

## THE PRESENT AND FUTURE

### REVIEW TOPIC OF THE WEEK

# How Recent Data Have Impacted the Treatment of Internal Carotid Artery Stenosis



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#### ABSTRACT

Carotid atherosclerosis accounts for approximately 10% of ischemic stroke cases. Multifaceted medical therapy reduces the risk of stroke in patients with carotid stenosis. Revascularization with endarterectomy or stenting can benefit select patients. In recent years, new information has been obtained regarding optimal selection of revascularization candidates. In addition, new concepts have been formulated regarding the relationship between carotid stenosis and vascular cognitive impairment. Finally, the declining rate of stroke with improved medical therapy has led to the launch of new clinical trials to determine the contemporary risk/benefit ratio of revascularization relative to aggressive medical therapy. (J Am Coll Cardiol 2015;65:1134–43) © 2015 by the American College of Cardiology Foundation.

Carotid atherosclerosis accounts for 7% to 10% of ischemic strokes. Intensive medical therapy and carotid revascularization procedures reduce the risk of stroke. Several developments in the area of carotid stenosis treatment include carotid artery stenting (CAS) and improvements in multimodal medical therapy.

In this update, we shall review current recommendations for management of symptomatic and asymptomatic internal carotid artery (ICA) stenosis. In addition, we shall identify new clinical correlates in “asymptomatic” patients and review the impact of contemporary medical therapy on stroke rates for carotid stenosis patients. Finally, we will discuss current clinical trials regarding ICA stenosis.

#### PREVALENCE AND PREDICTORS OF CAROTID STENOSIS AND STROKE RISK

In the Framingham Heart Study, the degree of carotid stenosis was predicted by common baseline vascular

risk factors such as older age, cigarette smoking, systolic blood pressure, and total cholesterol (1). Patients with asymptomatic ICA stenosis of 60% to 99% have an annual risk of stroke, based on 1990s medical therapy, of 2% to 2.5% per year (2,3). On the other hand, symptomatic carotid stenosis over 70% carries an annual stroke risk of 10% to 15%, based on 1990s medical therapy (4).

The prevalence of severe ( $\geq 70\%$ ) asymptomatic stenosis in the general population varies according to age and baseline risk factors. In a meta-analysis of 4 individual participant longitudinal studies, the prevalence of severe stenosis ranged from 0% to 3.1% in various age and sex groups (5). Among men, severe stenosis was present in 0.1% (95% confidence interval [CI]: 0% to 0.3%) of subjects <50 years of age and in 3.1% (CI: 1.7% to 5.3%) of those >80 years of age. Among women, the prevalence of severe stenosis was minimal (95% CI: 0% to 0.2%) in subjects <50 years of age and 0.9% (95% CI: 0.3% to 2.4%) in women >80 years of age. The same investigators developed a

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predictive instrument for identifying the presence of severe stenosis. Elements of the score are provided in **Table 1**.

Although some advocate screening higher-risk patients with coronary artery disease or peripheral arterial disease for ICA stenosis, the evidence to support this practice is limited. The US Preventive Services Task Force reviewed studies pertaining to population screening through 2014 and concluded that routine screening of the general population to detect asymptomatic ICA stenosis is not warranted (6). Among the reasons for this recommendation were the following: 1) concern that low complication rates after carotid endarterectomy (CEA) and CAS could not be replicated in community practice; 2) lack of studies comparing CAS to optimal medical therapy; 3) falling rates of stroke with contemporary medical therapy; and 4) significant generation of “false positives” with duplex ultrasound as the screening tool.

**CURRENT EVIDENCE FOR THE TREATMENT OF CAROTID STENOSIS**

Contemporary recommendations for patients with symptomatic or asymptomatic ICA stenosis include medical therapy for all patients and revascularization (CEA or CAS) for select patients. With regard to medical therapy, all patients should receive the core elements of vascular disease therapy (7). This includes the following: 1) antiplatelet therapy; 2) aggressive treatment of dyslipidemia; 3) treatment of hypertension to national guideline targets; 4) treatment of diabetes mellitus to national guideline targets; 5) smoking cessation; and 6) lifestyle modification, including dietary modification and exercise.

It is beyond the scope of this review to discuss each of these in detail, but certain observations are worthwhile. For antiplatelet therapy, aspirin is typically used (81 to 325 mg/day) for asymptomatic

patients, although there is no level A evidence that aspirin reduces stroke in the setting of asymptomatic carotid stenosis (ACS). There are no data comparing alternative antiplatelet regimens (e.g., clopidogrel or aspirin plus extended-release dipyridamole) to aspirin for patients with ACS. For symptomatic patients, either aspirin, clopidogrel, or aspirin plus extended-release dipyridamole are recommended (8). Ongoing trials are evaluating the 90-day use of clopidogrel plus aspirin compared with aspirin alone for patients with acute transient ischemic attack (TIA) and minor stroke (POINT [Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke] trial), as well as ticagrelor compared with aspirin (SOCRATES [Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes] trial), of whom a small subgroup could have symptomatic carotid stenosis. Currently, long-term treatment with aspirin and clopidogrel is not recommended in stroke prevention guidelines (8).

The role of lipid lowering with statins in patients with carotid stenosis has been established from several sources. In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, atorvastatin 80 mg/day was compared with placebo in patients with a prior stroke or TIA (9). In a subgroup analysis of patients with carotid stenosis, 1,007 patients had a mean stenosis of 51% (10). In the patients given atorvastatin, low-density lipoprotein (LDL) was lowered from 132 mg/dl at baseline to an average of 70 mg/dl during trial follow-up. In the patients given placebo, LDL decreased from 133 to 130 mg/dl. The atorvastatin-treated patients had a 33% reduction in any stroke, a 43% reduction in coronary events, and a 56% reduction in later carotid revascularization procedures. In ACST (Asymptomatic Carotid Surgery Trial), there was increasing use of lipid-lowering treatment during the course of the trial (3). For patients not undergoing lipid-lowering therapy and treated in the medical arm of the study, the 10-year risk of stroke was 24.9%, much greater than the 14.5% observed among patients who were treated with lipid-lowering therapy. As a result of these observations (and other studies), treatment with high-potency statins is an important element of the management of patients with carotid stenosis (8,11).

As pertains to carotid revascularization, current recommendations were revised on the basis of data from CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial) (12). In CREST, 2,502 patients with either symptomatic stenosis or ACS were randomly assigned to either CEA or CAS. Patients were

**ABBREVIATIONS AND ACRONYMS**

- ACS** = asymptomatic carotid stenosis
- CAS** = carotid artery stenting
- CEA** = carotid endarterectomy
- ICA** = internal carotid artery
- LDL** = low-density lipoprotein
- MI** = myocardial infarction
- MMSE** = Mini-Mental Status Examination
- OMT** = optimal medical therapy
- TIA** = transient ischemic attack

**TABLE 1 Predictors of the Presence of Severe (>70%) Carotid Stenosis\***

| Predictor                              | Odds Ratio (95% Confidence Interval) |
|--|--------------------------------------|
| Age (per 10 yrs)                       | 2.2 (1.7-2.8)                        |
| Male                                   | 2.5 (1.7-3.6)                        |
| History of vascular disease            | 2.5 (1.7-3.5)                        |
| Systolic blood pressure (per 10 mm Hg) | 1.3 (1.2-1.5)                        |
| Cholesterol/HDL ratio (per point)      | 1.2 (1.1-1.4)                        |
| Diabetes mellitus                      | 1.6 (1.0-2.5)                        |
| Current smoking                        | 3.0 (2.1-4.4)                        |

\*Data are from de Weerd et al. (5).  
 HDL = high-density lipoprotein.

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