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Carotid stenosis in women: time for a reappraisal

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ABSTRACT

The treatment approach for patients with internal carotid artery stenosis is receiving increased scrutiny. Major advances in optimal medical therapy have been associated with a declining stroke rate for symptomatic and asymptomatic patients with carotid stenosis. Customising treatment according to gender is worthy of consideration, since earlier clinical trials showed reduced benefit with carotid endarterectomy in women compared to men. In this review, clinical trial results in women are summarised, studies pertaining to carotid plaque imaging in men and women are discussed and new clinical trials are identified. Finally, the rationale for a women's carotid trial is provided.

INTRODUCTION

Stroke is the second leading global cause of death and the fifth leading cause of death in the USA. Stroke is also a significant cause of disability, with 39.4 million daily adjusted life years (DALYs) lost due to ischaemic stroke globally, in 2010.[1] Women are disproportionately affected by stroke, in part because they live longer, but they also have worse recovery from stroke than men.[2] Mechanisms of ischaemic stroke include large artery atherosclerosis, cardioembolism, small artery occlusion, stroke of other determined aetiology (ie, dissection, vasculopathy, prothrombotic disorder) and stroke of undetermined aetiology.[3] Large-vessel cerebrovascular disease accounts for about 15–20% of ischaemic stroke, and internal carotid artery (ICA) stenosis accounts for about half of these.[4 5]

In order to make medical decisions regarding revascularisation for patients with carotid disease, we use clinical trial data that dichotomise carotid disease into symptomatic and asymptomatic disease and focus largely on degree of stenosis. We weigh the expected benefit of carotid revascularisation with the potential surgical risk of periprocedural stroke or other medical complication. It is known that gender is a major determinant of the long-term outcome after carotid revascularisation. Two big issues complicate our ability to make evidence-based clinical decisions for any patient, but especially for women. First, the clinical trials we use to guide our decision-making in patients with carotid disease suffer from underrepresentation of women. Those that do assess outcomes in women have lacked power for adequate analysis, and this limits the generalisability of results among men and women. Second, it must be noted that many of the seminal trials were conducted in an era prior to our current standard which includes potent statin, antithrombotics and aggressive cardiovascular risk factor control, including tight blood pressure control, glycemic control, tobacco cessation and exercise. This brings into question whether we have an accurate understanding of the risk of stroke in the setting of modern medical therapy and how this changes the risk–benefit calculation of carotid revascularisation, specifically in women. Should we be making decisions based on data that is >20 years old? Do we have enough data on which to base decisions on optimal treatment for women?

In this article, we will review the data on carotid revascularisation in women in symptomatic and asymptomatic disease. We will discuss the usefulness and appropriateness of optimal medical therapy. Additionally, we will discuss possible aetiologies of gender-related differences in outcomes and the potential role of advanced imaging for risk stratification. Finally, we will discuss the importance of ongoing and new clinical trials to determine the benefit and risk of carotid revascularisation in women in the current era of medical therapy.

WOMEN AND ASYMPTOMATIC CAROTID DISEASE

Asymptomatic carotid is defined as the presence of atherosclerotic narrowing of the extracranial ICA in individuals without a history of recent ipsilateral carotid territory ischaemic stroke or transient ischaemic attack (TIA). The US Preventive Services

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Task Force recommends against screening for asymptomatic carotid artery stenosis in the general adult population, but nevertheless, with the availability of non-invasive diagnostic testing and ease, many patients are found to have asymptomatic disease and require guidance on management. In the prestatin era, annual rate of stroke in asymptomatic disease with >75% stenosis was 2–2.5% and 1.3% with <75% stenosis.[4] The medical management of patient with asymptomatic carotid disease has significantly improved over the past 20 years, with statin therapy, aggressive BP control and focus on lifestyle modification. Thus, these already relatively low numbers are likely not representative of the current setting of medical practice. For this reason, the management of asymptomatic disease is persistently a topic of debate. More recent studies showed between 0.5% and 1% per year annual rate of stroke in asymptomatic patients.[6–8] In a meta-analysis of 11 asymptomatic studies, rate of ipsilateral stroke/TIA and any stroke TIA on medical therapy was as low as 1%, which brings into question intervention for anyone with asymptomatic disease, let alone women, especially in the era of current medical therapy.[6]

The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) enrolled only 34% women. ACAS and ACST enrolled asymptomatic patients with >60% stenosis and assessed outcomes of carotid endarterectomy (CEA) +medical therapy versus medical therapy alone. ACAS showed an overall combined 5-year rate of ipsilateral stroke, perioperative stroke and death of 5.1% in CEA arm versus 11% in medical arm with absolute risk reduction (ARR) 5.1% and relative risk reduction (RRR) 53%. Post hoc subgroup analysis showed a higher risk of operative stroke or death in women versus men (3.6% vs 1.7%). Five year ARR for CEA was only 1.4% in women compared with 8% in men.[9] ACST showed an overall 6.4% risk of recurrent stroke in the surgical group versus 11.8% in the medical group, with an ARR of 5-year ipsilateral stroke, perioperative stroke or death of 5.3%. Unlike ACAS, ACST had prespecified sex subgroup analysis. Women had a lower ARR at 5 years than men (4.1% vs 8.2%).[10] A meta-analysis of data from ACAS and ACST1 showed a benefit of CEA for men, but not women in 5 year risk of any stroke or perioperative death (women OR 0.96, 95% CI 0.63 to 1.45 vs men OR 0.49, 95% CI 0.36 to 0.66).[11 12]

Preplanned analysis of sex differences in asymptomatic patients in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) did not show significant differences in 30-day composite perioperative risk of stroke/death/myocardial infarction (MI) (3.7% in women, 3.5% in men), stroke and death (1.6% in women, 1.3% in men) or MI (2.1% in women and 2.3% in men) between men and women who underwent CEA.[13] This finding is discordant with findings from older randomised control trials that suggested less benefit of CEA for women compared to men. However, statistical power for subgroup analysis by sex may have been limited by low number of women enrolled.

We do not currently have reliable evidence of benefit for women with asymptomatic carotid disease. Women have a higher perioperative risk, as well as lower risk of stroke without surgery. Given that more recent studies showed between 0.5% and 1% per year annual rate of stroke in asymptomatic patients overall, a lower number than in older studies, and given the inconsistencies in benefit of CEA or carotid artery stenting (CAS) in asymptomatic women, it is reasonable to consider medical therapy for women who are not enrolled in a clinical trial to assess this question. We recommend using all available risk reduction strategies in these patients, especially in light of the fact that carotid disease, even if asymptomatic, can be a marker of increased risk for CAD and MI.

In North America, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)-2 (clinical trials.gov identifier: NCT02089217) trial is actively enrolling patients with asymptomatic 70–99% stenosis in a National Institute of Neurological Disorders and Stroke-sponsored trial comparing intensive medical therapy (IMT) alone versus either CEA or CAS (This trial will have prespecified analysis of sex subgroups and will ideally enrol a more representative percentage of women; ideally >40%). This will help ensure clinicians have optimal information on the risk and benefit ratio of CEA and CAS for asymptomatic stenosis in women specifically.

WOMEN AND SYMPTOMATIC CAROTID DISEASE

Symptomatic carotid disease is defined as TIA or stroke ipsilateral to the carotid stenosis in the preceding 180 days. In the prestatin era, annual rate of stroke with symptomatic carotid disease with >70% stenosis was 10–15%.[5]

For severe disease, defined as stenosis >70%, two trials published in 1991 provided the initial basis for our current practice of surgical revascularisation with CEA in symptomatic carotid disease. The North American Symptomatic Carotid Artery Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) were published in 1991 and compared CEA alone versus CEA and medical management. It must be emphasised that in the late 1980s and early 1990s, when these trials were conducted and published, statin and optimal medical therapy as we know it today with aggressive blood pressure control, glycemic control and focus on lifestyle modification were not standard of care.

NASCET enrolled 30% women. Overall, NASCET showed 17% ARR (p<0.001) in ipsilateral stroke at 2 years for the CEA arm, with a number needed to treat of six.[14] ECST enrolled 28% women. Overall, ECST showed 11.6% RR in the surgical arm.[15] Combined analysis from NASCET and ESCT (29% women) showed that the 30-day risk of perioperative stroke or death after

CEA was higher in women compared to men (8.7% vs 6.8%). Five-year ARR of ipsilateral stroke and any perioperative stroke or death with surgery was higher in men (2.8% in women and 11% in men).[16]

Pooled analyses from NASCET and the Aspirin and Carotid Endarterectomy (ACE) Study showed increased 30-day risk of death in women (2.3% vs 0.8%, p=0.02).[17] Higher perioperative risk of stroke and death was also shown but was not significant. For stenosis ≥70%, 5-year ARR from stroke was similar for women and men (15.1% vs 17.3%). With 50–69% stenosis, CEA was not beneficial in women (ARR 3%, p=0.94), but was in men (ARR 10%, p=0.02). Women treated with medical therapy had a low risk of stroke. They only benefitted from surgery if they had additional risk factors (age >70, severe hypertension, history of MI or hemispheric event).[17]

Overall, in subgroup analyses of large trials comparing CEA to medical management, women appear to derive less benefit, and this is driven by increased risk of perioperative events. For less severe symptomatic disease, in the 50–69% stenosis range, revascularisation does not appear to be beneficial.

The Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial highlighted the superiority of IMT compared to stenting for intracranial atherosclerotic disease.[18] A similar trial focused on carotid disease revascularisation versus optimal medical therapy is needed. Women need to be included in representative numbers for preplanned subgroup analyses in order to provide a valid analysis of sex interaction.

WOMEN AND CAROTID ARTERY STENTING

CAS was developed as an alternative to CEA for patients who are high surgical risk, is widely available and in practice has been performed in patients with symptomatic and asymptomatic disease. As with CEA trials, CAS versus CEA trials suffer from under-representation of women participants. Another issue is that all comparisons of CAS to medical therapy are indirect; for example, CREST did not have a medical arm to compare medical treatment versus revascularisation.

Various trials have compared CEA and CAS in women with inconsistent results. Some have found that women have worse short-term outcomes with CAS than CEA. An analysis of 20 613 women undergoing carotid intervention from hospitals in the states of New York and Florida found that CAS in symptomatic women was associated with increased perioperative morbidity and mortality when compared to CEA. Combined perioperative stroke/mortality was 10.9% for CAS and 3.8% for CEA in symptomatic women. The difference was less pronounced in asymptomatic women: those who underwent CAS had 3.1% rate of perioperative death or stroke, compared to 1.7% after CEA.[19]

Another analysis from the state of New York hospital discharge database included 27 439 women, and 36 295 men with about 90% asymptomatic patients in both sexes, found increased periprocedural risk with CAS versus CEA in symptomatic women; those who had CAS had higher mortality (4.19% vs 0.47%, p=0.01) and higher rate of combined stroke and mortality (12.09% vs 6.05%, p=0.02).[20]

There is less evidence regarding the comparison of outcomes between men and women. Overall, trials examining CAS versus CEA were not powered to detect a difference between men and women, and thus outcomes of carotid stenting in women compared to men have not been adequately investigated.

A retrospective analysis including 228 patients, with 93 women, showed no significant differences in overall 30-day periprocedural stroke rate (2.1% in women vs 4.2% in men, p=0.48), death rate (0% vs 0.7%, p>0.99) or cardiac events (3.2% vs 0.7%, p=0.3). No differences were noted in long-term survival or stroke-free survival between genders.[21]

In CREST, analysis of asymptomatic and symptomatic patients demonstrated higher rates of combined periprocedural end points (stroke/death/MI) after CAS in women (6.8%, n=455) versus men (4.3%, n=807).[13 22] Women undergoing CAS had higher periprocedural stroke risk than those undergoing CEA (5.5% vs 1.7%, p=0.01). No significant difference was found in men. In 4 year follow-up, there were no significant sex-related differences.[13]

Available evidence suggest that CAS and CEA provide similar long-term outcomes for patients with asymptomatic and symptomatic carotid occlusive disease, but the periprocedural risk of stroke and death may be higher with CAS in women. Given that this elevated risk is in comparison to revascularisation with CEA, which carries higher periprocedural risk for women than men, it is difficult to recommend CAS routinely for women.

TIMING OF CAROTID REVASCULARISATION IN WOMEN

Timing of surgery for symptomatic carotid stenosis is more crucial in women than in men. Post hoc analysis of ECST and NASCET showed that there was significantly less benefit in women, and no change in men, with increased time from most recent index event. For stenosis >70–99%, women had ARR of 41.7% when surgery was conducted within 2 weeks, but this dropped to 6.6% at 2–4 weeks, and after 4–12 weeks, surgery was found to be harmful, with ARR −2.2%. This is in contrast to men, who had ARR 23% at 2 weeks, 23.8% at 2–4 weeks, 18.3% at 4–12 weeks and 20.4% after 12 weeks. For moderate stenosis, women showed ARR 13.8% at 2 weeks, vs 15.2% for men. Within weeks 2–4, surgery was harmful for women, with ARR −5.7%, while men still showed some benefit, with ARR 6.8%. Thus, women benefitted most when CEA was performed within 2 weeks, with a stark decline in benefit the longer out from index event. This was attributed to a more rapid decline in risk of stroke and death over time for women in the medical group.[23 24]

In actual practice, women tend to receive CEA later than men, even in the setting of severe, symptomatic stenosis. A study from California of patients seen at 19 emergency departments found that in patients with a TIA diagnosis and carotid stenosis >70%, the median time to carotid surgery was 18 days in men and 35 days in women. Women were also older than men (74 years vs 71 years) and were more likely to present with a ABCD2 score of ≥4.[25] Thus, timely CEA for symptomatic women is not often achieved in real world settings.

BASIS OF GENDER DIFFERENCES IN CAROTID DISEASE AND REVASCULARISATION OUTCOMES

The traditional risk predictors for stroke in carotid disease have been assumed to be dependent on degree and severity of vessel stenosis, but other factors such as plaque size, composition, intraplaque haemorrhage, ulceration and overall plaque stability should be considered when determining risk of stroke. This is emphasised by the observation that strokes due to carotid disease are usually atheroembolic and less likely due to reduced flow related to the stenosis. Newer pathological and imaging studies highlight that carotid plaque constitution may play a role in determining risk of stroke. Differences in plaque morphology and composition may help explain why women benefit less from carotid revascularisation and more from medical therapy than men. If women have more stable plaques that are less likely to embolise, then removal of the plaque may provide less benefit.

A study of duplex analysis of carotid plaque volume showed that plaque volume was higher in men than women at a comparable degree of stenosis, and that outcome of stroke, myocardial infarction and death were predicted by plaque area and not by degree of stenosis.[26] A study involving 135 women (25% asymptomatic) and 315 men (22% asymptomatic) examined CEA specimens and found that women had more stable, less inflammatory plaque that was less likely to disrupt; they had less atheromatous plaque (22% vs 40%, p>0.001), more smooth muscle (38% vs 24%, p=0.001) and less macrophage infiltration (14% vs 21%, p=0.05). Symptomatic women had the most stable plaque.[27] More prevalent stable plaque in women may help explain a lower benefit CEA.

Another study included 64 women and 67 men with ≥50% asymptomatic stenosis determined duplex ultrasound and assessed factors considered high-risk plaque features on 3 T multicontrast MRI. Men were significantly more likely to have a thin/ruptured fibrous cap (48% vs 17%, p<0.01) and lipid-rich/necrotic core (73% vs 50%, p<0.01) and showed a trend towards more haemorrhage (33% vs 17%, p=0.07).[28] Another study of 763 patients in which histological analysis was performed on carotid plaques found that plaques from men had higher rates of cellularity, more inflammatory infiltrates and less calcification.[29] Increased incidence of high-risk plaque features in men may contribute to explanation of greater benefit of CEA in men versus women.

In the future, advanced imaging modalities may aid in patient selection for carotid revascularisation by helping to determine who is at high risk of stroke based on plaque characteristics, instead of simply basing decision on degree of stenosis.

CLINICAL TRIALS FOCUSED ON WOMEN

On the basis of the findings described above, a carotid stenosis trial focused on women is worthy of serious consideration. A trial in which all the participants are women will circumvent the longstanding lack of representation of women in carotid trials. Further, since women appear to have a lower long-term stroke rate with medical therapy, they represent an ideal group to test the efficacy of current optimal medical therapy strategies. Finally, if the trial is designed to as a 'pragmatic' trial, with relatively few exclusion criteria, then a broader range of women can be enrolled, including greater representation of patients age 80 years and above. Inclusion of elderly patients is especially important considering the ageing of the population in most developed countries.

CONCLUSIONS

CEA to prevent stroke is less beneficial for women compared with men. Women with symptomatic carotid disease have a higher periprocedural risk and a lower risk of recurrent stroke on medical treatment. Current evidence for asymptomatic women demonstrates minimal benefit for women, in conjunction with known increased perioperative risk. For asymptomatic disease, it is uncertain whether anyone will derive significant benefit from revascularisation in the era of modern medical therapy and this is being investigated in the CREST-2 trial. Thus, for women with asymptomatic disease not able to be enrolled in a clinical trial, medical management can be considered, until we have more data regarding benefit of revascularisation from a trial that has sufficient representation of women. These women should receive aggressive medical therapy and lifestyle modification for stroke prevention.

Women should be counselled that risk reduction benefit from CEA is less than that for men. In general, women tend to be undertreated medically, and practitioners should ensure they optimise medical therapy, regardless of whether revascularisation is pursued.

The periprocedural risk of stroke and death may be higher with CAS than with CEA in women. Given that this elevated risk is in comparison to revascularisation with CEA, it is difficult to recommend CAS routinely for women.

A possible explanation for gender-associated differences in outcomes may be that women have different carotid plaque phenotypes, with more stable plaque. More advanced vascular imaging may help identify women with high-risk plaque and aid in clinical decision-making regarding revascularisation.

Representation of women in stroke clinical trials remains an issue. The fact that women have been under-

represented in carotid stenosis trials has led to uncertainty about the optimal treatment for women. A carotid stenosis trial focused on women is one potential solution to this vexing clinical problem.

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REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, *et al*. Writing Group Members. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;133:e38–360.
2. Bushnell C, McCullough LD, Awad IA, *et al*. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:1545–88.
3. Adams HP Jr, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.
4. Flaherty ML, Kissela B, Khoury JC, *et al*. Carotid artery stenosis as a cause of stroke. *Neuroepidemiology* 2013;40:36–41.
5. Chaturvedi S, Bhattacharya P. Large artery atherosclerosis: carotid stenosis, vertebral artery disease, and intracranial atherosclerosis. *Continuum (Minneap Minn)* 2014;20(2 Cerebrovascular Disease):323–34.
6. 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:e573–83.
7. den Hartog AG, Achterberg S, Moll FL, *et al*. Asymptomatic carotid artery stenosis and the risk of ischemic stroke according to subtype in patients with clinical manifest arterial disease. *Stroke* 2013;44:1002–7.
8. Marquardt L, Geraghty OC, Mehta Z, *et al*. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke* 2010;41:e11–17.
9. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;273:1421–8.
10. Halliday A, Mansfield A, Marro J, *et al*. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491–502.
11. Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? *Lancet* 2004;364:1122–3; author reply 25-6.
12. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: Asymptomatic Carotid Surgery Trial. *Stroke* 2004;35:2425–7.
13. Howard VJ, Lutsep HL, Mackey A, *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;10:530–7.
14. Clinical alert: benefit of carotid endarterectomy for patients with high-grade stenosis of the internal carotid artery. National Institute of Neurological Disorders and Stroke and Trauma Division. North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators. *Stroke* 1991;22:816–17.
15. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet* 1991;337:1235–43.
16. Rothwell PM, Eliasziw M, Gutnikov SA, *et al*. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;363:915–24.
17. Alamowitch S, Eliasziw M, Barnett HJ, *et al*. The risk and benefit of endarterectomy in women with symptomatic internal carotid artery disease. *Stroke* 2005;36:27–31.
18. Chimowitz MI, Lynn MJ, Derdeyn CP, *et al*. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365:993–1003.
19. Vouyouka AG, Egorova NN, Sosunov EA, *et al*. Analysis of Florida and New York state hospital discharges suggests that carotid stenting in symptomatic women is associated with significant increase in mortality and perioperative morbidity compared with carotid endarterectomy. *J Vasc Surg* 2012;56:334–42.
20. Bisdas T, Egorova N, Moskowitz AJ, *et al*. The impact of gender on in-hospital outcomes after carotid endarterectomy or stenting. *Eur J Vasc Endovasc Surg* 2012;44:244–50.
21. Goldstein LJ, Khan HU, Sambol EB, *et al*. Carotid artery stenting is safe and associated with comparable outcomes in men and women. *J Vasc Surg* 2009;49:315–23. discussion 23–4.
22. Brott TG, Hobson RW II, Howard G, *et al*. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;363:11–23.
23. Rothwell PM, Eliasziw M, Gutnikov SA, *et al*. 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;35:2855–61.
24. De Rango P, Brown MM, Leys D, *et al*. Management of carotid stenosis in women: consensus document. *Neurology* 2013;80:2258–68.
25. Poisson SN, Johnston SC, Sidney S, *et al*. Gender differences in treatment of severe carotid stenosis after transient ischemic attack. *Stroke* 2010;41:1891–5.
26. Iemolo F, Martiniuk A, Steinman DA, *et al*. Sex differences in carotid plaque and stenosis. *Stroke* 2004;35:477–81.
27. Hellings WE, Pasterkamp G, Verhoeven BA, *et al*. Gender-associated differences in plaque phenotype of patients undergoing carotid endarterectomy. *J Vasc Surg* 2007;45:289–96. discussion 96–7.
28. Ota H, Reeves MJ, Zhu DC, *et al*. Sex differences in patients with asymptomatic carotid atherosclerotic plaque: in vivo 3.0-T magnetic resonance study. *Stroke* 2010;41:1630–5.
29. Wendorff C, Wendorff H, Pelisek J, *et al*. Carotid plaque morphology is significantly associated with sex, age, and history of neurological symptoms. *Stroke* 2015;46:3213–19.