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Carotid Artery Stenting

Lessons From CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial)

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The results of the CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) (1) were recently published, and they confirmed that there is clinical equipoise for stenting versus surgery for symptomatic carotid artery disease in average risk patients.

The CREST is the largest prospective randomized trial to date, enrolling, from 117 U.S. and Canadian centers, 2,502 patients, of which 53% were symptomatic and 47% were asymptomatic patients. The patients were randomized to receive either carotid artery stenting (CAS) using the same stent and distal-protection devices (AccuLink and Accunet, Abbott Vascular, Redwood City, California) or the gold standard of carotid endarterectomy (CEA). The primary end point was a composite of any clinical stroke, myocardial infarction, or death during the periprocedural period, or any ipsilateral target vessel–related stroke within 4 years. The CREST found no difference in the primary end point between CAS (7.2%) and CEA (6.8%, $p = 0.51$) followed up to 4 years. There was no difference between either group for major stroke or death in the perioperative period. There was a higher risk of all stroke with CAS (4.1% vs. 2.3%, $p = 0.01$), although the majority of these were minor strokes. There was a doubling of the risk of myocardial infarction (2.3% vs. 1.1%, $p = 0.03$) with CEA as well as a 1 in 20 (4.8%) risk of cranial nerve injury with surgery. The CREST demonstrated a slight advantage for younger patients with CAS and older patients with CEA; both procedures had excellent durability (1).

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Procedure Risk

Carotid endarterectomy has well-described perioperative risks (2,3). A consensus panel has suggested that CEA is beneficial if the periprocedural risk of stroke and death did not exceed 3% for asymptomatic patients and 6% for symptomatic patients (4,5). However, these risks are increased in subsets of patients with repeat CEA (6), contralateral carotid occlusions (7), and adverse anatomical features and medical comorbidities (8). For CAS, the procedural risks are further compounded by anatomic features (including echolucent plaques, unfavorable aortic arches, tortuous vessels, lesion calcification, and complex lesions) that prolong catheter and guidewire manipulation in the carotid vascular bed, decrease successful deployment or retrieval of embolic protection devices, and limit accurate positioning of stent (9–11).

There are 3 large European randomized controlled trials comparing CAS with CEA in symptomatic patients at average risk for surgery: the EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Artery Stenosis-3S) (12), SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy) (13), and ICSS (International Carotid Stenting Study) (14) trials. The EVA-3S and SPACE trials have been completed, and the ICSS trial has reported interim results. These European trials contrast with the North American CREST by: 1) enrolling only symptomatic patients; 2) accepting inexperienced CAS operators compared with established CEA operators; and 3) performing CAS without embolization protection devices (EPD) (15).

Operator Experience

The experience of operators and volumes of centers have a direct impact on procedure outcomes (16). The lead-in phase of the CREST demonstrated

that catheter-based subspecialties (interventional radiology and cardiology) experienced one-half the number of complications as the surgical specialties (vascular surgery), which was statistically significant (17) at onset, but after successful completion of lead-in cases, the quality gap for surgeons had been closed. The European CAS trials including the EVA-3S (12), SPACE (13), and ICSS (14) trials allowed tutoring of CAS operators to enroll patients, which certainly biased the outcomes of these trials (15). The CREST took specific steps to only allow qualified operators to participate in CAS and CEA maintaining the highest minimum operator experience in both groups compared with the preceding European trials (2,15), which explains why the CREST had the lowest 30-day outcomes of stroke and death (5.2%).

Embolization Protection

The safety and efficacy of EPDs for retrieval of debris during CAS had made it impossible to construct a randomized trial with an unprotected control group. However, a meta-analysis of 4,747 patients in 24 CAS studies found a significant benefit for EPDs with CAS with a relative risk reduction of greater than 50% (18). Data supporting the use of EPDs include the finding of fewer transcranial Doppler embolic signals and fewer magnetic resonance diffusion-weighted imaging brain lesions during CAS (19). The CREST was the only trial to mandate use of EPDs, which were optional in the European trials; this helps to explain lower 30-day outcomes of stroke and death in the CAS group in the CREST. The CREST employed a filter-based EPD, although no difference has been found between distal occlusion and filter-based EPDs (20); however, fewer embolic signals were seen with a proximal occlusion EPD compared with a filter-based EPD (21). A recently published registry of 1,300 CAS procedures using a proximal occlusion EPD reported a 30-day stroke and death rate of only 1.4% (22), which, if reproduced in randomized clinical trials, would further support the adoption of CAS as the preferred method of carotid revascularization (23).

Reporting Bias

A major problem in assessing CEA results, outside of multicenter randomized trials, has been the significant heterogeneity in the reporting of surgical complications. In a systematic analysis of published reports of CEA, the complication rate was highest in studies that included an independent neurologist for post-operative assessment and it was the lowest in reports authored by a single surgeon (24). Another common source of error in reporting CEA results is an ascertainment bias that occurs when using third-party databases to compare CEA and CAS. The great majority of CAS procedures performed in the U.S., including the CREST, required an independent neurological examination whereas most CEA procedures were not performed in a clinical trial environment and therefore had complications self-reported by the surgeon without an independent neurological assessment. This ascertainment bias, often makes CAS look worse in databases that underreport CEA complications (25,26). For a meaningful comparison of CAS and CEA to occur, it is necessary to have independent neurological assessment of outcomes of both procedures, as is required in the NCDR–CARE (National Cardiovascular Database Registry–Carotid Artery Revascularization and Endarterectomy) (27,28).

Summary

The take-home message from the CREST is that for low to average surgical risk patients with symptomatic or asymptomatic carotid artery stenosis, CAS and CEA in qualified hands, have comparable outcomes. It also highlights the importance of factors such as operator experience and training, the use of embolic protection, and an awareness of the potential reporting and ascertainment bias that may occur in nonrandomized trials. The CREST results confirm that in experienced centers and with experienced operators, patients and their physicians should be able to individually tailor therapy for stroke prevention by choosing either CAS or CEA, a view reinforced by the editorialists of the study who concluded ". . . given the lack of significant difference in the rate of long-term outcomes, the individualization of treatment choices is appropriate" (29).

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REFERENCES

1. Brott TG, Hobson RW 2nd, Howard G, et al., on behalf of CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11–23.
2. White CJ. Carotid artery stent placement. J Am Coll Cardiol Intv 2010;3:467–74.
3. White CJ, Beckman JA, Cambria RP, et al., on behalf of American Heart Association Writing Group 5. Atherosclerotic Peripheral Vascular Disease Symposium II: controversies in carotid artery revascularization. Circulation 2008;118:2852–9.
4. Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 1998;29:554–62.
5. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:577–617.

6. Meyer F, Piepgras D, Fode N. Recurrent carotid stenosis. In: Meyer FB, editor. Sundt's Occlusive Cerebrovascular Disease. Philadelphia, PA: WB Saunders, 1994:310–21.
7. Gasecki AP, Eliasziw M, Ferguson GG, et al., on behalf of North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. J Neurosurg 1995;83: 778–82.
8. Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European Carotid Surgery Trialists' Collaborative Group. Lancet 1999;353: 2105–10.
9. Macdonald S, Lee R, Williams R, Stansby G, Delphi Carotid Stenting Consensus Panel. Towards safer carotid artery stenting: a scoring system for anatomic suitability. Stroke 2009;40:1698–703.
10. Roubin GS, Iyer S, Halkin A, Vitek J, Brennan C. Realizing the potential of carotid artery stenting: proposed paradigms for patient selection and procedural technique. Circulation 2006;113:2021–30.
11. Lam RC, Lin SC, DeRubertis B, Hynecek R, Kent KC, Faries PL. The impact of increasing age on anatomic factors affecting carotid angioplasty and stenting. J Vasc Surg 2007;45:875–80.
12. Mas JL, Chatellier G, Beyssen B, et al., on behalf of EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006;355:1660–71.
13. Ringleb PA, Allenberg J, Bruckmann H, et al., on behalf of SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006;368:1239–47.
14. Ederle J, Dobson J, Featherstone RL, et al., on behalf of International Carotid Stenting Study Investigators. 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;375:985–97.
15. Roffi M, Sievert H, Gray WA, et al. Carotid artery stenting versus surgery: adequate comparisons? Lancet Neurol 2010;9:339–41, author reply 341–2.
16. Vogel TR, Dombrovskiy VY, Graham AM. Carotid artery stenting in the nation: the influence of hospital and physician volume on outcomes. Vasc Endovascular Surg 2010;44:89–94.
17. Hopkins LN, Roubin GS, Chakhtoura EY, et al. The Carotid Revascularization Endarterectomy versus Stenting Trial: credentialing of interventionalists and final results of lead-in phase. J Stroke Cerebrovasc Dis 2010;19:153–62.
18. Garg N, Karagiorgos N, Pisimisis GT, et al. Cerebral protection devices reduce periprocedural strokes during carotid angioplasty and stenting: a systematic review of the current literature. J Endovasc Ther 2009;16:412–27.
19. Al-Mubarak N, Roubin GS, Vitek JJ, Iyer SS, New G, Leon MB. Effect of the distal-balloon protection system on microembolization during carotid stenting. Circulation 2001;104:1999–2002.
20. Kim SJ, Roh HG, Jeon P, et al. Cerebral ischemia detected with diffusion-weighted MR imaging after protected carotid artery stenting: comparison of distal balloon and filter device. Korean J Radiol 2007;8:276–85.
21. Garami ZF, Bismuth J, Charlton-Ouw KM, Davies MG, Peden EK, Lumsden AB. Feasibility of simultaneous pre- and post-filter transcranial Doppler monitoring during carotid artery stenting. J Vasc Surg 2009;49:340–4, 345.e1–2, discussion 345.
22. Stabile E, Salemme L, Sorrropago G, et al. Proximal endovascular occlusion for carotid artery stenting: results from a prospective registry of 1,300 patients. J Am Coll Cardiol 2010;55:1661–7.
23. White CJ. Proximal embolic protection: a "game changer" for carotid stents. J Am Coll Cardiol 2010;55:1668–70.
24. Rothwell PM, Slattery J, Warlow CP. A systematic review of the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. Stroke 1996;27:260–5.
25. McPhee JT, Schanzer A, Messina LM, Eslami MH. Carotid artery stenting has increased rates of postprocedure stroke, death, and resource utilization than does carotid endarterectomy in the United States, 2005. J Vasc Surg 2008;48:1442–50, 1450.e1.
26. White CJ. Liar, liar, pants on fire. Catheter Cardiovasc Interv 2008; 72:430–1.
27. White CJ, Anderson HV, Brindis RG, et al. The Carotid Artery Revascularization and Endarterectomy (CARE) registry: objectives, design, and implications. Catheter Cardiovasc Interv 2008;71:721–5.
28. Anderson HV, Rosenfield KA, White CJ, et al. Clinical features and outcomes of carotid artery stenting by clinical expert consensus criteria: a report from the CARE registry. Catheter Cardiovasc Interv 2010;75: 519–25.
29. Davis SM, Donnan GA. Carotid-artery stenting in stroke prevention. N Engl J Med 2010;363:80–2.