Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 25, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.01.087

EDITORIAL COMMENT

Asymptomatic Carotid Stenosis: The Not-So-Silent Disease

Changing Perspectives From Thromboembolism to Cognition*

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More than 100,000 carotid revascularization procedures are performed annually in the United States, primarily for asymptomatic stenosis to improve flow and provide protection from thromboembolic events to the ipsilateral hemisphere. Indications for asymptomatic carotid stenosis revascularization stem from ACAS (Asymptomatic Carotid Atherosclerosis Study) and ACST (Asymptomatic Carotid Surgery Trial) (1,2). In ACST, there was a reduction in cerebral ischemic events from 11.8% in patients treated with aspirin alone to 6.4% in those undergoing endarterectomy for ≥60% carotid stenosis over 5 years. Despite the benefit for revascularization of carotid stenosis of at least 60% in ACAS and ACST, most subsequent trials have established a higher standard for asymptomatic disease with inclusion criteria established at 80% carotid stenosis.

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The indication for carotid revascularization in asymptomatic patients has been recently vigorously challenged because of improvements in medical therapies now routinely available to patients, including rigorous management of hypercholesterolemia, hyperlipidemia, diabetes mellitus, antiplatelet regimens, and aggressive blood pressure and lifestyle interventions. This has particularly come to the fore in light of the CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial) results, where there was no significant difference in the incidence of the composite primary endpoint of stroke, myocardial infarction, and death between carotid endarterectomy and stenting (3). Even though most carotid revascularization procedures in the United States are carotid endarterectomies, and the vast majority of those are for >60% asymptomatic disease, plans for expansion of indications for carotid artery stenting (CAS) for asymptomatic disease have been essentially abandoned, despite demonstrated equipoise of the 2 procedures in CREST.

The principal reason for resistance to wider adoption of CAS appears to be the incidence of cerebral ischemic events following revascularization. Again, in CREST, there were no significant differences in major stroke or death between the 2 procedures, but there were clear differences between minor stroke and myocardial infarction (3). Also worth noting is a significant impact on longevity with myocardial infarction but not with minor stroke. Interestingly, access site complications were significantly more common with endarterectomy than with stenting; and cranial nerve injuries (5% after endarterectomy) did not occur with stenting. The focus from the community of physicians treating carotid stenosis has been directed primarily at the effectiveness of carotid revascularization as it pertains to prevention of periprocedural and post-procedural ischemic events.

Attempts have been made to distinguish higher-risk asymptomatic patients most likely to benefit from carotid revascularization. These have included transcranial embolic studies to detect high-intensity transients (asymptomatic embolic events) on ipsilateral middle cerebral artery insonation, plaque morphology on ultrasonography with hypoechoic, lipophilic, and/or necrotic plaque centers, or on plaque morphology assessment protocols on magnetic resonance (MR) imaging (4–8). Again, all such efforts are restricted to prediction and prevention of thromboembolic ischemic events to the cerebral circulation through revascularization approaches.

Evidence suggests that chronic carotid stenosis has a progressive effect on cognitive decline. Johnston et al. (9) evaluated a large, population-based cohort with asymptomatic carotid stenosis (4,006 patients over 5 years) and noted progressive cognitive declines in patients with severe carotid stenosis and increased intima-media thickness. The study reported by Huang et al. (10) in this issue of the *Journal* raises

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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the very pertinent question of effects on cognition that may be amenable to amelioration by carotid revascularization as a direct correlate to improvement in attenuated cerebral perfusion. There has been a steady focus on neurocognitive effects of carotid stenosis and response to reduction in carotid stenosis and improvement in cerebral perfusion following revascularization. However, results have been varied and are often contradictory. The intuitive notion that improved blood flow should enhance cognitive function has been essentially completely omitted from the discussion as we consider CAS for revascularization, maintaining the focus entirely on thromboembolic disease.

Huang et al. (10) looked at 61 patients, of whom 22 had complete occlusion and 39 had severe carotid stenosis. They performed psychometrics on these patients, including the Mini-Mental State Examination, Alzheimer Disease Assessment Scale–Cognitive subscale, Trail Making Test 1 and 2, and Color Trails Test. Interestingly, these were similar in all patients. They subsequently performed cerebral perfusion assessment using computed tomographic perfusion imaging with acetazolamide challenge to identify patients with marginal perfusion. Their results are quite interesting: only those with marginal perfusion status showed improvement in cognitive function following successful revascularization. To show these effects, they used 2 groups as controls, those with marginal perfusion and failed revascularization (only 64% of complete carotid occlusions could be reopened) and those with no perfusion deficits who underwent revascularization for stenosis. They excluded 2 periprocedural neurological complications (3.3%) from analysis.

This study provides yet another correlate to assess risk in asymptomatic carotid stenosis. Instead of the focus remaining on thromboembolic events, this report clearly provides evidence that revascularization in patients with asymptomatic disease selected on the basis of marginal cerebral perfusion may provide cognitive benefit. Our main criticism of this report pertains to the absence of a baseline difference in psychometric scores between the 2 control groups, which would be predicted based on the assumed hypothesis that marginal perfusion leads to cognitive decline. This may be explained by the fact that at the 3-month follow-up, there was an element of cognitive decline, which transpired in those who failed revascularization, amplifying the baseline differences to significance. As is expected, this report also has the inherent limitations (as the authors recognized) that this is a small study and deserves larger cohorts and additional psychometric and cerebral perfusion measures.

This group has previously reported a similar improvement in cognition after revascularization of chronic internal carotid artery occlusions (11). In another recent report, Cheng et al. (12) compared 17 patients with $\geq$70% unilateral asymptomatic stenosis with 26 healthy controls using a more comprehensive battery of psychometric testing as well as imaging correlates. In particular, they applied novel MR imaging–based protocols to assess functional hemispheric connectivity using diffusion-tensor imaging and whole-brain fractional anisotropy paradigms. Interestingly, they noted that patients with stenosis had worse memory and visuospatial performance. They also noted marked decreases in inter- and intrahemispheric functional frontoparietal connectivity in these patients. They noted an improvement in these functions following stent-assisted revascularization. Similar improvements have been reported by other groups as well, testing cognitive function before and after CAS for asymptomatic stenosis (13–16) and symptomatic stenosis (16,17). Improvements in cognition have also been reported following endarterectomy. In a study by Fearn et al. (18) that evaluated endarterectomy in patients with marginal cerebral perfusion, distinct improvement was noted at 8 weeks post-procedure, but not at 5 days. Others have contiguously evaluated both endarterectomy and stenting, and noted clear improvement in cognition after both at 4 to 6 months post-procedure (19).

In contrast to the rosy picture portrayed by the paper being editorialized and the additional supporting studies noted in the preceding text, there is a distinct body of literature that has assessed cognitive function with the aim of demonstrating the deleterious effects of periprocedural embolic events during carotid revascularization. Zhou et al. (20) noted that patients with periprocedural embolic events detected on post-procedure MR imaging were more likely to have a decline in memory function. Similarly, Altinbas et al. (21), in an ICSS (International Carotid Stenting Study) substudy, reported a nonsignificant decline in cognition following CAS and correlated it with twice more evident embolic events on post-procedure MR imaging. Of note, only 177 of 1,713 patients enrolled in ICSS were enrolled in this substudy. Of these, only 140 underwent pre-procedure testing; and of those, only 120 underwent post-procedure testing. Finally, post-procedure testing was performed 1 month post-procedure, compared to the study under discussion by Huang et al. (10) in which it was performed at 3 months post-stenting. Testing latency after the procedure may have an effect on the results; for instance, Witt et al. (22) performed a prospective randomized study comparing CAS and carotid endarterectomy in which patients were evaluated pre-procedure and at 1 month, and noted no significant differences, whereas Raabe et al. (23) tested a similar cohort at 1 year and noted significant improvements in cognitive function. Others have shown that early declines post-procedure (after both stenting and endarterectomy) reverse into significant improvements by 3 months and last beyond the first year (24).

Several authors have reviewed the literature and noted that among 22 studies evaluating cognition, 8 demonstrated improvements, 11 had mixed results, and 3 noted declines post-revascularization (25,26). For example, Lehrner et al. (27) evaluated 20 patients with symptomatic and asymptomatic stenosis who underwent stenting and noted no change at 6 months for most, and significant improvement and significant decline in smaller subsets (<10% each). This contradiction in varied cognitive outcomes is not isolated to studies evaluating stenting but also is found in the endarterectomy literature (28,29). Other studies have correlated