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EDITORIAL

How asymptomatic is "asymptomatic" carotid stenosis?

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

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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 trial[3] 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-analyses[4] or attempting to construct an alternative body of "new evidence." Such "new-evidence" observational studies, performed not infrequently in as few as 100 subjects[5] (rather than the usually referenced 1153 subjects)[5] followed for a relatively short time[5] (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 provdes 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

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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 guidelines[15] 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 al[16] 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 al[16] 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 al[16] 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.

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