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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 arteries[20] 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 CEA[13] 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.

References

1. World Health Organization Global Health Observatory (GHO) data. World Health Statistics 2014. Available at: http://www.who.int/gho/publications/world_health_statistics/en/ [cited 2018 Apr 5].
2. GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, Abd-Allah F, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet 2015;386(10009):2145-91.
3. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. The lifetime risk of stroke: estimates from the Framingham Study. Stroke 2006;37(2):345-50.
4. Abbott AL, Bladin CF, Levi CR, Chambers BR. What should we do with asymptomatic carotid stenosis? Int J Stroke 2007;2 (1):27-39.
5. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 2009;40(10):e573-83.
6. Abbott A. Critical issues that need to be addressed to improve outcomes for patients with carotid stenosis. Angiology 2016; 67(5):420-6.
7. Abbott AL, Silvestrini M, Topakian R, Golledge J, Brunser AM, de Borst GJ, et al. Optimizing the definitions of stroke, transient ischemic attack, and infarction for research and application in clinical practice. Front Neurol 2017;8:537.
8. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273(18):1421-8.
9. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339(20):1415-25.
10. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351(9113):1379-87.
11. Bond R, Rerkasem K, Cuffe R, Rothwell PM. A systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. Cerebrovasc Dis 2005;20 (2): 69-77.
12. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet 2010;376(9746):1074-84.
13. Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD 2nd, Gonzales NR, et al. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Lancet Neurol 2011;10(6):530-7.
14. Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev 2012; (9):CD000515.
15. Touze E, Trinquart L, Felgueiras R, Rerkasem K, Bonati LH, Meliksetyan G, et al. A clinical rule (sex, contralateral occlusion, age, and restenosis) to select patients for stenting versus carotid endarterectomy: systematic review of observational studies with validation in randomized trials. Stroke 2013;44 (12):3394-400.
16. Iemolo F, Martiniuk A, Steinman DA, Spence JD. Sex differences in carotid plaque and stenosis. Stroke 2004;35(2):477-81.
17. Hellings WE, Pasterkamp G, Verhoeven BA, De Kleijn DP, De Vries JP, Seldenrijk KA, et al. Gender-associated differences in plaque phenotype of patients undergoing carotid endarterectomy. J Vasc Surg 2007;45(2):289-97.
18. Ota H, Reeves MJ, Zhu DC, Majid A, Collar A, Yuan C, DeMarco JK. Sex differences in patients with asymptomatic carotid atherosclerotic plaque: in vivo 3.0-T magnetic resonance study. Stroke 2010;41(8):1630-5.

19. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Sex difference in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischemic attack and nondisabling stroke. Stroke 2004;35(12): 2855-61.
20. Krejza J, Arkuszewski M, Kasner SE, Weigele J, Ustymowicz A, Hurst RW, et al. Carotid artery diameter in men and women and the relation to body and neck size. Stroke 2006; 37(4):1103-5.
21. Kapral MK, Ben-Yakov M, Fang J, Gladstone DJ, Saposnik G, Robertson A, Silver FL. Gender differences in carotid imaging and revascularization following stroke. Neurology 2009;73(23):1969-74.
22. Poisson SN, Johnston SC, Sidney S, Klingman JG, Nguyen-Huynh MN. Gender differences in treatment of severe carotid stenosis after transient ischemic attack. Stroke 2010;41(9): 1891-5.
23. Olin JW, Gornik HL, Bacharach JM, Biller J, Fine LJ, Gray BH, et al. Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. Circulation 2014;129(9):1048-78.
24. Haussen DC, Grossberg JA, Bouslama M, Pradilla G, Belagaje S, Bianchi N, et al. Carotid web (intimal fibromuscular dysplasia) has high stroke recurrence risk and is amenable to stenting. Stroke 2017;48(11):3134-7.
25. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary [published erratum appears in Stroke 2011;42(8):e541]. Stroke 2011;42(8):e420-63.
26. Tekieli LM, Maciejewski DR, Dzierwa K, Kablak-Ziembicka A, Michalski M, Wojcik-Pedziwiatr M, et al. Invasive treatment for carotid fibromuscular dysplasia. Postepy Kardiol Interwencyjnej 2015;11(2):119-25.
27. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004;363(9413): 915-24.
28. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis [published errata appear in N Engl J Med 2010;363(2):198 and N Engl J Med 2010;363 (5):498]. N Engl J Med 2010;363(1):11-23.
29. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. N Engl J Med 2016; 374(11):1011-20.
30. Ansel GM. ACT 1: Carotid stenting beneficial in women, heavy atherosclerotic burden [Internet]. Available at: https://www.healio.com/cardiac-vascular-intervention/cerebrovascular/news/online/%7B8fcb99d9-5626-4399-967c-bfce2a0d12fb%7D/act-1-carotid-stenting-beneficial-in-women-heavy-atherosclerotic-burden [2007 Sep 13; cited 2018 Apr 9].
31. Carotid revascularization and medical management for asymptomatic carotid stenosis trial (CREST-2) [Internet]. Available at: https://clinicaltrials.gov/ct2/show/NCT02089217 [updated 2018 Mar 29; cited 2018 Apr 9].
32. Endarterectomy combined with optimal medical therapy (OMT) vs OMT alone in patients with asymptomatic severe atherosclerotic carotid artery stenosis at higher-than-average risk of ipsilateral stroke (ACTRIS) [Internet]. Available at: https://clinicaltrials.gov/ct2/show/NCT02841098 [updated 2018 Jan 25; cited 2018 Apr 9].
33. The 2nd European Carotid Surgery Trial (ESCT-2). Available at: http://s489637516.websitehome.co.uk/ECST2/index2.htm [cited 2018 Apr 9].