greatest stenosis divided by the diameter of the carotid beyond the carotid bulb) (absolute risk reduction (ARR) 7.8%, CI 3.1–12.5), and was highly beneficial in patients with 70–99% stenosis (15.3%, CI 9.8–20.7), but showed no benefit in patients with a near occlusion. Quantitatively similar results were seen for disabling stroke [50]. CEA, therefore, proved to be beneficial in stenosis more than 50% according to NASCET criteria, which are equivalent to 65% stenosis by ECST criteria. In ECST trial, CEA reduced the risk of recurrent TIAs in patients with a near occlusion (ARR 15%, $P = 0.007$).

While the degree of stenosis is a major determinant of benefit from CEA, there are other clinical characteristics that influence the risks and benefits of surgery. Subgroup analyses of pooled data from the large RCTs [51] showed the greatest benefit from CEA in men, patients aged ≥75 years, and patients randomized within 2 weeks after their last ischemic event. Both ECST and NASCET showed that for patients with ≥50% ICA stenosis, the number needed to treat (NNT) by CEA to prevent one ipsilateral stroke in 5 years was 9 for men versus 36 for women, 5 for age ≥75 years versus 18 for age <65 years, and 5 for patients randomized within 2 weeks after the last ischemic event versus 125 for patients randomized >12 weeks. Women had a lower risk of ipsilateral ischemic stroke on medical treatment and a higher operative risk in comparison to men [52]. CEA was more beneficial in women with ≥70% stenosis, but not in women with 50–69% stenosis. At the same time, CEA reduced the 5-year ARR by 8.0% CI 3.4–12.5 in men with 50–69% stenosis. This sex difference was statistically significant even when the analysis of the interaction was confined to the group of 50–69% stenosis [52].

8. CEA Surgical Considerations

CEA has been established as "the gold standard" for carotid stenosis treatments for many years, yet the surgical techniques of performing the procedure continue to evolve. In traditional endarterectomy, the plaque is removed via a longitudinal arteriotomy. Another technical variant is eversion endarterectomy, which employs a transverse arteriotomy and reimplantation of the carotid artery. There was no significant difference in the rates of perioperative stroke, stroke, death, or local complication rates in a review of five RCTs comparing eversion and conventional endarterectomy performed either with primary closure or patch angioplasty [53]. To reduce the risk of restenosis, many surgeons use a patch of autologous vein or synthetic material to close the artery and to enlarge the lumen. Although the patch increases the surgery time and complication rate, it was associated with a 60% reduction in the perioperative risk of stroke or death during the postoperative period and long-term followup, 85% reduction in the risk of perioperative arterial occlusion, and 80% reduction in the risk of vessel restenosis during long-term followup. Although some surgeons routinely insert a temporary intralumenal shunt [54], the number of patients who need shunting with different shunting policies has been too small, and the results of clinical studies inconclusive [55].

CEA was traditionally performed under general anesthesia (GA), but surgery under local anesthesia (LA) is becoming more widespread. While a systematic review of seven small randomized trials showed the use of LA to be associated with a borderline statistically significant trend towards a reduced risk of operative death, no evidence of a reduction in risk of perioperative stroke was found [56]. A large multicenter randomized trial has shown no major difference in operative risk of stroke or death combined (risk ratio for LA versus GA RR = 0.94; CI 0.70–1.27) [57]. The anesthesiologist and surgeon, in consultation with the patient, should determine the method of appropriate anesthesia [58]. For patients with a contralateral carotid occlusion, LA may offer some benefit.

9. Carotid Stenting

Carotid angioplasty and stenting (CAS) was developed to be a less invasive and involved procedure compared to carotid endarterectomy. It has emerged as an alternative for patients who are considered to have high surgical risks due to medical comorbidities or anatomical high-risk features. Since its development over twenty years ago, the technique of endovascular carotid revascularization has been undergoing a continuous maturation process due to the shift from the initial use of balloon expandable stents to self-expanding stents, the introduction of and continuously expanding array of embolic protection devices (EPDs), and increasing operator experience.

The procedure is usually done under local anesthetic, with the subsequent expectation of less nerve injuries, venous thromboembolisms, and myocardial infarctions—all well-known clinical costs of going to the operating room. CAS also carries some potential disadvantages such as arterial dissection, dislocation of atherothrombotic debris and embolization to the brain or eye, late embolization due to thrombus formation on the damaged plaque, and

bradycardia and hypotension as a result of carotid sinus stimulation. Local complications at the site of arterial cannulation such as hematoma and aneurysm formation may also occur. Rarely, the stent may erode through the arterial wall or fracture upon deployment. In the longer term, restenosis appears to be more common after stenting than after endarterectomy.

Several trials have compared CAS and CEA in secondary stroke prevention, mostly in patients lacking high surgical-risk [49, 59–65]. Most studies were designed to assess the noninferiority of stenting compared to endarterectomy with regard to the early risks of the procedures. None of these studies were adequately powered to show the noninferiority (or superiority) of stenting looking at both the early risks and late benefits of these techniques. Initially, locating studies with the desired target populations has also proved a challenge. For example, The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial included more than 70% of asymptomatic patients, and therefore should not be used for decisions about secondary prevention [49]. In Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), on the other hand, the majority of the patients in the endovascular group underwent angioplasty, and only 26% were treated with a stent [65].

The comparison of CEA and CAS has produced many different (and often contradictory) results. Stent-protected angioplasty versus carotid endarterectomy in symptomatic patients (SPACE) marginally failed to prove the noninferiority of CAS compared to CEA with the endpoint being ipsilateral stroke or death up to post-op day 30. The event rates for 1,200 enrolled patients were 6.8% for CAS and 6.3% for CEA patients (absolute difference 0.5%; CI −1.9 +2.9%; $P = 0.09$) [66]. The Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA3S) trial was stopped prematurely after the inclusion of 527 patients because of safety concerns and a lack of efficacy. The RR of any stroke or death after CAS, compared with CEA, was 2.5 CI 1.2–5.1 [59].

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial (SAPPHIRE) [61] was one of the first trials comparing carotid stenting (CAS) (with the use of an emboliprotection device) to CEA in patients considered at high surgical risk for CEA. Patients were eligible if they either had a symptomatic stenosis of 50% or greater or an asymptomatic stenosis of 80% or greater. The primary end point of the trial was the cumulative incidence of death, stroke, or myocardial infarction with 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. The primary end point occurred in 20 patients (12%) in the CAS group and in 32 patients (20%) in the CEA cohort. For patients with asymptomatic lesions, the cumulative incidence of the primary end point at 1 year was lower among those who were treated with CAS (10%) than who underwent a CEA (22%). In the periprocedural period, the cumulative incidence of death, myocardial infarction, or stroke among patients with asymptomatic carotid artery stenosis was 5% among those who received a stent, as compared to 10% among those who underwent a CEA. The SAPPHIRE trial was one of the first trials to select high-risk patients with medical comorbidities (these criteria were the basis of *exclusion criteria* for the NASCET/ACAS trials). The major adverse events (death, stroke, and MI) at 1 year were 12.2% in the CAS group compared to 20.1% for CEA ($P = 0.053$). The trial did not include a best medical treatment arm and therefore failed to answer a question of what will happen to the surgical high-risk CEA patient if they were to receive maximal medical treatment.

The International Carotid Stenting Study (ICSS) trial [67] was a randomized, double-blinded study comparing CAS and CEA in patients with symptomatic carotid stenosis of greater than 50% within 6 months prior to randomization. Between randomisation and 120 days, there were 34 (Kaplan-Meier estimate 4.0%) events of disabling stroke or death in the stenting group compared with 27 (3.2%) events in the endarterectomy group (HR = 1.28, CI 0.77–2.11). The incidence of stroke, death, or periprocedural myocardial infarction was 8.5% in the stenting group compared with 5.2% in the endarterectomy group (72 versus 44 events; HR = 1.69, CI 1.16–2.45, $P = 0.006$). Risks of any stroke (65 versus 35 events; HR = 1.92, CI 1.27–2.89) and all-cause death (19 versus seven events; HR = 2.76, CI 1.16–6.56) were higher in the stenting group than in the endarterectomy group. Three procedural myocardial infarctions were recorded in the stenting group, all of which were fatal, compared with four, all nonfatal, in the endarterectomy group. There was one event of cranial nerve palsy in the stenting group compared with 45 in the endarterectomy group. There were also fewer hematomas of any severity in the stenting group than in the endarterectomy group (31 versus 50 events; $P = 0.02$). A magnetic-resonance-imaging (MRI) substudy was carried out at 5 ICSS centers, with scans analysis being performed blinded to the choice of treatment [68]. New ischemia was found in about half of CAS patients versus about 15% of CEA patients. On followup imaging 4 to 6 weeks later, FLAIR was abnormal at the site of early ischemia in 30% of patients after CAS versus 8% of patients after CEA, a result that was also highly significant.

Subgroups analyses from RCTs suggest some heterogeneity of risk between stenting and endarterectomy. In particular, the excess risk associated with stenting was greater in patients aged 70 years or older [62, 63]. However, owing to the drawbacks of post hoc analysis such as low statistical power and the risk of chance findings, these subgroup analyses should be interpreted with caution. The best evidence of subgroup treatment effect interaction will be obtained from a planned combined analysis of individual patient data from current larger trials that compare stenting versus endarterectomy.

In various RCTs, the risk of ipsilateral stroke beyond the perioperative period was low (<1% per year) and similar in both the stenting and endarterectomy groups, which strongly suggests that stenting is as effective as surgery for the medium-term prevention of ipsilateral stroke—at least up to 4 years after the procedures [49, 62, 65, 69]. As the incidence of recurrent carotid stenosis may be significantly higher after

CAS compared to CEA [70], there is a need to assess the long-term effects of carotid stenting, and particularly the long-term incidence of restenosis.

After analyzing the various comparison studies, CAS has not been shown to be as safe as CEA in patients with symptomatic carotid artery stenosis in RCTs. The recent meta-analyses [66, 71, 72] of RCTs that compared CAS and CEA treatment of patients with mainly symptomatic carotid artery stenosis indicated that patients who received CAS had a significantly increased risk of 30-day mortality or stroke compared with patients who received CEA (odds ratio (OR) 1.60; CI 1.26–2.01) and concluded that CEA should remain the first-line intervention in "standard risk," symptomatic patients.

What about the patients who are not "standard risk" and who cannot tolerate surgery? The registry of high-surgical risk patients undergoing CAS (recruited to postmarketing surveillance in the EXACT and CAPTURE trials) has shown different outcomes [70]. In a cohort of 6320 patients, 12% who had suffered stroke or TIA 6 months prior to CAS, a subgroup analysis was performed, stratified for age. The 30-day rate of death/stroke in 589 patients aged <80 years was 5.3% (CI 3.6–7.4), compared to 10% in 172 patients aged >80 years (CI 3.3–16). The authors concluded that CAS had demonstrated real-world outcomes consistent with established American Heart Association (AHA) guidelines in symptomatic patients and should be a viable alternative to CEA in this "high-risk" cohort. There are some questions that need to be answered before relying on these results in recommending CAS to patients who are at high risk for CEA [73]. The low procedural risk observed in nonoctogenarian patients in the amalgamated registry must be maintained and regularly audited; if it exceeds 8%, the therapeutic benefit will likely shift away from intervention. The etiology of the carotid stenosis is also important in interpreting the studies' restenosis results: primary atherosclerotic disease or nonatherosclerotic disease (e.g., radiation arteritis, restenosis after CEA, etc.) are distinct disease processes and likely behave differently after stenting. The post hoc analysis from the Acculink for Revascularization of Carotids in High-Risk Patients (ARCHeR) CAS Registry showed that the 30-day risk following CAS in patients with nonatherosclerotic disease was 14 times lower than in their atherosclerotic counterparts [74]. Clearly, what treatment is best for which particular patient is not all that clear.

Furthermore, Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) [75] was the only RCT comparing CAS and CEA in patients with symptomatic and asymptomatic carotid stenosis that showed equal risk of the composite primary outcome of stroke, myocardial infarction, or death. During the periprocedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy. Recent subgroup analysis showed sex differences of primary endpoints did exist: women fared worse with CAS compared to CEA, while men did equally well with either procedure [76]. Another study compared subgroups of patients who had suffered an MI (clinical or biochemical) and found MIs to be more common in CEA and to be independently associated to increased future mortality [77]. Given the main finding of therapeutic equivalence between CAS and CEA, the obvious questions arose about the discrepancies between CREST and the preceding trials.

There are certain key differences in trial methodology and design. The first important methodological difference was operator experience across the studies [78]. Lifetime endovascular requirements were as follows: in CAVATAS (year 2001), 504 patients, operators had training in neuroradiology and angioplasty (but not necessarily in the carotid artery), and tutor-assisted procedures were allowed; in SAPPHIRE (year 2004), 334 patients, procedures were submitted to an executive review committee, CAS periprocedural death or stroke rate had to be less than 6%, and no tutor-assisted procedures were allowed; in SPACE (2006) with 1200 patients, at least 25 successful CASs or assistance of a tutor for interventionalists who have done at least 10 CAS was required; in EVA 3S (2006), with 527 patients, operators had to have performed at least 12 CAS cases or at least 5 carotid stent procedures and more than 30 cases of endovascular treatment of supra-aortic trunks, or tutor-assisted CAS was allowed for centers not fulfilling minimum requirements; in ICSS (2010) with 1710 patients, a minimum of 50 total stenting procedures of which at least ten should be in the carotid artery or tutor-assisted procedures were allowed for interventionalists with insufficient experience. The trend across all of these studies was that many operators may have had some experience with peripheral stent placement, but that experience was not necessarily equivalent to stenting in the carotid vasculature. As aortic arch tortuosity is emerging as one of the critical factors determining procedural risk with CAS. Lack of proof of experience with carotid catheterization as a prerequisite for participation as an interventionalist across all the Europeans trials is probably the factor responsible for high rates of stroke reached in these studies. In contrast, prospective CAS registries (mentioned earlier) in North America preceding CREST required a higher level of experience with brachiocephalic catheterization and carotid interventions and have reported rates of stroke that are significantly less than those reported in the European studies. CREST study (2010), with 2502 patients, was even more rigorous and required a minimum experience of 10–30 carotid stent procedure with 0.14' wire systems, experience with EPD, and a documented 30-day stroke and death rate of 6–8% [79]. In addition, after admittance into the study, there was a required lead-in phase of up to 20 patients designed to ensure operators had adequate experience and acceptable complication rates prior to randomizing patients. The standards of rigorous vetting for proceduralists performing carotid revascularization were set by NASCET (perioperative risk of stroke or death <6% at 30 days) and ACAS [9, 45], in which only experienced surgeons chosen according to strict criteria were allowed to participate. As opposed to the stenting arm operators, carotid surgeons in the European randomized trials of CAS versus CEA were more experienced compared to their interventionalist counterparts, and there were no inexperienced surgeons allowed to perform the procedure whether or not a tutor was present.

The second major protocol difference was the use or periprocedural dual antiplatelet medications. In the ICSS and EV-3S studies, the use of dual antiplatelet medication was recommended but not required—in EVA-3S [59], 17% of patients were not on dual antiplatelet medications prior to the procedure, and nearly 15% did not have these medications after procedure. In the CREST study, the use of dual antiplatelet therapy was required and part of the protocol.

The third issue was the lack of exclusion criteria for stenting, a stark contrast to high surgical-risk criteria precluding randomization present for the CEA arms in the EVA-3S, ICSS, and SPACE trials. Absence of angiographic exclusion criteria for stenting in combination with inexperienced interventionalists may have resulted in a significant rate of perioperative stroke and death seen in the CAS arm in EVA-3S. In the CREST trial, rigorous angiographic exclusion criteria such as severe tortuosity and calcification, intraluminal, thrombi, and large, bulky plaques may explain discrepant results. Also, ICSS, EVA-3S, and SPACE all allowed the use of many different types of stents and EPD, further tipping the scales towards unfavorable outcomes, when deployed in the hands of inexperienced operators. Contrary, in the CREST study, the same stent and EPD system (Acculink stent and Accunet EPD) was used across the board, allowing the operator to become very familiar with the idiosyncrasies of one single device. Moreover, the lack of protocol in the European studies resulted in the variable use of EPDs, while in the CREST study, the protocol required the use of an embolic protection device in all enrolled patients.

10. Stenting Consideration

Certain vascular and local anatomical features are considered relative contraindications depending on experience of an interventional radiologist/neurologist/neurosurgeon and the type of anatomical substrate for CAS. These include complex bifurcation disease with long, multifocal lesions or extensive aortic or brachiocephalic trunk plaque, severe tortuosity or calcification of the aortic arch vessel, or ring-like, heavy calcifications of the carotid bifurcation. Based on experts' opinion and not on RCTs, CAS is indicated in patients with contralateral laryngeal nerve palsy and previous radical neck dissection or cervical irradiation and with prior CEA (restenosis), because the rate of cranial nerve injuries following surgery is higher in this subset. Also, CAS can be offered to patients with a high bifurcation or intracranial extension of a carotid lesion, where surgical access could be difficult or to patients with a high risk of cerebral ischemia during carotid clamping (occlusion of the contralateral ICA and anomalies of the circle of Willis).

Carotid stenting in symptomatic patients with a standard risk should only be considered in high-volume CAS centers with a 30-day risk of death/stroke as independently audited and maintained <6% [58] and where patients are treated without delay, preferably within 14 days. If these two caveats cannot be achieved, the patient should be referred for CEA.

11. Extracranial-Intracranial Anastomosis (EC-IC Bypass)

About 5–10% of patients with carotid TIA or minor stroke have occlusion of the origin of the ICA, or occasionally the distal ICA or proximal middle cerebral artery. These lesions can be bypassed by anastomosing a branch of the external carotid artery, usually the superficial temporal artery, via a skull burr hole to a cortical branch of the middle cerebral artery. Such collateral was developed to improve the blood supply in the distal middle cerebral artery bed and to reduce the risk of stroke or the severity of stroke. However, in an RCT, these anastomoses between the superficial temporal and middle cerebral arteries were not beneficial in preventing stroke in patients with middle cerebral artery or internal carotid artery stenosis or occlusion [80]. A recent Carotid Occlusion Surgery Study did not show additional benefits of bypass surgery when added to medical management in patients with symptomatic atherosclerotic internal carotid artery occlusion [81].

12. Medical Treatment of Patients with Carotid Stenosis

In patients with carotid stenosis undergoing either primary or secondary prevention, the treatment of risk factors such as hypertension, diabetes mellitus, lipid, or homocysteine metabolic disorders, as well as modification of lifestyle, particularly smoking cessation, are of utmost importance to reduce both early and long-term risks of vascular events, dementia, and death [82, 83].

Aspirin and the combination of aspirin and extended released dipyridamole, clopidogrel, ticlopidine, and triflusal have been shown to be effective as antiplatelet agents in long-term secondary prevention of ischemic stroke [84, 85]. Currently, aspirin, aspirin/extended dipyridamole, or clopidogrel is used in clinical practice.

To date, only aspirin has been shown to be safe and effective in the acute postischemic phase (first 48 hours) and should be started *immediately* in patients with TIA/ischemic stroke after the exclusion of brain hemorrhage and if iv-tPA has not been given (in that case, antiplatelets are held for the first 24 hours). Aspirin is effective in the range of doses (30–1,300 mg/day), but doses >150 mg/day are associated with more side effects [86]. In the Antithrombotic Trialists' Collaboration, a meta-analysis of >60 aspirin trials, the best risk reduction was found in trials using a 75-to-150 mg dose of aspirin [87–89]. In patients with a history of aspirin-induced ulcer bleeding, aspirin in combination with a proton-pump inhibitor was superior to clopidogrel alone in the prevention of recurrent ulcer bleeding [90].

Clopidogrel (75 mg/day) was slightly more effective than aspirin monotherapy (325 mg/day) in preventing vascular events (ischemic stroke, myocardial infarction, or vascular

death) in the CAPRIE trial, resulting in a relative risk reduction (RRR) of 8.7% (CI 0.3–16.5) [91]. The highest benefit of clopidogrel was seen in patients with peripheral artery disease.

The combination of aspirin (30–300 mg/day) and extended release dipyridamole (200 mg twice a day) was shown to be more effective compared with aspirin alone in two studies [92, 93]. Combination therapy reduced vascular events (ischemic stroke, myocardial infarction, or vascular death) by 18% (CI 9–26). The incidence of headache, a common side effect with combination therapy, can be greatly reduced by a slow titration of the drug.

The PRoFESS trial [94] was a head-to-head comparison of clopidogrel and the combination of aspirin/extended release dipyridamole. There was no difference in efficacy across all endpoints and all subgroups of patients. The combination of aspirin/extended release dipyridamole resulted in more intracranial bleeds and a higher dropout rate due to headaches compared with clopidogrel (5.9 versus 0.9%).

In the MATCH trial (secondary prevention in high-risk patients with TIA or ischemic stroke) [95] and CHARISMA (Combined Primary and Secondary Prevention Study) trial [96], comparison of clopidogrel or aspirin monotherapy with its combination failed to show superiority of the combination therapy, which had an increased bleeding rate. The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial showed that in patients with recently symptomatic carotid stenosis combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing asymptomatic embolization in a short-term followup [6]. The combination of clopidogrel and aspirin cohort had fewer patients with MESs, fewer MESs per hour, and fewer strokes compared to patients treated with aspirin alone in the first week after the initial clinical presentation.

A systematic review identified four randomized trials directly comparing oral anticoagulants (OAC) with high international normalized radio (INR) (3.0–4.5) versus antiplatelet therapy in patients with previous TIA or minor stroke of presumed arterial origin [97]. Therapy with OAC was associated with a significantly higher rate of recurrent serious vascular events (1.70, CI 1.12–2.59), with a highly significant increase in major bleeding complication (9.02, CI 3.91–20.84), and a significant increase of recurrent serious vascular events or major hemorrhage (2.30, CI 1.58–3.53) compared with antiplatelet therapy. Therapy with OAC was associated with a significant increase of death from any cause compared with antiplatelet therapy (RR 2.38, CI 1.31–4.32).

Therefore, the best medical treatment of patients with carotid stenosis includes treatment of hypertension, diabetes mellitus, dyslipidemia and homocysteine, metabolic disorders, modification of lifestyle, and statin and antithrombotic therapy. High-dose statins' use may have pleiotropic effects in acute and subacute settings. An LDL goal of <70 mg/dL has been recommended. A blood pressure regimen needs to be carefully selected based on patient's comorbidities and treatment goals. It is recommended that anticoagulation should not be used after noncardioembolic ischemic strokes since high-intensity anticoagulation (INR 3.0–4.5) is more hazardous than effective compared to antiplatelet therapy.

13. Consensus Challenges and Future Directions

Despite numerous RCT studies and significant resources devoted to studying carotid disease, a unified approach to treatment is still far on the horizon. Many contributing factors make consensus elusive. Professional society guidelines in the US (AHA/ASA) [98], New Zealand/Australia [99], and Europe [58] all offer differing and occasionally contradictory recommendations based on regional studies and policies. The Unites States government offers two more diverging opinions in its official statements in regulating medical devices (Food and Drug Administration) and payments for medical services (Centers for Medicare & Medicaid Services). Multiple medical specialties (primary care physicians, interventionals, cardiologists, neurologists, and vascular surgeons) are involved in treating patients with carotid stenosis, each with its own understanding and approach to the subject. The debate between specialties is alive and well [100, 101]. Best medical therapy, interventional stenting techniques, and the surgical knowhow for CEA are rapidly evolving, constantly tipping the risk-benefit ratio in a different direction. The prevalence of the underlying risk factors, the carotid disease itself, and the health care delivery are also different than they were in the past when some of the earlier trials were conducted. Current best medical therapy including statins and antithrombotics in combination with blood pressure and glucose-lowering medications and lifestyle changes has become a powerful tool for reduction of stroke risk in patients with carotid stenosis. New trials comparing CAS, CEA, and best medical therapy are once again needed, with careful selection and followup of the patients using Transcranial Doppler, carotid plaque morphology imaging, and vascular disease burden stratification [74].

14. Conclusion

Carotid stenosis accounts for up to twenty percent of ischemic strokes and TIAs. It is a potentially preventable cause of stroke, and therefore, its detection and management is of an utmost importance. Many treatment modalities exist. Best medical therapy including risk factor management and antithrombotic treatment should be administered effectively. In appropriately selected patients, interventions on carotid arteries should be considered in high-volume CEA and CAS centers with low periprocedural complication rates.

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