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Issues to Be Addressed and Hopefully Resolved in the Carotid Revascularization Endarterectomy Versus Stenting Trial 2

Wesley S. Moore, MD[1]

Abstract

The superiority of carotid endarterectomy (CEA) plus best medical treatment (BMT) over BMT alone for the management of patients with asymptomatic carotid stenosis is based on randomized controlled trials that recruited patients up to 30 years ago. Best medical treatment has improved considerably since that time with respect to stroke prevention. Furthermore, a new carotid intervention has emerged during the last 2 decades and has gradually become established, that is, carotid artery stenting (CAS). Consequently, the efficacy of current BMT alone needs to be compared not only with CEA plus BMT but also with CAS plus BMT to determine which strategy achieves the optimal stroke prevention rates. This article highlights the purpose of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) 2 and discusses the issues that CREST-2 will hopefully provide answers to.

Keywords

carotid stenting, CREST-2, carotid stenosis, stroke, carotid endarterectomy

Since the publication of several prospective randomized trials demonstrating that carotid endarterectomy (CEA) plus best medical treatment (BMT) resulted in fewer long-term deaths and strokes than BMT alone, CEA has been established as the treatment of choice for good risk asymptomatic patients with hemodynamically significant carotid stenosis. The first trial, conducted in the Veterans Affairs Hospitals (published in 1993), randomized 444 men with >50% stenosis by angiography to CEA plus what was then considered as BMT including aspirin (n = 211 patients) or BMT plus aspirin alone (n = 233 patients). The composite end point of transient ischemic attack (TIA), stroke, and death at the end of 5 years (including periprocedural events) was 8% for CEA plus BMT versus 20% for BMT alone ($P < .001$).[1]

The Asymptomatic Carotid Atherosclerosis Study (ACAS) sponsored by the National Institutes of Health was the next study to be published (in 1995). Men and women (n = 1660) with >60% asymptomatic carotid stenosis by angiography were randomized to CEA plus BMT versus BMT alone. The study was stopped by the Data Safety and Monitoring Committee (DSMB) prior to the expected date of completion because an end point had been reached. The composite 5-year end point of stroke and death was 5.1% for CEA plus BMT versus 11% for BMT alone ($P < .05$).[2]

The Asymptomatic Carotid Stenosis Trial (ACST) sponsored by the Medical Research Council of the United Kingdom was the third relevant randomized controlled trial to publish their results (in 2004).[3] Patients received immediate CEA plus BMT, and 1560 patients were randomized to BMT and delayed CEA (ie, no CEA unless symptoms developed). The 5-year combined end point of stroke and death was 6.4% for CEA including perioperative events versus 11.8% for BMT ($P < .0001$).

The problem with these trials is that they represent old data. Patients entered these trials nearly 30 years ago. Medical management has improved during this time, particularly with the addition of statins.[4-6] This was first noted in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (published in 2006), where patients with a history of TIA or stroke treated with atorvastatin demonstrated a significant reduction in subsequent TIA and stroke episodes compared with patients in the placebo group.[7] More recently (2011), the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial[8] randomized patients with intracranial stenosis to balloon angioplasty plus intensive medical therapy (IMT) versus IMT alone. The study was stopped by the DSMB because the group on IMT alone had statistically fewer deaths and strokes.[8] This temporal difference showing the effectiveness of modern medical therapy was recently shown in a meta-analysis (published

[1] Division of Vascular and Endovascular Surgery, UCLA Medical Center, Los Angeles, CA, USA

Corresponding Author:
Wesley S. Moore, Division of Vascular and Endovascular Surgery, UCLA Medical Center, Los Angeles, CA, USA.
Email: wmoore@mednet.ucla.edu

in 2013) comparing average annual stroke rates among patients at risk prior to and after the year 2000. The average stroke event rate in patients prior to the year 2000 was 2.38%/year. This is consistent with the medical control arms of ACAS[2] and ACST.[3] However, in patients treated and reported after the year 2000, the average annual stroke rate dropped to 1.13%.[9] This number is competitive with the CEA-treated patients in ACAS[2] and ACST.[3]

Recent findings suggest that contemporary medical management including antiplatelet drugs, statins, and angiotensin-converting enzyme inhibitors has reached equipoise with CEA.[10-12] At the same time, however, CEA results have also improved with time, with some centers reporting perioperative stroke rates in asymptomatic patients as low as 0.5%.[13] There is consequently a need for a new randomized trial comparing the current results of invasive intervention plus IMT versus IMT alone.

Carotid Revascularization Endarterectomy Versus Stenting Trial 2

Carotid Revascularization Endarterectomy Versus Stenting Trial 2 (CREST-2) is a multicenter prospective randomized controlled study to test the hypothesis that IMT alone is superior to invasive carotid intervention plus IMT in the prevention of death and stroke.[14] The study will be 2 track, and carotid artery stenting (CAS) will be tested separately from CEA. Twelve hundred forty patients will be randomized to CAS plus IMT versus IMT alone, and 1240 patients will be randomized to CEA plus IMT versus IMT alone. The statistical calculations tell us that there will be a 85% power to detect a 4.8% difference between IMT alone and either CAS or CEA plus IMT by the end of 4 years. The end points will be any stroke or death within 44 days of randomization or ipsilateral stroke and death up to four years of follow-up. Intensive medical therapy will follow the successful program that was used in the SAMMPRIS trial.[8] Low-density lipoprotein cholesterol levels will be maintained $\leq$70 mg/dL, systolic blood pressure will be maintained at $\leq$140 mm Hg, and for diabetics, the glycated hemoglobin (HbA1c) levels will be kept at <7%. Secondary objectives will be to keep the non–high-density lipoprotein cholesterol <100 mg/dL. Patients who participate in the trial will be signed up with a counseling service who will actively work with them in areas of smoking cessation, weight management, and establishing an exercise program of 30 minutes 3 times weekly. All patients will take 325 mg aspirin daily. Patients undergoing CAS will also receive clopidogrel 75 mg daily.

Secondary Objectives of CREST-2

In addition to comparing stroke morbidity/mortality between IMT and the 2 invasive intervention options, the CREST-2 trial will also assess cognitive function.[14] A deterioration in cognitive function over time may be a surrogate for silent brain infarction or embolization to intellectual areas of the brain.[15-17] Cognitive testing will be carried out at the time of randomization, during the course of the trial, and upon completion of the trial.[14]

Finally, it is well recognized that stenosis alone does not place a patient at high risk for stroke.[18,19] It is likely that plaque characteristics may identify, in retrospect, a high-risk group of patients. Plaque characteristics can be categorized by the core laboratory. Those patients in the medically randomized groups who, over time, have stroke may be compared with those who remain stroke free with respect to their plaque characteristics in order to determine whether there are plaque characteristics that could have identified a high-risk group.[14]

Questions That Should Be Answered by CREST-2

Upon completion of the trial, it is anticipated that several important clinical questions will be answered.[14]

1. Is IMT superior to CAS?
2. Is IMT superior to CEA?
3. Is cognitive function altered in patients undergoing CAS compared with IMT?
4. Is cognitive function altered in patients undergoing CEA compared with IMT?
5. Are there definable plaque characteristics that can identify patients at high risk for stroke among those randomized to IMT alone?

Long-Term Implications Following Study Completion

There are approximately 250 000 patients in the United States who undergo invasive carotid intervention each year, and of these, 92% are asymptomatic.[20] If CREST-2 shows that IMT is superior to invasive carotid intervention plus IMT, then hundreds of thousands of patients will be spared invasive carotid intervention. This will have huge implications regarding patient safety as well as cost to the health care system. On the other hand, if CEA and/or CAS turn out to be more effective than IMT alone in prevention of stroke and maintenance of cognitive function, then invasive carotid intervention will clearly be established as the correct approach for the treatment of the asymptomatic patient with hemodynamically significant stenosis of the internal carotid artery in the era of modern IMT. Finally, it is conceivable that one invasive intervention will be better than IMT alone and the other not, in which case that one invasive intervention will be established as the procedure of choice. The information and the questions to be answered by this trial are critical and will have long-standing impact for our patients and the health care system. We, as physicians, are encouraged to actively support this trial by referring appropriate patients for consideration of participation. The sooner this trial is completed, the better.

Declaration of Conflicting Interests

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References

1. Hobson RW II, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1993;328(4): 221-227.
2. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273(18):1421-1428.
3. Halliday A, Mansfield A, Marro J, et al; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without neurological symptoms: randomised controlled trial. *Lancet*. 2004;363(9420):1491-1502.
4. Biggs KL, Moore WS. Current trends in managing carotid artery disease. *Surg Clin North Am*. 2007;87(5):995-1016.
5. Paraskevas KI, Hamilton G, Mikhailidis DP. Statins: an essential component in the management of carotid artery disease. *J Vasc Surg*. 2007;46(2):373-386.
6. Giannopoulos A, Kakkos S, Abbott A, et al. Long-term mortality in patients with asymptomatic carotid stenosis: implications for statin therapy. *Eur J Vasc Endovasc Surg*. 2015;50(5):573-82. pii: S1078-5884(15)00545-6. doi:10.1016/j.ejvs2015.06.115
7. Amarenco P, Bogousslavsky J, Callahan A III, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355(6):549-559.
8. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011;365(11):993-1003.
9. Raman G, Moorthy D, Hadar N, et al. Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis. *Ann Intern Med*. 2013;158(9):676-685.
10. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke*. 2009;40(10):e573-e583.
11. Naylor AR, Gaines PA, Rothwell PM. Who benefits most from intervention for asymptomatic carotid stenosis: patients or professionals? *Eur J Vasc Endovasc Surg*. 2009;37(6):625-632.
12. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke*. 2010;41(1):e11-e17.
13. Vikatmaa P, Mitchell D, Jensen LP, et al. Variation in clinical practice in carotid surgery in nine countries 2005-2010. Lessons from VASCUNET and recommendations for the future of national clinical audit. *Eur J Vasc Endovasc Surg*. 2012;44(1):11-17.
14. Lal BK, Meschia JF, Brott TG. CREST-2: Guiding treatments for asymptomatic carotid disease. *Endovascular Today*. September 2013:73-76. Web site. http://evtoday.com/pdfs/et0913_F4_brott.pdf.
15. Chang XL, Zhou HQ, Lei CY, et al. Association between asymptomatic carotid stenosis and cognitive function: a systematic review. *Neurosci Biobehav Rev*. 2013;37(8):1493-1499.
16. Zavoreo I, Basic Kes V, Lisak M, Marsic N, Ciliga D, Trost Bobic T. Cognitive decline and cerebral vasoreactivity in asymptomatic patients with severe internal carotid artery stenosis. *Acta Neurol Belg*. 2013;113(4):453-458.
17. Rocque BG, Jackson D, Varghese T, et al. Impaired cognitive function in patients with atherosclerotic carotid stenosis and correlation with ultrasound strain measurements. *J Neurol Sci*. 2012; 322(1-2):20-24.
18. Kakkos SK, Nicolaides AN, Charalambous I, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. *J Vasc Surg*. 2014;59(4):956-967.
19. Kakkos SK, Griffin MB, Nicolaides AN, et al. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. *J Vasc Surg*. 2013;57(3):609-618.
20. McFee JT, Hill JS, Ciocca RG, Messina LM, Eslami MH. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. *J Vasc Surg*. 2007;46(6):1112-1118.