Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST): current and future implications for carotid artery stenting

Current reimbursement guidelines from the Centers for Medicare & Medicaid Services, prior to the publication of the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) results, reserve carotid artery stenting for stenosis in patients who are symptomatic, with severe stenosis, and considered high risk for carotid endarterectomy (CEA). CREST is a prospective, multicenter, randomized controlled trial, which compared surgical endarterectomy to endovascular stenting with primary end points of periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke up to 4 years in standard-risk patients. CREST results indicate that stenting may be equal to CEA. Overall, the trial demonstrated fewer strokes in the CEA group, with a lower risk of myocardial infarction associated with carotid artery stenting. The study suggests that younger patients may actually have improved outcomes with stenting, whereas CEA may be superior for older patients.

KEYWORDS: carotid artery stenting ■ carotid stenosis ■ CREST

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Carotid artery stenosis is responsible for 10% of all ischemic strokes. Furthermore, carotid revascularization remains the principal surgical tool in the management of ischemic stroke [1]. This is corroborated by an estimated 99,000 inpatient carotid endarterectomy (CEA) procedures performed in the USA in 2006 [1]. Therefore, determining the optimum surgical treatment of these lesions carries substantial importance. Current reimbursement guidelines from the Centers for Medicare & Medicaid Services, disseminated prior to the publication of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) results [2], reserve endovascular carotid artery stenting (CAS) for stenosis in patients who are symptomatic with severe stenosis, and considered high risk for surgical CEA. These guidelines came as a result of numerous trials in symptomatic patients (including the North American Symptomatic Carotid Endarterectomy Trial [NASCET] [3,4] and European Carotid Surgery Trial [ECST] [5,6]) and asymptomatic patients (including the Asymptomatic Carotid Atherosclerosis Study [ACAS] [5] and the Asymptomatic Carotid Surgery Trial [ACST] [6]) that provided evidence of the superiority of CEA as the best medical therapy. For symptomatic carotid stenosis exceeding 50%, the 2-year stroke risk was 9% with CEA versus 26% with medical therapy under NASCET. The ECST similarly demonstrated an absolute 5-year stroke risk reduction of 21.2% for lesions with stenosis severity greater than 70%, and 5.7% for lesions between 50 and 70% treated by CEA. For asymptomatic disease, ACAS demonstrated an absolute 5-year stroke risk reduction of 5.9% (relative risk reduction: 53%) for lesions with stenosis severity exceeding 60% treated by CEA. ACST produced a similar 5.4% rate of 5-year stroke risk reduction. Importantly, ACAS and ACST set an ambitious 1.5 and 3% surgical morbidity and mortality standard for CEA treatment of asymptomatic carotid artery disease.

In addition, as a result of these trials, subgroups of high-risk patients were identified who had more complications with surgery. Both anatomical and functional criteria were considered. High-risk anatomical features included lesions located at or above the level of C2, contralateral carotid occlusion, severe ulceration and tandem intracranial stenosis. Functional considerations included age over 80–85 years, active coronary artery disease or congestive heart failure, and a recent major stroke in the reference vascular territory, although debate exists as to whether 'functional' high-risk criteria really exist. Other high-risk criteria included 'hostile neck', meaning an immobile neck, previous irradiation, previous surgery on the same side, or previous surgery on the contralateral side, with vocal cord paralysis. As a result, stenting has often been reserved for high-risk patients.

It should be noted that, since the time of NASCET and ACST, medical therapy has improved, and many would question the current

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validity of these trials. In 2009, Abbott reported a review of published data, demonstrating that the rates of stroke (with or without transient ischemic attack) have fallen significantly since the mid-1980s with medical intervention alone [7]. Results obtained with medical intervention alone may actually overlap with those for asymptomatic patients in randomized trials. Abbott contends that current vascular medical intervention, including statin therapy, in asymptomatic severe carotid stenosis may be sufficient as a standalone treatment.

In stride with the advances in medical therapy, CAS has benefitted from increasing refinement in device technology and technique over the past decade. Sufficient momentum around these advancements prompted research interest in the comparison of CAS and CEA.

Initiation of CREST

By 2000, the safety of CAS, demonstrated in case series, justified comparison to CEA in standard or standard-risk patients. Against this background, CREST was initiated [2]. The trial involved 117 locations (108 US and nine Canadian sites) comparing CEA and CAS outcomes in the treatment of symptomatic and asymptomatic carotid artery disease (asymptomatic patients were eligible for inclusion in CREST in 2005). The team at each center included a neurologist, an interventionist, a vascular surgeon or neurosurgeon, and research coordinator.

Trial design

The CREST is a prospective, multicenter, randomized, controlled trial, with primary end points of composite occurrence of stroke, myocardial infarction (MI), or death from any cause during a 30-day periprocedural period, or postprocedural ipsilateral stroke within 4 years of randomization. Stroke was defined as an acute neurological ischemic event of at least 24-h duration, with focal signs and symptoms, and the diagnosis of a stroke was adjudicated by at least two neurologists blinded to treatment. An MI was defined as the combination of elevation of cardiac enzymes (creatinine kinase-MB or troponin) to a value of two or more times the upper limit of normal, at the laboratory at the individual clinical center, plus chest pain or equivalent symptoms consistent with ischemia or ECG evidence of ischemia, including new ST-segment depression or elevation of more than 1 mm in two or more leads. The diagnosis of MI was determined by two cardiologists blinded to treatment. The secondary aims of the study were differential efficacy by symptomatic status, sex, age, differential restenosis, quality of life and cost. Preprocedure, CAS patients were placed on a dual antiplatelet regimen, whereas CEA patients were placed on a single antiplatelet agent and treatment for hyperlipidemia, based on the standard of care at the time and at the institution.

The CREST boasts the most rigorous credentialing and training process of any of the CAS trials. Patients could not be randomized at the 117 sites until the operators performing CEA and CAS were certified [2,8]. Certification was achieved by 477 surgeons who had performed more than 12 procedures per year, with a rate of complication of less than 3% among asymptomatic patients and 5% among symptomatic patients. Of 429 interventionists who applied, 225 (52%) at 122 sites were approved to be part of the interventional/CAS arm of the trial. These operators were certified after evaluation of their CAS results, participation in hands-on training with the devices, and participation in a lead-in phase of training. Of the 429 operators, 70 were deemed to have adequate experience with the study devices to be exempt from the trial lead-in.

Inclusion criteria for CREST included asymptomatic patients with carotid stenosis of at least 60% by angiography, 70% by ultrasonography, or 80% by computed tomographic angiography (CTA) or magnetic resonance angiography (MRA), if stenosis on ultrasonography was 50–69%; inclusion criteria for symptomatic patients was at least 50% stenosis by angiography, 70% by ultrasound, or 70% by CTA or MRA if stenosis on ultrasonography was 50–69%. Major exclusion criteria included evolving stroke or major stroke likely to confound study end points, chronic atrial fibrillation, MI within the previous 30 days or unstable angina. The decision as to whether a lesion was symptomatic was made independently by two neurologists, and required confirmation of a transient ischemic attack or stroke, clearly referable to the appropriate distal vascular distribution.

Results

The CREST results included 2502 patients: 1262 assigned to CAS and 1240 to CEA. The CREST combined primary end point demonstrated equivalence between CAS and CEA (7.2 vs 6.8%; p = 0.51, for stroke, death, MI or long-term [4-year] ipsilateral stroke event). Periprocedural end points were similarly statistically equivalent (5.2% for CAS vs 4.5% for

CEA; p = 0.38). Moreover, CAS and CEA demonstrated countervailing and complementary risks in subset analysis. Although the rates of major stroke for CAS and CEA were approximately equal (0.9 vs 0.6%; p = 0.52), the rate of minor stroke for CAS exceeded that for CEA (4.1 vs 2.3%; p = 0.01). CAS was superior to CEA with respect to the incidence of periprocedural MI (1.1 vs 2.3%; p = 0.03) and the expected rates of cranial neuropathies (0.3 vs 4.7%; p < 0.0001). There was no differential treatment effect with regard to the primary end point according to symptomatic status. The quality-of-life analyses among survivors at 1 year suggest that stroke had a greater adverse effect on a variety of categories than MI. A subset analysis further suggests that younger patients may actually have improved outcomes with stenting [2], whereas CEA may be superior for older patients. As our experience with CAS increases, these results are not surprising. Older patients often harbor tortuous or atherosclerotic aortic arches and great vessel disease; the catheter manipulation of these vessels required to perform CAS poses a risk for embolic complications. Open surgery with CEA spares the patient this risk and, therefore, may represent a superior alternative for older patients with increasing rates of challenging endovascular access. Although CAS is still recommended for 'high-risk' patients, CREST shows that octogenarians may fall into a category of 'higher risk' for CAS, owing to an increased risk of stroke in this group.

The results of CREST confirm the findings from the Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial [8,9], which details that rigorous training requirements and experience can make a difference, even with first-generation technology, as was the case with CREST (for CAS, the protocol specified use of the RX Acculink® stent and, whenever feasible, the RX Accunet embolic-protection device [Abbott Vascular] [2]). By contrast, the International Carotid Stenting Study (ICSS) concluded that CEA was safer for the treatment of symptomatic carotid stenosis, as the risk of stroke and death were higher with CAS [10], in addition to a higher rate of diffusion-weighted changes on MRI in the CAS group [11]. However, embolic protection devices were not required in the study, with approximately 30% of patients stented without proximal or distal protection. In addition, there was significant disparity in the required experience of surgeons and interventionists, with surgeons required to have performed 50 CEAs and interventionists required to have performed only ten CAS procedures. CAS is a relatively new technique in comparison with CEA. Each trial provides different information, with no single trial giving all of the answers. We will learn a lot from CREST, as we have from the other well-designed trials that preceded it. The CREST results suggest overall equivalence between CEA and CAS for the primary composite end point of the study. In addition, CEA and CAS appear, to a large extent, to be complementary procedures (i.e., patients at high risk for CEA are often at low risk for CAS, and *vice versa*).

The CREST does have some limitations. The study had a prolonged enrollment period, during which stenting technology and operator experience improved greatly. With improved technology, such as proximal embolic protection devices, and with improvements in operator technique, it is possible that the stroke rate with CAS in current practice may be less than that noted in CREST. However, one may argue that the rigorous training and requirements for operators participating in CREST may make carotid stenting appear safer than it actually is in a standard population of practitioners with average experience.

In addition, the trial was initially designed to include only symptomatic patients; however, asymptomatic patients were accepted after the lead-in. Despite the high enrollment of asymptomatic patients (~50%), the trial was still appropriately powered to compare CEA with CAS in both symptomatic and asymptomatic patients [2]:

"*The addition of asymptomatic patients and the anticipated lower event rate for that group had the potential to compromise the statistical power. However, that lower event rate was offset by the higher number of events associated with the extended enrollment and follow-up periods*."

Finally, current medical therapy alone for asymptomatic severe carotid stenosis was not addressed by this study. As mentioned previously, some would argue that current medical therapy, including statins, may be the most cost-effective treatment for asymptomatic carotid stenosis.

Conclusion

The results of CREST indicate the equivalence of stenting to CEA, with the lowest rate of major stroke and death in any trial so far. The trial demonstrated fewer major strokes in the CEA group, with a lower risk of MI with CAS. However, quality-of-life studies suggest that even minor stroke may have a more adverse effect on long-term outcome than MI, whereas cranial

nerve palsies (observed more frequently with CEA) may affect quality of life in ways similar to minor stroke. Moreover, other studies, such as the Acculink for Revascularization of Carotids in High-Risk Patients (ARCHeR) trial [12], have shown that most minor strokes after CAS resolve completely within several months. Analyses of these outcomes are greatly anticipated. The CREST results suggest that both CEA and CAS are associated with low perioperative complication rates and excellent longer-term results at experienced centers. Finally, the rigorous credentialing and training process used for operators in the CREST trial is the most stringent to date, and will likely serve as a model for future trials.

Future perspective

The results of CREST carry the potential to change the way that many practitioners manage the care of patients with carotid artery disease. Whereas CAS has traditionally been reserved for high-risk surgical patients, including those aged 80 years and older, CREST reveals that the previously determined 'high-risk' designation for octogenarians may be wrong. It is likely that, not too far into the future, carotid stenosis patients will be evaluated on an individual basis, regardless of age, to determine which modality (CAS vs CEA) is the safest and most effective. Preoperative noninvasive studies, such as CTA or MRA, can help determine which patients have aortic arch disease and, therefore, are at higher risk for stenting. Overall, CREST provides the physician more options for the treatment of carotid stenosis in the future, with the confidence that both CEA and CAS are effective and safe when performed by experienced operators, and when patients are chosen appropriately. As our experience with CAS grows, the identification of high-risk CAS features, such as arch access, will allow increasingly mature and judicious application. Coupled with tremendous device advancements in distal protection, proximal protection, flow reversal and stents themselves, CAS will play an increasing role in the treatment of carotid artery stenosis.

Information resources

- Clinicaltrials.gov: a registry of federally and privately supported clinical trials conducted in the USA and around the world: http://clinicaltrials.gov/ct2/show/NCT00004732?term=crest&rank=1

Executive summary

Carotid artery stenting is typically reserved for patients who fall into a category of high risk for surgery

- Anatomic: lesion at or above C2, contralateral carotid occlusion, severe ulceration or tandem intracranial stenosis.
- Functional: aged older than 80–85 years (also increased risk for carotid artery stenting [CAS]), active coronary artery disease, congestive heart failure or recent major stroke in the reference vascular territory.
- Hostile neck: immobile neck, previous ipsilateral surgery, previous contralateral surgery with vocal cord paralysis or previous irradiation.

Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) was a prospective, multicenter, randomized controlled trial that compared carotid endarterectomy with carotid artery stenting

- Primary end points: periprocedural stroke, myocardial infarction (MI), or death or postprocedural ipsilateral stroke up to 4 years.
- Secondary aims: differential efficacy by symptomatic status, sex and age, differential restenosis, quality of life and cost.
- Inclusion criteria: asymptomatic patients with carotid stenosis of at least 60% by angiography or 70% by ultrasound, or 80% by computed tomographic angiography or magnetic resonance angiography; for symptomatic patients, inclusion criteria was at least 50% stenosis by angiography or 70% by ultrasound, computed tomographic angiography or magnetic resonance angiography.
- Major exclusion criteria: evolving stroke or major stroke probably confounds study end points, chronic atrial fibrillation, MI within the previous 30 days or unstable angina.
- It has the most stringent credentialing and training process of any of the carotid stenting trials.

Results

- The combined primary end point of CREST demonstrated equivalence between CAS and carotid endarterectomy (CEA).
- Major stroke rate between CAS and CEA was similar.
- CAS minor stroke rate exceeded that for CEA.
- CAS was superior to CEA, with respect to the incidence of periprocedural MI, and the expected rate of cranial neuropathies.
- Quality-of-life studies suggest that stroke has more affect on patient outcomes than MI.
- Subset analysis suggests younger patients may actually have improved outcomes with stenting, whereas CEA may be superior for older patients.
- No effect detected for symptomatic status or sex.
- CREST is the first prospective, randomized trial to demonstrate equivalence between CEA and CAS in standard-risk patients.
- CREST shows that octogenarians may fall into a category of 'higher risk' for CAS, owing to an increased risk of stroke in this group. If CAS is contemplated for octogenarians, careful attention to anatomic risk factors for stenting in elderly patients, and the use of newer embolic protection technology not available in CREST, should be considered.

- CREST website: www.umdnj.edu/crestweb
- The Internet Stroke Center: an independent web resource for information about stroke care and research, sponsored by Washington University in St Louis: www.strokecenter.org

Financial & competing interests disclosure

L Nelson Hopkins receives research study grants from Abbott (ACT 1 Choice), Boston Scientific (CABANA), Cordis (SAPPHIRE WW), and ev3/Covidien Vascular Therapies (CREATE) and a research grant from Toshiba (for the Toshiba Stroke Research Center); has an ownership/financial interest in AccessClosure, Boston Scientific, Cordis, Micrus, and Valor Medical; serves on the Abbott Vascular Speakers' Bureau; receives honoraria from Bard, Boston Scientific, Cordis, and from the following for speaking at conferences – Complete Conference Management, Cleveland Clinic, and SCAI; receives royalties from Cordis (for the AngioGuard device), serves as a consultant to or on the advisory board for Abbott, AccessClosure, Bard, Boston Scientific, Cordis, Gore, Lumen Biomedical, and Toshiba; and serves as the conference director for Nurcon Conferences/Strategic Medical Seminars LLC. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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