

COMMENTS AND OPINIONS

When Will We Have What We Need to Advise Patients How to Manage Their Carotid Stenosis?: Lessons From SPACE-2

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ABSTRACT: The recently published SPACE-2 trial (Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy-2) compared 3 treatments to prevent stroke in patients with asymptomatic carotid stenosis $\geq 70\%$: (1) carotid endarterectomy plus best medical treatment (BMT), (2) transfemoral carotid artery stenting plus BMT, or (3) BMT alone. Because of low enrollment, the findings of similar safety and efficacy for carotid endarterectomy, carotid artery stenting, or BMT alone were inconclusive. Publication of the CREST (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial)-2 results should provide level A evidence that has been lacking for 2 to 3 decades, to guide treatment of asymptomatic patients with severe carotid stenosis. For symptomatic patients with $\geq 70\%$ stenosis, no trials are underway to update the degree of benefit reported for carotid endarterectomy by NASCET (North American Carotid Endarterectomy Trial) and ECST (European Carotid Surgery Trial), published in 1991. Subsequently, the use of cigarettes has plummeted, and major improvements in medical treatments and in carotid revascularization have emerged. These advances have coincided with abrupt decline in the clinical end points necessary for treatment comparisons in procedural trials. One of the advances in the invasive management of carotid disease has been transcatheter artery revascularization, already with limited approval by the US Food and Drug Administration. Establishing safety and efficacy of transcatheter artery revascularization compared with carotid endarterectomy, carotid artery stenting, or BMT alone may be challenging because of enrollment, regulatory, and funding barriers to design and complete an adequately powered randomized trial.

Key Words: carotid stenosis ■ constriction ■ endarterectomy ■ medical treatment ■ stents

Results were recently reported for SPACE-2 (Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy-2)¹—a randomized controlled trial in 513 asymptomatic patients with $\geq 70\%$ carotid bifurcation stenosis. SPACE-2 compared carotid endarterectomy (CEA) or transfemoral carotid artery stenting (TFCAS) plus best medical treatment (BMT) to BMT alone. SPACE-2 was initially a 3-arm trial with patients randomized 2.9:2.9:1.0 to CEA+BMT or TFCAS+BMT or BMT alone. After 401 patients were recruited, to accelerate recruitment, the study was redesigned to 2 parallel randomized trials: in 1 trial, patients were randomized 1:1 to CEA+BMT versus BMT alone and in the other trial, 1:1

to TFCAS+BMT versus BMT alone. The final trial numbers were 203 for CEA+BMT, 197 for TFCAS+BMT, and 113 for BMT alone. The primary end point was any stroke or death within 30 days or subsequent ipsilateral ischemic stroke. Event rates over 5 years were 2.5% (95% CI, 1.0–5.8) for CEA+BMT, 4.4% (95% CI, 2.2–8.6) for TFCAS+BMT, and 3.1% (95% CI, 1.0–9.4) for BMT alone. SPACE-2 found no difference in risk for the primary end point for CEA+BMT versus BMT alone ($P=0.93$) or for TFCAS+BMT versus BMT alone ($P=0.52$). Small sample size compromised statistical power to detect a difference among the treatments. The investigators concluded that the results of SPACE-2 should be interpreted with caution.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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This manuscript was sent to Erica M. Jones, Editor-in-Training, and Seemant Chaturvedi, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 1455.

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LESSONS TO GUIDE TREATMENT OF ASYMPTOMATIC PATIENTS

For asymptomatic patients, SPACE-2 is the first sizeable randomized controlled trial including a medical arm to be completed in ≈2 decades. The 5-year risk in the BMT-alone cohort, 3.1%, suggests lower risk from high-grade asymptomatic carotid stenosis today compared with the risk reported in earlier comparable trials.²⁻⁴ As examples, in the ACAS (Asymptomatic Carotid Atherosclerosis Study; n=1662), the 5-year risk for any periprocedural stroke and ipsilateral postprocedural stroke was 11%.² In the ACST (Asymptomatic Carotid Surgery Trial; n=3120) the 5-year risk for any perioperative or postoperative stroke was 11.8%.³

Outcomes of later randomized trials have improved (Figure),^{1-3,5-7} and more recent observational studies also report lower risk for high-grade asymptomatic carotid stenosis.^{8,9} The largest and most recent, a retrospective cohort analysis from the Kaiser Permanente health system, identified 3737 asymptomatic patients with 70% to 99% stenosis for the years 2008 to 2012.⁹ Patient outcomes were evaluated out to 2019. The mean follow-up period was 4.1 years. The mean annual ipsilateral rate

for stroke thought to be related to carotid disease was 0.9% for a 5-year rate of 4.7%. Both stenosis deemed high grade at baseline (peak systolic velocity >350 cm/s by Doppler ultrasound or stenosis 90%–99% by axial imaging) and progression to high-grade stenosis during follow-up were associated with higher risk of stroke. Statin use was associated with lower risk. This report and others¹⁰ have shown substantial improvements in medical treatments and patient adherence and have documented a decline in cigarette smoking—secular trends that are potentially associated with the decreased stroke risk. In the Kaiser study, statin use increased to 91.1% during follow-up, adherence among treated hypertensive patients during follow-up was 88.5%, and current smoking was only 13.7%.

Because of the declining risk from high-grade asymptomatic stenosis, CEA or TFCAS may not be necessary in many, if not most, asymptomatic patients. CREST (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial)-2 may soon provide these answers. CREST-2 consists of 2 parallel trials, one contrasting CEA+BMT to BMT alone (the CEA trial) and the other contrasting transfemoral or transradial carotid artery stenting plus BMT to BMT alone (the

Outcomes of Asymptomatic Trials

1995 - 2022

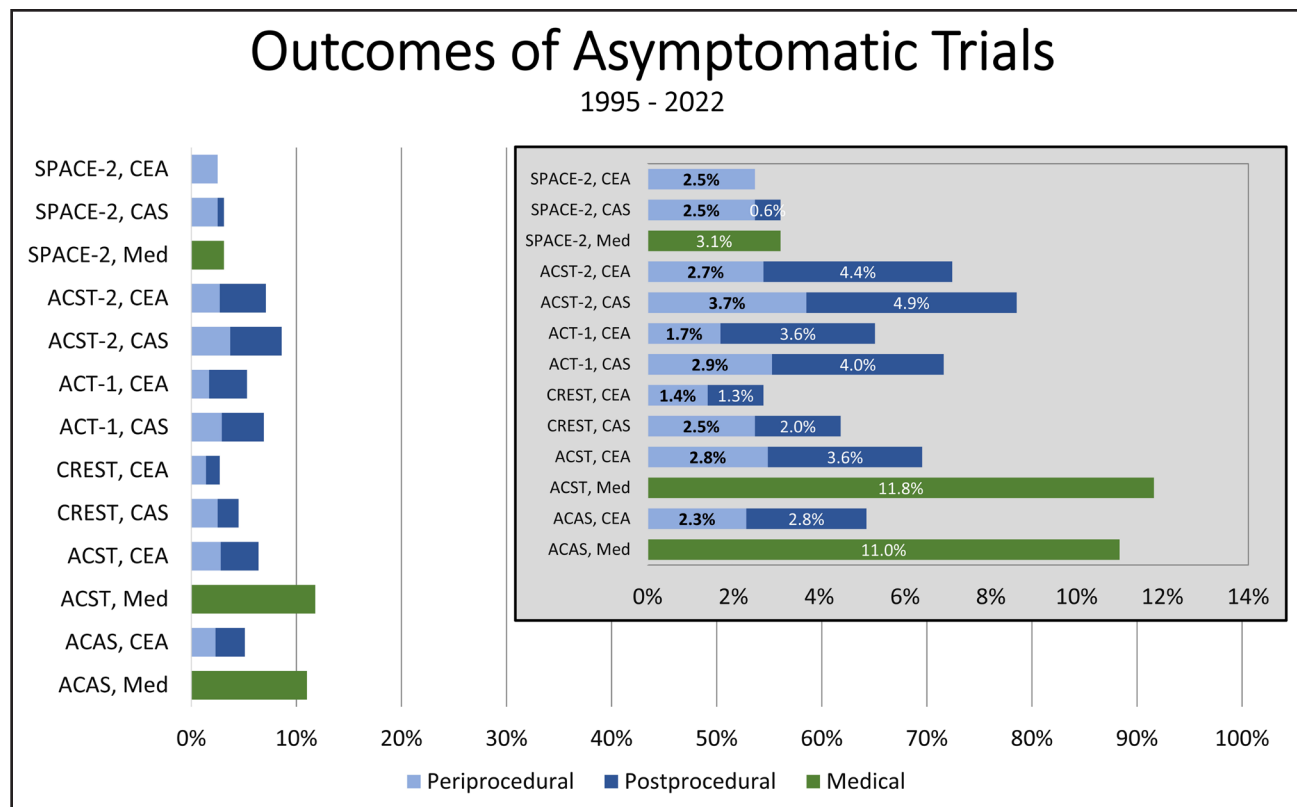


Figure. The graphs are in a graph-within-a-graph format, with the larger graph showing a horizontal axis extending to 100% and the smaller graph showing the horizontal axis extending to 15%.

The horizontal extent of the bars represents periprocedural stroke and death plus postprocedural ipsilateral stroke at 5 y, except for CREST (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial), which was at 4 y. The numerical percentages shown in the light blue bars represent periprocedural stroke and death, and the percentages in the dark blue bars represent postprocedural ipsilateral stroke and death, except for ACST (Asymptomatic Carotid Surgery Trial) and ACST-2, which show the percentage of any stroke.

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CAS trial [Carotid Artery Stenting]).¹¹ Each trial is targeted to randomize 1240 patients with $\geq 70\%$ stenosis, with a ratio of 1:1 to each arm. As of November 2022, 2178 patients have been enrolled in the CEA trial, and that trial should complete enrollment in mid-2023; 1009 patients have been enrolled in the CAS trial, and that trial should complete enrollment in early 2025. The Data and Safety Monitoring Board performed a prespecified interim analysis in early 2022 and advised the investigators to complete enrollment and continue follow-up as planned, up to 4 years. ECST (European Carotid Surgery Trial)-2 is also underway,⁸ comparing CEA or TFCAS (by physician preference) plus BMT to BMT alone in asymptomatic patients with carotid stenosis $\geq 50\%$. Symptomatic patients are eligible if they are low risk, defined as a 5-year risk of stroke $< 20\%$ calculated using the carotid artery risk score.⁸

CREST-2 is near the finish line, but clinicians need to be advising patients today. SPACE-2, observational studies, and the recently reported ACST-2 (Asymptomatic Carotid Surgery Trial-2)⁷ suggest equipoise for CEA, TFCAS, and BMT overall, but only SPACE-2 included a BMT-only medical group. Hence, up-to-date level A evidence is still lacking for the comparative efficacy of BMT alone. For individual asymptomatic patients, patient age, presence of prior infarction by imaging, degree of or progression of stenosis, plaque morphology, and other patient characteristics have been associated with increased risk.¹⁰ One or more of these characteristics are often cited as justification for CEA or TFCAS. Unfortunately, none of these characteristics has predicted treatment differences in a randomized trial that included patients treated with BMT alone. New randomized trial evidence will be available in 2026 from CREST-2 to provide more precision in selection of treatments. Whatever the choice, careful attention to medical management of risk factors is of utmost importance for physicians and patients.¹⁰ In the interim, additional studies of markers of risk other than asymptomatic status are warranted.

LESSONS FROM SPACE-2 FOR SYMPTOMATIC PATIENTS

The risk of stroke in patients with symptomatic carotid stenosis in the 2020s is much lower than that reported from the prior large, randomized trials comparing CEA with BMT alone.¹⁰ These trials are obsolete. In 1991, NASCET (North American Carotid Endarterectomy Trial)¹² reported that patients with symptomatic stenosis $\geq 70\%$ in the BMT alone group had an ipsilateral stroke rate of 26% over 2 years. Also in 1991, ECST¹³ reported a similar rate, 28.9% over 3 years. The benefit of CEA plus BMT versus BMT alone as treatment during that period is not surprising, but no randomized trials with a medical group have been reported subsequently. The natural history of patients treated with BMT but

without revascularization is unknown. However, event rates for symptomatic patients with 70% to 99% stenosis treated with CEA were reported in CREST in 2010⁵ and were remarkably lower than in NASCET and ECST. In NASCET, the perioperative stroke and death rate was 5.8%. In CREST, that rate was 2.9%. In NASCET, the ipsilateral stroke rate for patients with CEA was 9% over 2 years—a rate which included perioperative stroke. In CREST, that rate was 7.9%, over 10 years.¹⁴ Recurrent stroke risk in patients with symptomatic carotid stenosis could be even lower today than the rates reported in CREST more than a decade ago. Such lower rates would be consistent with the low event rates reported for asymptomatic patients in SPACE-2. Because the ECST-2 investigators are including selected symptomatic patients in their ongoing trial, pertinent results will become available soon.

LESSONS FROM SPACE-2 FOR TRANSCAROTID REVASCULARIZATION

Transcarotid artery revascularization (TCAR) with reversal of flow emerged as a new treatment option for high-grade carotid stenosis.¹⁵ Even in the absence of a randomized trial data, TCAR has been approved as safe and effective by the US Food and Drug Administration for patients at high and conventional risk for complications related to CEA. TCAR gained regulatory approval and widespread use primarily through engineering, laboratory testing, and clinical testing with patient registries.^{16,17} The use of TCAR has proliferated in the United States as an alternative to CEA or TFCAS. US surgeons performed about 12 000 TCAR procedures in 2021, exceeding the number of TFCAS performed over the same period.

The TCAR scenario is seen by many as appropriate, though validating results from randomized trials would be ideal as has already been accomplished for CEA versus TFCAS.^{5,6,18} Ironically, advances in CEA, TFCAS, and BMT and the decline in periprocedural and postprocedural events have become major barriers to completion of such trials. Statistical power to assess treatment differences is a function of the number of outcome events, not the number of patients enrolled. To illustrate, consider a hypothetical randomized trial comparing CEA to TCAR. A total of 256 events would be required to detect a 33% reduction in risk with 90% statistical power.¹⁹ With the 5-year 4.4% event rate in SPACE-2, even without adjusting for withdrawal and crossover, a randomized trial would require 5818 patients. Funding for such a trial would be forbidding. In addition, the time needed to complete enrollment could overlap with advances in technology impacting either CEA, TCAR, or both. Timely enrollment in SPACE-2, ECST-2 as originally designed, and ACTRIS (Endarterectomy Combined With Optimal Medical Therapy Versus Optimal Medical Therapy Alone in Patients With Asymptomatic Severe

Atherosclerotic Carotid Artery Stenosis at Higher-Than-Average Risk of Ipsilateral Stroke)²⁰ from France was not possible. SPACE-2 enrolled 513 patients from 2009 to 2014, at 2.65 patients per center per year. CREST-2 has enrolled 2179 patients from 2014 to 2022, at 2.2 patients per center per year.

For TCAR, navigation of guidewires and catheters from groin to carotid bifurcation is not necessary because access to the common carotid artery is direct, and stenting is performed under conditions of backward flow. Embolic debris from catheter manipulation and stent placement may be minimized.²¹ The patient registries that have led to the popularity of TCAR, completed primarily by surgeons trained in vascular surgery, have enrolled >45 000 patients from 2015 to 2021.²² The rates of postprocedural stroke have ranged from 2% to 4%. We note that these outcomes cannot reflect the ascertainment quality and comparison validity provided by randomized trials. Long-term outcomes are also not reliable, because patient dropout has been high.

CONCLUSIONS

Before SPACE-2, contemporary level A evidence was not available to guide treatment decisions for patients with high-grade asymptomatic carotid stenosis. Unfortunately, SPACE-2 does not provide that evidence. The small sample size and the small number of end point events in SPACE-2 fail to provide estimates with sufficient precision to reliably describe any true treatment differences. As such, the SPACE-2 suggestion that CEA, TFCAS, and BMT alone may be similar in efficacy should be interpreted with great caution. Level A evidence will be available in 2026 to provide more precision in the choice of treatment with the report of the CREST-2 outcomes. For high-grade symptomatic carotid stenosis, no contemporary level A evidence to guide treatment of symptomatic patients is available. TCAR can reasonably be seen as a promising procedural alternative to CEA and TFCAS.

ARTICLE INFORMATION

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Sources of Funding

Dr Brott reports grants from the National Institutes of Health (NIH): U01NS080168-09. Dr Meschia reports grants from NIH: U01NS080168-09, R01NS097876-06, U19NS115388-04, and U01NS119169-02 and compensation from NIH for data and safety monitoring services. Dr Lal reports grants from NIH: U01NS080168-09 and U01NS119169-02. Dr Howard reports grants from NIH: U01NS041588-21, U01NS119169-02, and U01NS080165.

Disclosures

Each author is an investigator in the CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial).

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