The High Risk of Low Distal Flow

James F. Meschia, MD

Symptomatic atherosclerosis of the vertebral artery remains a challenging condition with no proven interventional therapy. Completed randomized trials of angioplasty with or without stenting involving patients with symptomatic vertebral artery stenosis include Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS),1 Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS),2 and Vertebral Artery Stenting Trial (VAST).3 As the largest (N = 115) completed trial, VAST illustrates many of the challenges of developing interventional therapy for this patient population. During a median follow-up of 3 years, 12% of the patients in the stenting group and 7% of those in the medical group developed stroke in the symptomatic vertebral arterial territory. The VAST investigators estimated that, with this cumulative absolute rate of stroke events in the medical group, 9500 patients would have to be randomized in a future trial to provide compelling evidence of a 20% reduction in risk. With this in mind, it may be more productive—indeed, perhaps necessary—to reserve the development of interventional therapy for higher-risk populations. It may be useful for future trials to focus on providing treatment for patients sooner after their qualifying event. In VAST, only one-third of the medical group was enrolled within 14 days of their qualifying event.

Beyond timing, imaging may help to identify a population of patients with symptomatic vertebralbasilar (VB) disease who are at high risk for stroke. A single-center retrospective study4 of 47 patients concluded that those with symptomatic VB disease were at higher risk of stroke if they had evidence of low distal flow as assessed by quantitative magnetic resonance angiography (QMRA). The investigators then took the important next step of independently replicating their findings in the multicenter prospective study Vertebrabasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS), the results of which are reported in this issue of JAMA Neurology.5 VERiTAS enrolled 81 patients across 5 North American academic medical centers. Patients were enrolled within 60 days following a stroke or transient ischemic attack referable to atherosclerotic stenosis of at least 50% in the VB system. Every patient had stenosis defined by either conventional or computed tomographic angiography. The investigators used QMRA to divide patients into 2 groups: low distal flow and normal distal flow. Patients were monitored for a mean of 22 months. Low distal flow, present in 25% of the patients analyzed, predicted a dramatically higher risk of VB stroke (hazard ratio, 11.55). The investigators suggest that the absence of low distal flow could be used to identify patients with symptomatic VB arterial disease at sufficiently low risk of stroke to rule out interventional therapy and, inversely, the presence of low distal flow could be used to identify patients at sufficiently high risk of stroke to consider enrolling them in a trial of interventional therapy.

VERiTAS has numerous strengths.5 Patients were carefully selected, imaged, and monitored for outcomes. An experienced panel of vascular neurologists blinded to the QMRA findings assessed stroke outcomes. Blinding reduces the risk of differential misclassification of events as VB stroke when they are not VB stroke and vice versa. However, nondifferential misclassification remains a risk. Agreement rates of clinical impression of vascular territory involved in stroke are only moderate.6 In addition, some VB strokes can present with syndromes such as acute vestibular syndrome that can be misdiagnosed as a nonstroke.7 Having an expert adjudication panel helps to minimize misclassification. There is also the potential that event rates are underestimated because site teams may not suspect some events as being stroke, and thus, these events may never come up for adjudication by the central blinded adjudication panel.

Some lessons can be inferred from key VERiTAS protocol modifications made during the course of the study.5 The investigators stopped enrolling patients with unilateral vertebral artery stenosis or occlusion because most of these patients had normal distal flow status demonstrated on QMRA. Ending the enrollment was done to preserve statistical power to address the primary aim of the study, namely, whether low distal flow represented a risk for subsequent VB stroke. It is regrettable, though, that there were insufficient resources to increase the final sample size to include a large analyzable subset of patients with unilateral vertebral arterial stenosis or occlusion. Adapting the study in this way would have allowed assessment of whether unilateral disease could be considered low risk. Physicians might be able to identify many low-risk patients with symptomatic VB disease simply with a conventional magnetic resonance or computed tomographic angiogram. In addition, the investigators ultimately excluded 8 patients from the final analysis because the patients had isolated unilateral vertebral artery occlusion and the investigators could not be certain that occlusion in these patients was due to atherothrombosis rather than dissection. Again, ideally, enough patients with isolated unilateral vertebral artery occlusion would have been enrolled to provide reasonable estimates of the relative risk of this condition vs other patterns of VB disease.

VERiTAS treated VB stroke as a dichotomous outcome: either patients had it or they did not.5 This is a common practice in stroke prevention studies. Further characterization of
the stroke end points in VERITAS may be informative. The results of VB strokes can range from distracting to devastating. Strokes in patients with low distal flow may be more or less severe and larger or smaller than those without low distal flow. One methodologic obstacle to detailed characterization of stroke end points is that patients may not present to the enrolling clinical center with their end point stroke. Rather, patients may seek care at centers that are relatively unsophisticated in the evaluation of acute stroke. Fortunately, image-negative cerebral infarcts are becoming less prevalent with the ubiquity of brain magnetic resonance imaging.

Medical therapy in VERITAS involved encouraging treating physicians to adhere to evidence-based guidelines on secondary stroke prevention. However, it is becoming increasingly apparent that encouraging physicians to follow guidelines is insufficient to ensure optimal medical management. At 24 months, although 100% of the analyzed patients were receiving antithrombotic agents, only 41% met the risk factor target level for blood pressure. Only 59% of the analyzed patients met the body mass index target level of less than 30 (calculated as weight in kilograms divided by height in meters squared) at 24 months. Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), a phase 3 trial of endarterectomy vs stenting for prevention of stroke in patients with high-grade symptomatic and asymptomatic cervical carotid stenosis, also encouraged treating physicians to adhere to guidelines, and the result was that less than 40% of the patients had optimal risk factor control even after being in the trial for 48 months.8

The rates of VB stroke observed in VERITAS (28% for patients with low distal flow and 9% for the remaining patients),3 likely would have been lower had patients received centrally guided intensive medical therapy and lifestyle coaching as was done in SAMMPRIS.2 Patients in SAMMPRIS had half the risk of key vascular end points compared with comparable patients in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, where patients did not receive the same type of intensive medical therapy.9 CREST-2 is currently testing intensive medical therapy with or without revascularization in patients with asymptomatic cervical carotid stenosis across 62 actively recruiting centers.10 The VERITAS investigators suggest that intensive medical therapy administered in trials is not achievable in the real world setting. However, such criticism may be less valid over time, as the health care system begins to incentivize population health.11

One of the key components in intensive medical therapy is tight blood pressure control, something not easily achieved without an iterative, stepped approach that often requires multiple medications. However, it is safe to tightly control blood pressure in individuals with symptomatic VB disease and low distal flow? Similar safety concerns exist for patients with symptomatic carotid occlusion. However, patients with symptomatic carotid occlusion and ipsilateral increased oxygen extraction fraction randomized to the medical management arm of the Carotid Occlusion Surgery Study (COSS) trial had a lower risk of stroke with lower blood pressure.12 Pending compelling evidence to the contrary, it may be reasonable to strive for tight blood pressure control in patients with symptomatic VB disease whether or not there is distal low flow.

VERITAS shows the high risk of low distal flow to symptomatic stenosis in the VB system.5 Stenting (or primary angioplasty) may be of net benefit to these patients, but it would be premature to act on this assumption without putting it to the test in future trials. These same patients may be at high risk for complications of an intervention. Meanwhile, it is not only appropriate, it is essential to provide intensive medical therapy for these patients.

ARTICLE INFORMATION

Author Affiliation: Department of Neurology, Mayo Clinic Florida, Jacksonville.

Corresponding Author: James F. Meschia, MD, Department of Neurology, Mayo Clinic Florida, 4500 San Pablo Rd, Cannaday Bldg, 2E, Jacksonville, FL 32224 (meschia.james@mayo.edu).


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REFERENCES


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