The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

Stenting Versus Carotid Endarterectomy for Carotid Disease

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Background and Purpose—Carotid artery stenosis causes up to 10% of all ischemic strokes. Carotid endarterectomy (CEA) was introduced as a treatment to prevent stroke in the early 1950s. Carotid stenting (CAS) was introduced as a treatment to prevent stroke in 1994.

Methods—The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is a randomized trial with blinded end point adjudication. Symptomatic and asymptomatic patients were randomized to CAS or CEA. The primary end point was the composite of any stroke, myocardial infarction, or death during the periprocedural period and ipsilateral stroke thereafter, up to 4 years.

Results—There was no significant difference in the rates of the primary end point between CAS and CEA (7.2% versus 6.8%; hazard ratio, 1.11; 95% CI, 0.81 to 1.51; $P=0.51$). Symptomatic status and sex did not modify the treatment effect, but an interaction with age and treatment was detected ($P=0.02$). Outcomes were slightly better after CAS for patients aged <70 years and better after CEA for patients aged >70 years. The periprocedural end point did not differ for CAS and CEA, but there were differences in the components, CAS versus CEA (stroke 4.1% versus 2.3%, $P=0.012$; and myocardial infarction 1.1% versus 2.3%, $P=0.032$).

Conclusions—In CREST, CAS and CEA had similar short- and longer-term outcomes. During the periprocedural period, there was higher risk of stroke with CAS and higher risk of myocardial infarction with CEA.

Clinical Trial Registration—www.clinicaltrials.gov. Unique identifier: NCT00004732.

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Carotid endarterectomy (CEA) has been shown effective as preventive treatment for symptomatic and asymptomatic disease.[1–3] Carotid artery stenting (CAS) was introduced in 1994 and provides another option for treatment. Results of randomized trials comparing CAS with CEA for symptomatic participants have varied.[4–6] The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) compared CAS with CEA in both symptomatic and asymptomatic patients.[7]

Methods

CREST is a randomized trial with blinded end point adjudication.[8] The protocol was approved by all appropriate Institutional Review Boards, and written informed consent was provided by all participants. Enrollment was carried out at 117 CREST centers, and participants could not be randomized until operators had been selected at each site through a validated selection process (CEA)[9] or a training and credentialing program (CAS).[10]

To be eligible, symptomatic patients had to have had a transient ischemic attack, amaurosis fugax, or minor nondisabling stroke in the distribution of the study artery within 180 days of randomization and had to have carotid artery stenosis ≥50% by angiography, ≥70% by ultrasound, or ≥70% by CT angiography or MR angiography if ultrasound was 50% to 69%. Asymptomatic patients had to have carotid artery stenosis of ≥60% by angiography, ≥70% by ultrasound, or ≥80% by CT angiography or MR angiography if ultrasound was 50% to 69%. Patients were not eligible if they had a previous disabling stroke or had chronic atrial fibrillation. Complete eligibility criteria have been reported.[8]

CAS was performed with the use of the RX Acculink stent; the RX Accunet embolic protection device was required except when not technically feasible. For both CAS and CEA, antiplatelet therapy was required before and after the procedure.

The National Institutes of Health Stroke Scale, modified Rankin Scale, Transient Ischemic Attack Stroke Questionnaire, cardiac enzymes, electrocardiogram, and carotid ultrasound were performed at baseline. Cardiac enzymes were obtained 6 to 8 hours postprocedure; repeat neurological evaluation, National

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Table 1. Selected Characteristics of the Study Cohort by Treatment Group*

Characteristic	CAS (N=1262)	CEA (N=1240)
Age, years*	68.9±9.0	69.2±8.7
Male sex, % of patients	63.9	66.4
Asymptomatic arteries, % of patients	47.1	47.3
Risk factors, % of patients		
Hypertension	85.8	86.1
Diabetes	30.6	30.4
Dyslipidemia†	82.9	85.8
Current smoker	26.4	26.1
Percent stenosis at randomization		
Severe (≥70%)	86.9	85.1
Median time from randomization to treatment (no. of days)	6	7

*Means±SD.

†P=0.05 for the difference in the baseline rate of dyslipidemia between the 2 groups.

Institutes of Health Stroke Scale, and Transient Ischemic Attack Stroke Questionnaire were performed at 18 to 54 hours; and an electrocardiogram was obtained at 6 to 48 hours and at 1 month. The National Institutes of Health Stroke Scale, modified Rankin Scale, and carotid ultrasound were also performed at 1, 6, and 12 months and annually thereafter.[8] A telephone follow-up call was performed at 3 months and every 6 months thereafter. The Medical Outcomes Study 36-item Short Form Instrument was obtained at baseline, 2 weeks and 1 month postprocedure, and 1 year after randomization.[11,12]

The primary end point was the occurrence of any stroke, myocardial infarction (MI), or death during the periprocedural period or ipsilateral stroke thereafter up to 4 years. Stroke was defined as an acute neurological event with focal symptoms and signs lasting ≥24 hours consistent with focal cerebral ischemia. MI was defined as elevation of cardiac enzymes (CK-MB or troponin) to a value twice or greater than the upper limit of normal for the local center laboratory plus either the occurrence of chest pain or equivalent symptoms consistent with myocardial ischemia or electrocardiogram evidence of ischemia including new ST segment depression or elevation >1 mm in ≥2 contiguous leads (as determined by the centralized core laboratory).[13]

Analysis was intention to treat. Proportional hazards analysis adjusting for age, sex, and symptomatic status was used to test for treatment differences.

Secondary aims were analyzed by including interaction terms in the proportional hazards models.

Results

For a total of 2502 participants (Table 1), there was no significant difference in the primary end point between CAS and CEA (7.2% versus 6.8%; hazard ratio, 1.11; 95% CI, 0.81 to 1.51; P=0.51; Table 2). During the periprocedural period, the incidence of the primary end point was similar for CAS and CEA, but there were differences in the end point components (stroke 4.1% versus 2.3%, P=0.012; MI 1.1% versus 2.3%, P=0.032; and death 0.7% versus 0.3%, P=0.18). Thereafter, ipsilateral stroke was infrequent for both CAS and CEA (2.0% versus 2.4%, P=0.85). Neither symptomatic status nor sex showed an effect on treatment difference per preplanned effect modification analyses. Patient age did interact with treatment efficacy (P=0.02). Outcomes were slightly better after CAS for patients aged <70 years and better after CEA for patients aged >70 years.

During the periprocedural period, the occurrence of the primary end point components (stroke, MI, or death) for CAS and CEA was not different for symptomatic (6.7% versus 5.4%; hazard ratio, 1.26; 95% CI, 0.81 to 1.96) or asymptomatic subjects (3.5% versus 3.6%; hazard ratio, 1.02; 95% CI, 0.55 to 1.86). The risk of stroke and death was significantly higher for CAS in symptomatic patients (6.0% versus 3.2%; hazard ratio, 1.89; 95% CI, 1.11 to 3.21), but not for asymptomatic patients (2.5% versus 1.4%; hazard ratio, 1.88; 95% CI, 0.79 to 4.42); however, a smaller total number of events occurred in the asymptomatic strata, resulting in lower statistical power to detect treatment differences. Cranial nerve palsies were less frequent for CAS (0.3% versus 4.7%; hazard ratio, 0.07, 95% CI, 0.02 to 0.18). At 1 year, periprocedural major and minor stroke had an effect on the physical component

Table 2. Composite Primary End Point and Components of the Primary End Point

	4-Year Study Period (Including Periprocedural Period*)			
	No. of Patients (%±SE)		Absolute Treatment Effect of CAS Versus CEA (95% CI)	
	CAS (N=1262)	CEA (N=1240)	Percentage Points	P†
Stroke				
Any stroke	105 (10.2±1.1)	75 (7.9±1.0)	2.3 (−0.6 to 5.2)	0.03
Major ipsilateral	16 (1.4±0.3)	6 (0.5±0.2)	0.8 (0.1 to 1.6)	0.05
Minor ipsilateral	52 (4.5±0.6)	36 (3.5±0.6)	1.0 (−0.7 to 2.7)	0.10
Primary end point (any periprocedural stroke, myocardial infarction, or death or post procedural ipsilateral stroke)	85 (7.2±0.8)	76 (6.8±0.8)	0.4 (−1.7 to 2.6)	0.51

*For patients who received the assigned procedure within 30 days after randomization, the periprocedural period was defined as the 30-day period after the procedure. For patients who did not receive the assigned procedure within 30 days after randomization, the periprocedural period was defined as the 36-day period after randomization.

†P values were calculated based on significance of the hazard ratios.[7]

summary scale of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), whereas periprocedural MI did not. Minor stroke had a significant effect on the mental component scale at 1 year.[7]

Discussion

CAS and CEA had similar net outcomes for symptomatic and asymptomatic men and women. However, there was a lower incidence of MI immediately after CAS and a lower incidence of stroke immediately after CEA.[14,15] Exploratory analyses among 1-year survivors with regard to quality of life suggested a sustained effect for stroke but not for MI. In addition, older patients had better outcomes after CEA and younger patients had slightly better outcomes after CAS.[16] Consequently, the preferences of the patient and his or her age may be important considerations in choice of treatment for carotid stenosis. The relationship between advancing age and increasing adverse events after CAS has been observed previously,[10,5,17] and the effect of advancing age on treatment differences, CAS versus CEA, has been observed in the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial.

The periprocedural safety outcomes for CAS and CEA are the best reported to date for patients with pre- and postprocedural medical, neurological, electrocardiogram, and enzyme evaluations. These excellent CREST outcomes may reflect a validated and effective surgeon credentialing process, the rigorous training and credentialing of interventionists, and the increasing assimilation of endovascular expertise.[10] Improved and more widely used medical therapies may also account for the better outcomes observed after CEA in CREST compared with outcomes in previous randomized clinical trials of CEA.[9,18–21]

Inference from the CREST results should be done in the context of several notable limitations. Changes occurred during the course of the study in preprocedural medical management, CAS and CEA procedural techniques and technology, and in postprocedural medical management. Only 1 stent system was used among several available. The definitions of stroke and MI and methods to detect them have raised questions regarding the importance of stroke or MI for the individual patient. In addition, improvements in the medical treatments for carotid disease have evolved, and CREST did not include a medical arm. Accordingly, the results of landmark trials that favored carotid revascularization (CEA) over medical treatment may or may not be applicable today.

Summary

CAS, when done by experienced and skilled interventionists, has patient outcomes similar to those of CEA done by experienced and skilled surgeons. During the perioperative period, more strokes occur after CAS and more MIs occur after CEA. Younger patients have slightly better outcomes with CAS and older patients have better outcomes with CEA. For the future, both CEA and CAS appear to be useful tools for preventing stroke.

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References

1. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, DeGraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006; 37:1583–1633.
2. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Sacco RL, Schwamm LH. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke*. 2008;39:1647–1652.
3. Ederle J, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev*. 2007;4:CD000515.
4. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351: 1493–1501.
5. Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stingele R, Zeumer H, Hacke W. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*. 2006;368:1239–1247.
6. Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lievre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garnier P, Viader F, Touze E, Giroud M, Hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355:1660–1671.
7. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; the CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23.
8. Sheffet AJ, Roubin G, Howard G, Howard V, Moore W, Meschia J, Hobson RW II, Brott TG. Design of the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST). *Int J Stroke*. 2010;5:40–46.
9. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*. 1995;273:1421–1428.

10. Hopkins LN, Rougin GS, Chakhtoura EY, Gray WA, Ferguson RD, Katzen BT, Rosenfield K, Goldstein J, Cutlip DE, Morrish W, Lal BK, Sheffet AJ, Tom M, Hughes S, Voeks J, Kathir K, Meschia JF, Hobson RW II, Brott TG. The Carotid Revascularization Endarterectomy vs Stenting Trial: credentialing of interventionalists and final results of lead-in phase. *J Stroke Cerebrovasc Dis*. 2010;19:153–162.
11. Ware J Jr, Sherbourne C. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Med Care*. 1992; 30:473–483.
12. Ware J Jr, Kosinski M, Bayliss M, McHomey C, Rogers W, Raczek A. comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care*. 1995;33:AS264–AS279.
13. Rautaharju PM, MacInnis PJ, Warren JW, Wolf HK, Rykers PM, Calhoun HP. Methodology of ECG interpretation in the Dalhousie Program; NOVACODE ECG classification procedures for clinical trials and population health surveys. *Methods Inf Med*. 1990;29:362–374.
14. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol*. 2003;42:1547–1554.
15. van Wijk I, Koudstaal P, Kappelle L, van Gijn J, Gorter J, Algra A, LiLAC Study Group. Long-term occurrence of death and cardiovascular events in patients with transient ischaemic attack or minor ischaemic stroke: comparison between arterial and cardiac source of the index event. *J Neurol Neurosurg Psychiatry*. 2008;79:895–899.
16. Chiam PT, Roubin GS, Iyer SS, Green RM, Soffer DE, Brennan C, Vitek JJ. Carotid artery stenting in elderly patients: importance of case selection. *Catheter Cardiovasc Interv*. 2008;72:318–324.
17. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375: 985–997.
18. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1991;325:445–453.
19. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, Spence JD. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415–1425.
20. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998;351:1379–1387.
21. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491–1502.

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