

Asymptomatic Carotid Stenosis

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Introduction

Case Presentation: A 78-year-old woman, a retired primary school principal, was referred for a second opinion regarding a recommendation that she undergo stenting of a severe carotid stenosis. A bruit in the right carotid had led to a carotid ultrasound study and a diagnosis of 80% stenosis of the right internal carotid artery. This was confirmed by computed tomography angiography, which also showed moderate stenosis of the right vertebral origin. Her only symptoms were vertebrobasilar: She recently had an episode of vertigo accompanied by numbness in the left side of her tongue, which lasted 10 minutes. Her only past history was of a partial hysterectomy at 54 years of age. Her only medications were atorvastatin 10 mg daily and amlodipine 5 mg daily. Her father died at 62 years of age of a myocardial infarction; her mother died at 88 years of age with Alzheimer disease, and a brother was alive and well at 74 years of age. Her height was 5'7", weight 150 pounds. Her blood pressure was 137/78 mm Hg; her general physical examination was unremarkable except for the right carotid bruit and diagonal ear lobe creases. Her neurological examination was normal except for reduced nasal tickle and reduced corneal sensation on the left; there was no indication of cognitive decline. Her serum lipids (in mg/dL) were total cholesterol 164, triglycerides 125, high-density lipoprotein 1.2, and low-density lipoprotein 2.56.

Her cardiologist told her that she was a walking time bomb and offered to stent her right internal carotid artery, but she subsequently read a column by Jane Brody in *The New York Times* on August 16, 2012,¹ and wanted more information about the potential risks and benefits of stenting.

Because her symptoms were in the vertebrobasilar territory, her carotid stenosis was asymptomatic. To determine whether she might be a candidate for carotid endarterectomy (or stenting, which is less desirable because it carries twice the risk of stroke), a 1-hour transcranial Doppler embolus detection study was performed. This showed that she did not have microemboli from the asymptomatic carotid stenosis. The patient was therefore advised that she would be better treated with intensive medical therapy than with endarterectomy or stenting. She was advised to follow a Cretan Mediterranean diet, exercise for a half hour daily, add aspirin 81 mg daily and perindopril 4 mg daily, increase the dose of atorvastatin to 40 mg daily, and add ezetimibe 10 mg daily.²⁻⁴ Repeat transcranial Doppler embolus detection was planned in 1 year.

Background

In the field of clinical pharmacology, it is not regarded as legitimate to compare drugs across studies; to compare the efficacy and safety of one treatment against another, therapies should be assessed in a double-blind, head-to-head comparison of one treatment versus the other. Many confounders, including the baseline characteristics of the patients included in studies, could account for different outcomes. A comparison of treatments across studies is regarded as equivalent to comparing apples and oranges. For this reason, it is disturbing that in the United States, the indication for $\approx 90\%$ of carotid endarterectomy and stenting is asymptomatic carotid stenosis⁵ based on extrapolation from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), a modern study of stenting versus endarterectomy without a medical arm of therapy,⁶ to historical results from the medical arms of 2 early studies of carotid endarterectomy,^{7,8} the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Stenosis Trial (ACST), which were performed during a time when medical therapy was much less effective.

This extrapolation is not valid, because with modern medical therapy, the risk of stroke in patients with asymptomatic carotid stenosis is much lower than it was in the 2 historical trials that are used to justify this practice. To illustrate this, [Figure 1](#) shows the decline in serum levels of low-density lipoprotein cholesterol

among patients referred for secondary stroke prevention between 1997 and 2007.

Figure 1.

Decline in plasma levels of low-density lipoprotein (LDL) cholesterol at the time of referral to my vascular prevention clinics, by year, from 1997 to 2007. LDL cholesterol is shown in millimoles per liter; to convert to milligrams per deciliter, multiply by 38.67. The data are from 4378 patients referred to the Stroke Prevention Clinic or the Premature Atherosclerosis Clinic at University Hospital, London, Ontario, Canada. Reproduced from Spence et al.⁴

Decline in the Risk of Stroke in Asymptomatic Carotid Stenosis

Although the annual risk of stroke in the ACAS and ACST trials was $\approx 2\%$ per year,^{7,8} it is increasingly clear that with modern intensive medical therapy, the risk of stroke is much lower than the risk of either stenting or endarterectomy in CREST. In CREST, the procedural (30-day) risk of stroke or death for asymptomatic patients was 2.5% for stenting and 1.4% for endarterectomy; the 4-year risk was 4.5% with stenting and 2.7% with endarterectomy. Compared with the historical risks in ACAS and ACST, the risk of stenting or endarterectomy appears reasonable.

However, with modern intensive medical therapy, the risk of stroke in patients with asymptomatic carotid stenosis is now much lower than it was when ACAS and ACST were conducted. A prospective population-based study in Oxfordshire, United Kingdom,⁹ a clinic-based observational study in Canadian patients attending a stroke prevention clinic,¹⁰ and a meta-analysis of published studies¹¹ have all shown that the risk of stroke in patients with asymptomatic carotid stenosis is now $\approx 0.5\%$ per year. This is substantially lower than the risk of either stenting or endarterectomy in CREST. Objections from advocates of intervention that severity of stenosis was not taken into account in these studies were answered in a meta-analysis by Naylor.¹² In contrast to symptomatic carotid stenosis, in asymptomatic carotid stenosis, the severity of stenosis does not predict risk.¹³ Therefore, the risks of stroke or death in CREST cannot legitimately be used to justify stenting or endarterectomy in unselected patients with asymptomatic carotid stenosis.

Can Patients With Asymptomatic Carotid Stenosis Who Are at Higher Risk Be Identified?

There are ways to assess which patients with asymptomatic carotid stenosis are at higher risk of stroke. We showed in 2005¹⁴ that transcranial Doppler embolus detection identified the 10% of patients who would be at high enough risk to benefit from endarterectomy or stenting ([Figure 2](#)); this was validated in 2010.¹⁵ Additional indications of high-risk asymptomatic carotid stenosis include ulceration of carotid plaques on 3-dimensional carotid ultrasound¹⁶ ([Figure 3](#)), intraplaque hemorrhage on magnetic resonance imaging,¹⁷ and echolucency of carotid plaques.¹⁸ New approaches to identifying vulnerable plaque that may justify endarterectomy or stenting are being studied; these include examination of plaque inflammation on positron emission spectroscopy to identify inflamed plaques.¹⁹

Figure 2.

Microembolic signal on transcranial Doppler. **A**, M-mode recording from the middle cerebral artery; **arrow** points to an image of a microembolus. **B**, Doppler velocity envelope; **arrow** points to high-intensity transit signal created by the microembolus.

Figure 3.

Carotid plaque ulceration by 3-dimensional ultrasound. Carotid plaque images obtained with 3-dimensional ultrasound and analyzed on 3D Quantify software. The carotid artery can be examined in any axis for detection of ulcers in atherosclerotic plaques. White **arrows** show ulcers. Reproduced from Madani et al.¹⁶

What Is Needed

To sort out this problem, what is needed is a randomized controlled trial with a medical arm that compares stenting, endarterectomy, and modern intensive medical therapy in patients with asymptomatic carotid stenosis. The CREST-2 trial proposes exactly that comparison. It is to be hoped that the study will be funded, because the results are urgently needed to stem the flood of inappropriate stenting of patients such as the case subject presented in this report.

The Patient

With asymptomatic carotid stenosis, this patient clearly warrants intensive

medical therapy to reduce her high risk of coronary events in addition to her risk of stroke.²⁰ With her negative transcranial Doppler embolus detection results, she will be at lower risk of stroke with medical therapy than with stenting or endarterectomy. So would 90% of patients with asymptomatic carotid stenosis.

References

Original URL:

<http://circ.ahajournals.org/content/127/6/739.long>