

Carotid Artery Stenosis in Women

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Stroke imposes a high socioeconomic burden and persistently ranks among the top 3 causes of death and premature disability worldwide.^{1,2} Women have a higher lifetime risk of stroke than do men.³ Approximately 7% to 12% of all strokes and 9% to 15% of all ischemic strokes are attributable to advanced carotid artery stenosis (50%–99%).⁴ Medical management of atherosclerotic disease has decreased this risk during the last several decades; regardless, patients with advanced carotid artery stenosis have a relatively high risk of complications.^{5–7} Women are more likely to have strokes or to die after carotid artery procedures that are intended to reduce stroke risk, including surgical carotid endarterectomy (CEA) and endovascular carotid artery stenting (CAS).^{8–15} Ongoing clinical investigation is needed to characterize optimal treatments for women with carotid artery stenosis.

Differences in carotid plaque may explain observed sex differences in treatment outcomes. For example, men have larger-volume carotid plaque than do women, and plaque volume is a strong predictor of ischemic events.¹⁶ Histologically, women have less inflammatory, more stable carotid plaque, with more smooth-muscle infiltration and fewer thin, fibrous caps and lipid-rich necrotic cores, which tend to rupture and embolize.^{17,18} Such differences may explain the comparatively shorter high-risk period after stroke in women who have carotid stenosis.^{9,10,19} The higher procedural risk in women may be partially related to their smaller carotid arteries²⁰ and their tendency to present later in life with more comorbidities.^{21,22}

Carotid stenosis is not always caused by atherosclerosis. Fibromuscular dysplasia (FMD), a noninflammatory condition, can cause arterial stenosis, dissection, or aneurysm.²³ It is more prevalent in women and generally presents in younger patients than does atherosclerosis.²³ Fibromuscular dysplasia typically manifests itself with the classic “beads-on-a-string” or web appearance on images, with involvement of the mid and distal parts of the internal carotid artery.^{23,24} Once thought to be benign, FMD is now recognized as an important cause of stroke in young adults.^{23,24} Symptomatic FMD may be treated with CEA or angioplasty, depending on lesion characteristics.²⁵ Because of pathologic underlying arterial architecture, the high risk of dissection and residual stenosis from angioplasty alone can necessitate stenting.²⁶

Advances in medical management during the last 3½ decades have greatly improved the prognosis of patients with atherosclerotic carotid disease. The average annual ipsilateral stroke rate in asymptomatic patients with advanced disease has decreased by more than 67%, corresponding with advances in diagnosis and modification of arterial disease risk factors.^{5–7} Guideline-directed medical management includes statins, antiplatelet agents such as aspirin, blood pressure control, smoking cessation, and glycemic control.²⁵ Investigators in early trials of CEA in asymptomatic patients—chief among these the Asymptomatic Carotid Atherosclerosis Study (ACAS)⁸ and the Asymptomatic Carotid Surgery Trial (ACST)¹²—underestimated the benefit of medical therapy alone. Although ACAS was underpowered statistically, the women assigned to CEA had a 17% decrease in the 5-year risk of ipsilateral stroke or perioperative stroke or death (95% CI, –0.96 to 0.65).⁸ Nevertheless, in randomized trials, no definite benefit of CEA was seen in women who had asymptomatic carotid stenosis.^{8,12}

In contrast, symptomatic women who underwent CEA for high-grade stenosis (70%–99%) had significant overall stroke prevention.²⁷ In a pooled analysis of the North American Symptomatic Carotid Artery Endarterectomy Trial and the European Carotid Surgery Trial, these women had a 9.9% absolute reduction (95% CI, 1.8–18) in 5-year risk of ipsilateral ischemic stroke or death, within 30 days of CEA.²⁷ When randomized within 2 weeks of their last ischemic event, these women

had a 41.7% absolute risk reduction over 5 years.¹⁹ No significant benefit was seen, however, when CEA was performed later than 2 weeks after randomization of women with 70% to 99% stenosis, or in those with 50% to 69% stenosis regardless of timing.¹⁹ Notably, despite this potential benefit, symptomatic women are less likely than men to undergo expeditious CEA.²²

Although developed as a less hazardous alternative to CEA, CAS has been associated with increased risk of periprocedural events, especially stroke due to catheter manipulation in the aortic arch and carotid artery. The increased risk of stroke has not been compensated for by a decreased risk of myocardial infarction, as was initially hypothesized.^{6,14} A meta-analysis of symptomatic women who underwent CEA or CAS revealed a periprocedural rate of stroke or death 1.53 times higher after CAS than after CEA (95% CI, 1.02–2.29).¹⁴ For asymptomatic patients, even the largest randomized trials that compared CEA with CAS have been underpowered, thus precluding the ability to determine any clinically significant differences in rates of stroke or death.^{6,28,29} In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), a subgroup of 872 mixed asymptomatic and symptomatic women assigned to CAS were significantly more likely—1.8 to 2.6 times—to have periprocedural stroke or to die than were those assigned to CEA¹³ and somewhat more likely than were men (OR=1.51; 95% CI, 0.87–2.6). The latter sex-related trend was not seen in association with CEA (OR=0.89; 95% CI, 0.4–1.96).¹³ In ACT 1, a contemporary trial with experienced operators using embolic-protection devices, there is preliminary evidence of improved outcomes beyond the 30-day periprocedural period in asymptomatic women undergoing CAS when compared with CEA.³⁰ However, future publication of relevant data, including all periprocedural events, is necessary for appropriate interpretation.

In conclusion, major clinical attention should focus on maximizing medical therapy in all women who have carotid artery stenosis. More clinical trials are needed to evaluate the efficacy and selection of modern procedural interventions. This is especially true for women, who have been underrepresented in major investigations into carotid stenosis. Multiple ongoing large clinical trials might shed light on many prevailing clinical questions^{31–33}; to advance clinical practice, analyses of their results must include known sex- and age-specific differences in disease behavior.

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