Carotid Intervention
Is It Warranted in Asymptomatic Individuals if Risk Factors Are Aggressively Managed?

Katherine Pahigianis, PhD; Petra Kaufmann, MD; Walter Koroshetz, MD

Asymptomatic Carotid Artery Stenosis
It is estimated that 2% to 12% of adults have >50% stenosis of the carotid arteries. Carotid stenosis is a strong indicator of systemic atherosclerotic disease with subsequent adverse health outcomes including myocardial infarction, stroke, and renal and peripheral arterial disease. The risk of stroke, usually resulting from carotid embolism to the middle cerebral artery or its branches, is low in asymptomatic carotid stenosis but spikes once persons experience ischemic symptoms (ipsilateral transient ischemic attack or stroke). The principal health objective is to prevent conversion to symptomatic stenosis. Even greater public health impact can be achieved with risk factor reduction that attenuates associated myocardial infarction, strokes from noncarotid causes, and peripheral arterial disease. Direct vascular intervention, carotid endarterectomy (CEA), or carotid artery stent/angioplasty (CAS) can reduce stroke risk in persons with symptomatic carotid stenosis, but evidence for their absolute value in improving health for the millions with asymptomatic stenosis is less firm. The Carotid Revascularization using Endarterectomy or Stenting Trial-2 (CREST2) team is embarking on an ambitious clinical trial to assess this question, and their success will require widespread buy-in from the stroke community.

Surgical Interventions to Reduce Stroke Risk
Following results of the Asymptomatic Carotid Atherosclerosis Study (ACAS; 1987–1993) and the Asymptomatic Carotid Stenosis Trial (ACST; 1993–2003), which found that CEA cut 5-year stroke risk of 11% to 12% in half compared with medical management, surgical endarterectomy for asymptomatic carotid stenosis became one of the most common surgical procedures, with >100,000 performed annually in the United States. However, reduction of disabling strokes was less pronounced, and the procedure was not adopted widely in other countries. In the last decade, the frequency of CAS has increased in the United States, with tens of thousands performed annually. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST1; 2000–2012) compared these 2 interventions, showing similar 4-year combined stroke and death rates for asymptomatic patients. Estimated annual healthcare cost for these procedures exceeds $2 billion. However, CAS has not been compared with medical management, and the Center for Medicare and Medicaid Services does not currently reimburse for CAS in asymptomatic patients.

Medical Management of Stroke Risk
With major improvements in the management of stroke risk factors such as hypertension and hyperlipidemia, as well as promotion of healthier lifestyles, the true risk of stroke in persons with asymptomatic carotid stenosis is unknown. In the recent Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, patients were assigned to aggressive medical management as opposed to the standard of care medical regimens of previous National Institute of Neurological Disorders and Stroke (NINDS) studies. SAMMPRIS patients achieved far better risk factor control than seen previously, and their stroke risk was cut in half compared with the immediately preceding Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, which used traditional standard of care medical management. Registry data and systematic reviews also raise the question whether lower stroke rates in well-managed patients may temper the potential net benefits of carotid interventions.

Aggressive Medical Therapy Alone, Plus CEA, Plus CAS… What Works Best?
In light of these developments in both medical and interventional management of carotid stenosis, a clinical trial is needed to inform patients on the best treatments for their overall health. Answering this critical public health question could reduce stroke and optimize use of healthcare resources.

The CREST2 investigator team, led by Drs Thomas Brott and George Howard, is launching 2 parallel, randomized, multicenter trials to compare the effectiveness of intensive medical management with that of CEA and with that of stenting for patients with ≥70% asymptomatic carotid stenosis. The primary end point will be stroke or death within 30 days, plus ipsilateral stroke up to 4 years, with potential for longer follow-up supported by a second grant period. Vascular risk factors will be managed in all patients using modern aggressive targets as in SAMMPRIS. Conducting parallel trials will allow practitioners to assign patients to 1 of the 2 trials based on their current practice; however, the patient populations may differ, precluding direct comparison of CEA and CAS. The CREST2 trial is powered to determine whether long-term...
reduction of stroke and death offered by CEA and CAS continues to be clinically significant and similar to improvements observed in ACAS.

Working Together to Find the Answer—A Call for Commitment From the Community
The National Institutes of Health is partnering with key federal agencies, including the Center for Medicare and Medicaid Services, the Agency for Healthcare Research and Quality, the Patient Centered Outcomes Research Institute, and the Food and Drug Administration, as well as trialists in the stroke community to maximize the impact of CREST2 on public health. The potential for the results to optimize patient care and improve outcomes is enormous, but successful completion hinges on commitment from the medical, endovascular, and surgical communities to enroll every eligible patient. Currently, reimbursement for stenting procedures in this patient population requires enrollment in a trial. In contrast, financial disincentives to enrolling patients into the parallel CEA trial will need to be overcome by desire and responsibility of the stroke community to know whether the answer to the question has changed in the past 2 decades. A concerted effort will ensure that stroke prevention care provided to patients is based on up-to-date evidence-driven data.

Disclosures
None.

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