EDITORIAL

Commentary by the Society for Vascular Surgery regarding Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial-2

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The purpose of this commentary is to critically examine the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial-2 (CREST-2) results, discuss their implications for clinical decision-making for asymptomatic carotid artery disease, and guide clinicians toward optimizing patient outcomes. Patients with severe carotid stenosis have several treatment options available, including transfemoral carotid artery stenting (TF-CAS), transcarotid artery revascularization (TCAR), and carotid endarterectomy (CEA), all along with best medical therapy. Vascular surgeons are uniquely trained to offer all of these modalities and offer an approach through a collaborative process involving vascular medicine physicians and primary care teams, using risk stratification principles outlined in the Society for Vascular Surgery Carotid Guidelines.[1] We congratulate the CREST-2 investigators for a well-designed and exhaustive study. However, there are several issues with their conclusions that warrant careful examination and discussion.

REAL-WORLD CLINICAL DATABASE

The only database to evaluate real-world outcomes of TF-CAS, TCAR, and CEA is the Society for Vascular Surgery Vascular Quality Initiative (VQI). This registry is a multidisciplinary database used as the primary repository of data regarding carotid stenting and endarterectomy. The VQI comprises vascular surgeons, cardiologists, radiologists, neurosurgeons, and other specialties performing CAS and CEA. Based on VQI data and multiple published articles that include thousands of patients, superior outcomes of both CEA and TCAR compared with TF-CAS have been consistently demonstrated in standard and high-risk asymptomatic and symptomatic patients. We strongly encourage physicians performing TF-CAS, TCAR, or CEA to join the VQI to accurately track real-world outcomes among specialists and procedures. Ongoing participation across specialties will help ensure that the VQI continues to generate high-quality real-world evidence that informs practice and supports the best possible patient care moving forward.

Real-world medical management. The best medical management in CREST-2 is unlikely to be replicated by real-world physicians and patients outside of a controlled study such as this one. Medical management has not progressed as far as once surmised, as the annual stroke risk in the Asymptomatic Carotid Artery Study was 2% per year and decreased to <1% over time.[2] However, even with the most highly resourced and aggressive medical management targets, medication payments, routine check-in phone calls, and lifestyle coaching, CREST-2 achieved an annual stroke risk with medical management of 1.7% in the TF-CAS arm and 1.5% in the CEA arm of the trial. Thus, even with what is likely nonreproducible medical management, revascularization had a small benefit. If medical management from the trial is not generalizable, the benefit of revascularization could be even greater.

The role of TCAR. The authors point out that TCAR was not evaluated because it had not yet been broadly implemented when CREST-2 began. However, TCAR has since become widely disseminated and is now a central component of carotid revascularization practice in the United States; thus, any modern evaluation of treatment options must include this technology. TCAR has been shown to result in lower stroke and death rates compared with TF-CAS in both high-risk and standard risk populations.[3,4] Compared with CEA, TCAR has repeatedly demonstrated similar rates of stroke and death but with lower rates of myocardial infarction (MI) and cranial nerve injury.[5] TCAR has also been shown to be as safe as CEA and significantly safer than TF-CAS in octogenarians.[6-8]

Results of other trials. The stroke rate for TF-CAS has been reported to be twice that of CEA in nearly all

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randomized trials preceding CREST-2, with statistically significant differences most consistently observed in symptomatic patients, who have higher baseline event rates. The asymptomatic trials were underpowered to detect a difference in stroke. When Strauss et al[9] evaluated over 100,000 CEA, 50,000 TCAR, and 25,000 TF-CAS procedures, TF-CAS had a 50% to 90% higher stroke rate than CEA and TCAR, even in asymptomatic patients.

Selective interventionalist and anatomic factors favoring TF-CAS in CREST-2. There were notable differences in operator selection and anatomic considerations between TF-CAS and CEA. Potential interventionalists had to submit 100 TF-CAS operative notes with at least 25 cases performed in the past year; only 50% of applicants were accepted. Potential surgeons had to submit 50 CEA operative notes over any time period; 90% of applicants were accepted. Exclusion criteria from the TF-CAS arm included unfavorable anatomy or disease in inflow vessels (aortic arch imaging where the investigator believed that the sheath, protection device, and stent could not be delivered safely, such as type 3 arch and especially in patients over 70 years; innominate or common carotid artery severe angulation, tortuosity, calcification, or stenosis) or in the internal carotid artery (circumferential calcification, lesions >2 cm long). These exclusion factors would play a much less important, if any, role when considering CEA and TCAR.[10,11] These stringent and uneven exclusion factors create a study population that differs meaningfully from real-world patients, making the results less applicable to routine clinical decision-making.

Learning curve of interventions. Multiple studies have demonstrated the long learning curve associated with TF-CAS; at least 50 to 100 cases are required for early proficiency.[12,13] The same has not been demonstrated with TCAR, where those performing their first cases had no increased risk of stroke or death compared with those with extensive experience.[14] We have concerns that less experienced TF-CAS interventionalists will apply CREST-2 recommendations to a broad swath of asymptomatic patients without the same careful selection of low-risk anatomy. Also, resident involvement in both TCAR and CEA has not been demonstrated to increase adverse events, while the same has yet to be demonstrated for TF-CAS.[15]

Continued utility of CEA. Depending on individual risk factors and anatomy, CEA is still appropriate for selected asymptomatic patients.[1,2] Meta-analysis of several randomized trials showed superiority of CEA over TF-CAS in terms of stroke and death. Kakkos et al[16] summarized nine randomized carotid trials and concluded that a stroke/death rate at 30 days was significantly higher for TF-CAS (2.9%) than for CEA (1.9%, odds ratio [OR]: 1.6; $P = .044$), the 30-day stroke rate was significantly higher for TF-CAS (2.9%) than for CEA (1.8%, OR: 1.6; $P = .032$); the 30-day MI rate was nonsignificantly lower for CAS (0.66%) than for CEA (1.5%, OR: 0.5; $P = .105$), and the stroke/death rate at 30-day plus ipsilateral stroke during 1-year follow-up was significantly higher for TF-CAS (3.6%) than for CEA (2.4%, OR: 1.5; $P = .04$).

Saratzis[17] reported a meta-analysis of 6659 patients in the four largest randomized controlled trials (ACT-1, Asymptomatic Carotid Surgery Trial-2, CREST-1, SPACE-2, Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy-2) and noted that the 30-day stroke/death/MI rate was not significantly different between CAS and CEA (3.5% vs 3.1%; OR: 1.18; $P = .25$), but the 30-day "any" stroke rate was still higher after CAS (3.0% vs 1.95%; OR: 1.61; $P = .0046$), as was the 30-day stroke/death rate (3.1% vs 2.2%; OR: 1.47; $P = .017$). Once the perioperative period had elapsed, the four randomized controlled trials documented that ipsilateral strokes were very low after CAS or CEA (0.4-0.5 per year after TF-CAS and 0.2-0.5 per year after CEA). Recently, the Asymptomatic Carotid Surgery Trial-2 reported a similar disabling stroke/death prevention rate between CEA and TF-CAS but noted a much higher number of minor strokes in TF-CAS compared with CEA subgroups (48 vs 29).[18]

Different outcomes in each medical arm. CREST-2 was not designed to compare TF-CAS vs CEA because there were two separate medical arms. Of note, the medical arm of the TF-CAS study had 6.0% stroke and death rate at 4 years in contrast to 5.2% in the surgical arm patients who had medical therapy. If the same patients in the medical arm of the TF-CAS study were used compared with the CEA patients, the difference might have been more significant. At the interim analysis, the CEA arm showed more favorable outcomes than TF-CAS. However, there were six late stroke events in the CEA arm 2 to 4 years postoperatively that were unrelated to the procedure or carotid restenosis or reintervention. Because these strokes occurred years after surgery and were not linked to restenosis or reinterventions, it is difficult to understand how they meaningfully reflect the comparative performance of the treatment options. Moreover, with event rates this low, even a small number of unrelated outcomes can disproportionately influence the apparent differences between treatment arms.

Limitations of each intervention. TF-CAS, TCAR, and CEA each has their own limitations and drawbacks.[10] Carotid stenting with either TF-CAS or TCAR is less favorable with heavy calcification, angulation, or tortuosity of the internal carotid artery compared with CEA. TF-CAS may be contraindicated or pose higher risk for diseased, tortuous, or angulated aortic arch inflow vessels.

TCAR is less favorable if there is a low carotid bifurcation or disease at the common carotid puncture site. CEA is less favorable when there is severe cardiac or pulmonary disease, neck radiation, prior major neck surgery, very cephalad lesions, cervical spine immobility, contralateral vocal cord paralysis, and possibly contralateral internal carotid artery occlusion. These strengths and weaknesses underscore the value of having all revascularization strategies available, allowing clinicians to match each patient with the modality best suited to their anatomy, risk profile, and goals.

CONCLUSIONS

Carotid interventions are perhaps the most widely studied of all medical procedures. Although CREST-2 certainly adds to this abundance of data, the results are not so overwhelming as to cast aside our wealth of accumulated knowledge. We therefore wish to emphasize that the findings and recommendations in CREST-2 do not change the standard of care. We agree with the CREST-2 findings that medical management of all patients with carotid disease should be optimized and that TF-CAS procedures performed by highly trained, experienced interventionalists in carefully chosen patients may be appropriate treatment. However, TCAR and CEA continue to play an important role in appropriately selected patients with asymptomatic carotid disease.

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