

How asymptomatic is “asymptomatic” carotid stenosis?

Resolving fundamental confusion(s)—and confusions yet to be resolved

Piotr Musiałek¹, Iris Q. Grunwald^{2,3}

¹ Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland

² Neuroscience and Vascular Simulation, Anglia Ruskin University, Chelmsford, United Kingdom

³ Southend University Hospital NHS Foundation Trust, Westcliff-on-Sea, United Kingdom

Atherosclerotic stenosis of the internal carotid artery of 50% or more is a relatively common pathology (about 2% to 8% of the general population aged 60 to 80 years), with the prevalence similar to that of nonvalvular atrial fibrillation.¹ However, patients with manifest atherosclerosis in other vascular beds show a significantly greater prevalence of carotid stenosis (CS) and a greater risk of cerebral symptoms that occur through the thromboembolic or hemodynamic mechanisms.²

The ACST-1 trial³ in 3120 patients with asymptomatic CS followed for 10 years demonstrated, with an elective (rather than deferred) CS revascularization, a profound absolute risk reduction in nonperioperative stroke by 5.9% at 5 years (risk reduction from 11.0% to 5.1%) and 6.1% at 10 years (risk reduction from 16.9% to 10.8%, with the magnitude of the effect maintained in patients on lipid-lowering therapy).³ Surprisingly, in the absence of any new randomized data, there have been vocal calls recently to disregard the level-1 evidence from the ACST-1 trial through either ignoring the trial completely in some meta-analyses⁴ or attempting to construct an alternative body of “new evidence.” Such “new-evidence” observational studies, performed not infrequently in as few as 100 subjects⁵ (rather than the usually referenced 1153 subjects)⁵ followed for a relatively short time⁵ (and with most transient ischemic attacks [TIAs] leading—rightly—to carotid revascularization to prevent strokes)⁵ have been used to claim that “medical intervention alone is best for prevention of strokes”⁴ or that “the benefits of carotid revascularization remain uncertain”⁶ and “revascularization is not the solution.”⁶ In contrast, 2 recent independent studies demonstrated an annual stroke rate of 2.4%⁷ or 2.9%⁸ in vascular clinic patients

with asymptomatic CS on optimized medical therapy (OMT). As the risk is cumulative, the annual risk level of about 2.5% to 3.0% indicates—for instance for a 50-year-old man with an asymptomatic CS on contemporary OMT—a statistical stroke risk of about 25% to 30% by the age of 60 and 50% to 60% by the age of 70 (the actual risk can be still higher when additional risk factors, such as diabetes, are present).² As 85% of strokes occur without a warning sign, and of those who survive stroke (about 40% at 5 years) about half are disabled,² many families and physicians find it difficult to ignore such a risk.⁴ This is particularly relevant because contemporary CS revascularization studies continue to enroll patients with CS strokes despite OMT; this provides circumstantial evidence that OMT, at least in some patients, does not sufficiently protect against stroke.⁴

So why is the management of asymptomatic CS (to some at least) controversial today? Principal reasons seem to stem from: 1) definition problems (“asymptomatic” vs “symptomatic” CS; “stroke” vs “cerebral infarct”); 2) fundamental differences between the low-risk general population and higher-risk populations with atherosclerotic disease manifestations; 3) poor appreciation of increased stroke risk characteristics in CS; 4) risk of intervention (until recently) of about 3%⁹; and 5) lack of randomized data (OMT vs OMT + intervention) in current populations with asymptomatic CS across the whole risk spectrum.

What is the meaning of “symptomatic” in relation to CS? The English language, in contrast to many others, differentiates between “symptoms” and “signs.” A symptom is an indication of disease perceived by the patient and reported by the patient. Symptoms of CS-associated cerebral ischemia include ipsilateral TIA or clinical stroke.^{2,10} A sign is

Correspondence to:

Piotr Musiałek, MD, DPhil,
Klinika Chorób Serca i Naczyni,
Uniwersytet Jagielloński Collegium
Medicum, Krakowski Szpital
Specjalistyczny im. Jana Pawła II,
ul. Prądnicka 80, 31-202 Kraków,
Poland, phone: +48 12 614 22 87,
email: pmusialek@szpitaljp2.krakow.pl

Received: October 30, 2017.

Accepted: October 30, 2017.

Published online:

November 30, 2017.

Conflict of interest: none declared.

Pol Arch Intern Med. 2017;

127 (11): 718-719

doi:10.20452/pamw.4157

Copyright by Medycyna Praktyczna,

Kraków 2017

an observable physical phenomenon indicative of the presence of a pathology or disease. Signs are detected by the physician through clinical examination and accessory investigations. A clinically-silent cerebral infarct ipsilateral to CS is a sign, not a symptom, and the patient is, strictly speaking, “asymptomatic.” In such patients, however, there is evidence for an increased risk of further, clinically symptomatic, brain injury likely to occur in the absence of an intervention.^{2,8} While the definition of stroke includes an episode of clinically manifest neurological dysfunction,¹⁰ according to the same guidelines, the term “stroke” may be also used for brain infarction in the absence of clinical symptoms.¹⁰ According to some authors, patients with TIA or stroke become automatically “asymptomatic” from the point of 6 months after the event onwards.^{3,9,11} Further confusions arise from the fact that different studies have used different time points to change the “symptomatic”/“asymptomatic” label, such as 1, 3, 4, or 12 months.¹² More accurate terms have been proposed, such as “recently symptomatic” and “remotely symptomatic.”¹² The above, and other, inconsistencies greatly confuse physicians, leading to different approaches to the same patient type by various specialties or in various medical centers or countries.

A key question is whether it is ethical today to wait for clinically manifest symptoms as a threshold for intervention in patients with CS with signs of cerebral ischemia (or other increased-risk features), particularly in centers (and with novel technologies) that may offer a low-risk intervention. A selective approach to evidence (including ignoring level-1 data)⁴ and basing recommendations largely on observational studies,^{4,6} confusion between symptoms and signs of cerebral ischemia, and controversies over the CS features associated with an increased risk of stroke have led to large differences in recommendations issued by different specialties and professional societies.^{13,14} However, the recent joint guidelines¹⁵ of the European Society of Cardiology and European Society of Vascular Surgery, endorsed by the European Stroke Organization, provide an important attempt to resolve at least some of the key decision-making issues in asymptomatic CS. The guidelines are discussed in Supplementary material.

With their pioneering demonstration of the effect of carotid revascularization on retinal function in this issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Machalińska et al¹⁶ expand our understanding of the CS impacts. The retina is well-known to be extremely sensitive to ischemia.^{17,18} Acute ocular syndromes, resulting from acute hemodynamic insufficiency of the ophthalmic/retinal artery, are a fundamental part of the symptomatic presentation spectrum of CS.^{10,15,17,18} Employing a battery of retinal function tests in an “asymptomatic” CS patient series, Machalińska et al¹⁶ found, with carotid revascularization, a significant improvement in neuroretinal function on a multimodality electroretinogram in the eye ipsilateral to the CS (also, to a lesser extent, in the contralateral eye which may benefit due to

cerebral blood flow normalization). While more evidence (including external validation and establishing reference ranges) is needed before retinal function tests can be adopted into the standard risk evaluation portfolio in “asymptomatic” CS, the work by Machalińska et al¹⁶ is an important novel signal.

Concluding remarks and further discussion of the OMT vs OMT + intervention management strategy, the ongoing CREST-2 trial (Carotid Revascularization Endarterectomy Versus Stenting Trial 2), and progress in device technology can be found in the Conclusion section of Supplementary material.

Supplementary material Supplementary material is available with the article at www.pamw.pl.

REFERENCES

- 1 de Weerd M, Greving JP, Hedblad B, et al. Prevalence of asymptomatic carotid artery stenosis in the general population: An individual participant data meta-analysis. *Stroke*. 2010; 41: 1294-1297.
- 2 Musialek P, Hopf-Jensen S. Carotid artery revascularization for stroke prevention: A new era. *J Endovasc Ther*. 2017; 24: 138-148.
- 3 Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): A multicentre randomised trial. *Lancet*. 2010; 376: 1074-1084.
- 4 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-e583.
- 5 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-e17.
- 6 Hart RG, Ng KH. Stroke prevention in asymptomatic carotid artery disease: revascularization of carotid stenosis is not the solution. *Pol Arch Med Wewn*. 2015; 125: 363-369.
- 7 Conrad MF, Boulom V, Mukhopadhyay S, et al. Progression of asymptomatic carotid stenosis despite optimal medical therapy. *J Vasc Surg*. 2013; 58: 128-135.
- 8 Kakkos SK, Nicolaides AN, Charalambous I, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. *J Vasc Surg*. 2014; 59: 956-967.
- 9 Rosenfield K, Matsumura JS, Chaturvedi S, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med*. 2016; 374: 1011-1020.
- 10 Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013; 44: 2064-2089.
- 11 Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: A guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke*. 2011; 42: 517-584.
- 12 Musialek P, Tracz W, Tekieli L, et al. Multimarker approach in discriminating patients with symptomatic and asymptomatic atherosclerotic carotid artery stenosis. *J Clin Neurol*. 2013; 9: 165-175.
- 13 Abbott AL, Paraskevas KI, Kakkos SK, et al. Systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis. *Stroke*. 2015; 46: 3288-3301.
- 14 Musialek P, Hopkins LN, Siddiqui AH. One swallow does not a summer make but many swallows do: Accumulating clinical evidence for nearly-eliminated peri-procedural and 30-day complications with mesh-covered stents transforms the carotid revascularisation field. *Adv Interv Cardiol*. 2017; 13: 95-106.
- 15 Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Endorsed by the European Stroke Organization (ESO). *Eur Heart J*. 2017. [Epub ahead of print]
- 16 Machalińska A, Kowalska-Budek A, Kawa MP, et al. Effect of carotid endarterectomy on retinal function in asymptomatic patients with hemodynamically significant carotid artery stenosis. *Pol Arch Intern Med*. 2017; 127: 722-729.
- 17 Shin YW, Kim JM, Jung KH, et al. Light-induced amaurosis fugax due to severe distal internal carotid artery stenosis: In view of managing ocular ischemic syndrome. *J Neurol*. 2013; 260: 1655-1657.
- 18 Schwarz F, Bayer-Karpinska A, Poppert H, et al. Serial carotid MRI identifies rupture of a vulnerable plaque resulting in amaurosis fugax. *Neurology*. 2013; 80: 1171-1172.