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Brief Report

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Update on Percutaneous Management of Carotid Bifurcation Disease

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Abstract

Carotid artery revascularization has shown better outcomes for carotid artery disease management when compared to medical therapy alone, particularly for symptomatic patients. However, we still debate whether revascularization is beneficial for asymptomatic patients in the setting of contemporary medical therapy. The mode of revascularization Carotid Artery Stenting (CAS) or Carotid Endarterectomy (CEA) has also been debated. Earlier trials showed favorable outcomes for CEA versus CAS, but more recent data with contemporary devices and more operator experience suggest equivalent outcomes. Though some clinical guidelines for the prevention of stroke concluded equipoise for CAS and CEA, the Centers for Medicare and Medicaid Services (CMS) only reimburse CAS for symptomatic patients at a higher risk for surgical complications, thereby limiting its usage. Whether symptomatic or asymptomatic, a patient-centered approach should consider medical management, CAS and CEA as complementary to each other.

Keywords: Carotid Artery Disease; Carotid Artery Stenting; Carotid Endarterectomy; Carotid Revascularization; Extracranial Carotid Disease

Introduction

About 800,000 people in US have stroke every year, 87% are ischemic [1]. It is estimated that 20% of ischemic strokes in the United States are caused by carotid artery disease [2]. Medical therapy only was previously found inferior to CEA for symptomatic and asymptomatic patients. However, the benefit of carotid revascularization in asymptomatic patients is being revisited in this era of improved medical therapy [3]. Six Randomized Clinical Trials (RCT) have shown superiority of CEA over medical management only [*3 each among symptomatic (NASCET, VACS, ESCT)* [4-6] *and asymptomatic patients (ACCT, VA, ACAS)*] [7-9]. Of note, these trials have systematically excluded patients with higher risk profiles, which on subsequent assessments revealed mortality rates about three times greater with CEA than reported [10]. CAS is now considered a viable alternative to CEA, and this article intends to focus and review the evolution of CAS as a treatment option for extra-cranial carotid artery disease, and the future of this therapy.

Risk Profile and Percutaneous Revascularization

High Risk

High risk features for CEA is based on various factors considered in randomized trials and it comprises of many clinical and anatomic variables. Clinical variables include age > 75 - 80 years, congestive heart failure/ LVEF ≤ 30%, coronary artery disease (left main or two-vessel disease/ MI in <30 days/ unstable angina/ need for cardiac surgery within 30 days), chronic obstructive pulmonary disease, and renal insufficiency. High-risk anatomic variables include inaccessible lesions at or above C2 spinal level or below the clavicle, previous neck or head radiation therapy or neck surgery, spinal immobility, restenosis after a previous/ unsuccessful CEA, contralateral laryngeal palsy, presence of tracheostomy or contralateral carotid occlusion.

Among high-risk patients, outcomes of CAS using contemporary techniques have been reported in the randomized trial *SAPPHIRE* (*Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy),* various case series, and registry data. Studies of high-risk patients have grouped symptomatic and asymptomatic patients together and the trial eligibility was

based on exclusion criteria from prior CEA trials. The *SAPPHIRE* trial has been the only multicenter randomized trial of high-risk patients, comparing CEA with CAS in both symptomatic and asymptomatic disease. The results support the role of CAS with EPDs when compared with CEA at 30-days, 1-year and 3-years follow-up [11,12]. Event rates were comparable between CAS and CEA patients and it concludes that CAS with embolic protection is not inferior to CEA in high-risk patients and provides equivalent long-term protection from stroke events.

Registry data with independent adjudication of neurologic outcomes in >6,000 high surgical-risk patients in *EXACT* (*EmboShield and Xact Post Approval Carotid Stent Trial*) and *CAPTURE2* (*Carotid RX ACCULINK/RX ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events*) studies showed a death rate of 0.9%, and a rate of stroke of 3.6% in EXACT and 2.8% in CAPTURE2 [13]. These adverse event rates were lower than prior registries (study populations ranged from approximately 200 to 500) of carotid stenting with distal EPDs, suggesting CAS a safe and effective option among high risk surgical patients [14-17].

Standard Risk

The role of CAS in standard-risk patients is yet to be conclusively determined, and the evidence base has limitations. Given the lack of use of EPD and limited carotid stent usage, the relevance of the CAVATAS trial data [18] to contemporary practice is limited. Other trials including EVA 3S [19], SPACE [20] and ICSS [21] are limited by low CAS operator volume.

A well-designed, NIH-funded *CREST trial* (*Carotid Revascularization Endarterectomy Versus Stenting Trial)* enrolled > 2500 patients including both symptomatic (53%) and asymptomatic, standard-risk patients. Contrary to SPACE, EVA3S, and ICSS, there was a role-in phase to ensure experienced operators. There was no statistically significant difference in the primary outcome up to 4 and10 years after carotid revascularization [22,23]. During the periprocedural period, though the incidence of the primary end point was similar with carotid- artery stenting and CEA (5.2 and 4.5%, respectively; hazard ratio for stenting, 1.18; 95% CI, 0.82 to 1.68; P = 0.38), the rates of the individual end points differed between CAS and CEA groups [death, 0.7% vs. 0.3%; P = 0.18; stroke, 4.1% vs. 2.3%; P = 0.01 (driven by an increased incidence of minor rather than major stroke); myocardial infarction, 1.1% vs. 2.3%; P=0.03]. (22) Over 10 years of follow-up, there was no significant difference between patients who underwent stenting and those who underwent endarterectomy with respect to the primary outcome. The rate of post procedural ipsilateral stroke also did not differ between groups [23].

The most recent trial among standard-risk patients comparing CEA and CAS is ACT1 (Asymptomatic Carotid Trial), which enrolled 1453 patients and revealed no significant difference in the primary outcomes (death, stroke, myocardial infarction at 30 days and ipsilateral stroke at 1 year) between the CAS and CEA groups (P = 0.01 for non-inferiority) [24].

Current Guidelines for Carotid Stenting

The 2011 American College of Cardiology and American Heart Association (AHA) are the most recent guidelines, endorsed by various societies about the role of CAS in management of carotid disease, listed below; [25].

- CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%. (Class I, Level of Evidence: B),
- It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery (Class IIa, Level of Evidence: B),
- Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established. (Class IIb, Level of Evidence: B).

Discussion

Although the debate will likely continue, CREST and ACT1 appear to have restored confidence for CAS as a treatment option for carotid disease. Looking forward, the randomized trial CREST-2 is underway among patients with ≥70% asymptomatic stenosis to assess the treatment differences between medical management vs CEA and the treatment differences between medical management and CAS. The medical management in both trials will include aspirin 325 mg/d for the entire follow-up period. CAS patients will be on dual antiplatelet therapy for 1-month post-procedure. The primary risk factor targets include systolic blood pressure <140 mm Hg, and LDL cholesterol <70 mg/dl, whereas the secondary risk factors modifications include non-HDL cholesterol <100 mg/dl, hemoglobin A1c <7.0%, smoking cessation, targeted weight management, and >30 minutes of moderate exercise 3 times a week. The primary endpoint is the proportion of patients who experienced any stroke or death within 44 days of randomization or ipsilateral ischemic stroke thereafter up to 4 years [26]. This trial is expected to be completed in 2020, and it may dictate the future treatment strategy for asymptomatic patients with carotid disease.

Due to reimbursement restrictions, not only is there a growing lag in innovation for CAS (the only update in recent years is trans carotid stenting), but also compromise of operator experience. Nonetheless, there are few recent developments to overcome the challenges with CAS, most notably being trans carotid stenting and proximal embolic protection devices.

Catheter manipulation of the aortic arch in patients at high risk for traditional CEA adds to the risk of stroke among CAS patients. To overcome this, transcarotid stenting is being studied - a hybrid technique of carotid stenting, with a cut down and reversal of ante grade flow in the Common Carotid Artery (CCA), External Carotid Artery (ECA) and Internal Carotid Artery (ICA). This procedure provides protection against embolization by avoiding endovascular manipulation within the aortic arch via surgical CCA access and also by providing flow reversal in advance of any manipulation of the lesion and throughout the stenting procedure. The ROADSTER (Reverse Flow Used During Carotid Artery Stenting Procedure) trial enrolled sixty-seven patients as lead-in cases, and 141 enrolled in the pivotal phase. In the pivotal cohort, 26% were symptomatic and 74% were asymptomatic. Results showed a technical success rate of 99%. By hierarchical analysis, the all-stroke rate in the pivotal group was 1.4% (2 of 141), stroke and death was 2.8% (4 of 141), and stroke, death and MI was 3.5% (5 of 141). One patient (0.7%) experienced postoperative hoarseness from potential X^{th} cranial nerve injury, which completely resolved at the 6-month follow-up visit [27]. This may be a niche procedure for a patient with a hostile arch and/or high-risk CEA anatomy, and a complementary approach to existing carotid revascularization techniques. In addition to flow reversal it facilitates management by operators less comfortable with navigating arch and using embolic protection devices.

Proximal embolic protection devices provide another tool to prevent embolization while undergoing CAS. Flow stasis is established before crossing ICA lesion as the CCA and ECA are balloon occluded, with the brain perfused through the circle of Willis. In 14 European centers, 157 patients were enrolled in a prospective registry. Protected carotid stenting was performed with the Mo. Ma™ system (Medtronic; Minneapolis, MN), which occludes both the common and external carotid arteries via 2 independently inflatable compliant low-pressure balloons before any device is advanced across the lesion. The observed in-hospital stroke/death rate was low (2.5%). The 30-day death/stroke rate was 5.7% (9 patients) and the 30-day major stroke/death rate was 1.3% (2 patients) [28]. The multicenter ARMOUR (ProximAl PRotection with the MO.MA Device DUring CaRotid Stenting) trial evaluated the 30-day safety and effectiveness of the MO.MA device, prospective registry, enrolled 262 subjects from September 2007 to February 2009. The 30-day major adverse cardiac and cerebrovascular events rate was 2.7% [95% CI (1.0 - 5.8%)] with a 30-day major stroke rate of 0.9%. No symptomatic patient suffered a stroke during this trial [29].

In summary, though there is a potential for further refinement of CAS tools/techniques, more important may be a re-evaluation of the current paradigm for choosing patients for carotid revascularization. One may also need to move beyond using symptomatic status and percent carotid stenosis as the sole determinants of need for revascularization. Combining more sophisticated prediction models incorporating various clinical variables along with advanced imaging may allow a more accurate estimation of an individual's risk of any neurologic events. Finally, CAS, CEA, and medical therapy should be considered as complementary therapeutic modalities for the treatment of patients with carotid disease.

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