

# Management of Asymptomatic Carotid Stenosis. an Issue with Unresolved Queries that Need Disambiguation

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## 1. Editorial

Atherosclerotic carotid stenosis represents a harbinger of stroke, transient ischemic attack (TIA), and cognitive impairment. [1]. The prevalence of carotid disease is highly age-dependent, affecting approximately 7.5% and 5.0% of all men and women, respectively, over 80 years of age. [2] Compared with the wealth of data available for patients with symptomatic carotid stenosis, the management of patients with asymptomatic carotid stenosis (ACS) remains controversial. The guidelines proposed by the Society for Vascular Surgery (SVS, 2011) and the European Society for Vascular Surgery (ESVS, 2018) recognised the uncertainty in managing these patients and a series of redundant interventions offered in the past.[3, 4] However, both Societies strongly recommend implementing the best medical treatment in ACS patients to reduce the rate of ipsilateral cerebrovascular events (ESVS, class I recommendation, level of evidence A) (SVS, GRADE 1, Level of Evidence A). [3,4]

The proposed best medical treatment consists of lifestyle modification and pharmacological strategies. As lifestyle modification should be considered the promotion of a healthy diet and physical activity, a recommendation based on a recently published meta-analysis of nine randomized trials that showed that such interventions lowered the risk of cardiovascular events (pooled relative risk 0.80, [95% CI, 0.73-0.87]).[5] Smoking is another potential factor with dreadful complications for carotid stenosis amplifying the carotid plaque progression and increasing cerebrovascular events. Current smokers are more likely to be victims of vulnerable plaques with intraplaque haemorrhage and plaque ulcers.[1]. For this reason, all active smokers with ACS should be encouraged for smoking cessation and

effective pharmacotherapy for achieving cessation. Finally, physical activity represents another essential component of lifestyle modification. Effects of exercise (4 to 7 days per week) on cardiovascular risk factors are well documented, suggesting a slower rate of atherosclerosis if patients adopt exercise programs.[1]

On the other hand, pharmacological strategies have advanced since the first trials have been published 20 years ago. This effect results from a pleiad of factors such as widespread use of statins, more intensive antiplatelet regimens, better blood pressure control, and increased awareness of vascular risk factors.[1] The American Heart Association 2018 guidelines recommended an LDL-C goal of <1.8mmol/L (70mg/dl) and a blood pressure target of <130/80 mmHg in atherosclerotic patients, including those with ACS.[6] Particular attention should be given to patients with hypertension and bilateral carotid stenosis (>70%) who do not tolerate blood pressure lowering to this degree, due to impaired cerebral perfusion. The angiotensin-converting enzyme (ACE) inhibitor seems to be effective in these situations, lowering the blood pressure without further impairment in cerebral perfusion.[1]

While the recommendations of the best medical treatment are clearly presented, a significant controversy regarding the selection of patients for revascularization and the best invasive treatment option still exists in the literature. The 2018 ESVS guidelines attempted to identify patients on the best medical treatment with a “higher risk of stroke” who could benefit from an additional prophylactic carotid revascularization procedure.[4] After a thorough search of the literature, the committee proposed some clinical and/ or imaging features (stenosis progression, large plaque area, plaque echolucency, intraplaque haemorrhage on magnetic resonance imaging, silent brain infraction or large juxta-luminal black area, detected by computed tomography angiography, impaired cerebral vascular reserve and spontaneous embolization on transcranial Doppler monitoring) to detect these “high risk for stroke” ACS patients. These proposed features remain to be proved in daily clinical practice, hoping that the upcoming 2021 guidelines by the SVS shed more light on this grey area.

Concerning the best invasive treatment option for ACS patients, some evidence from the Asymptomatic Carotid Surgery Trial ACST-2 trial is available.[7] In the Lancet, Halliday and colleagues presented the findings from an international multicenter randomized trial designed to compare the outcomes of carotid endarterectomy (CEA) versus carotid stenting (CAS) in patients with asymptomatic severe carotid disease. The authors showed that there is

treatment equipoise between the two modalities as far as 30-day mortality and morbidity, as well as long-term outcomes, are concerned.[7] However, some queries regarding the study design and some of its conclusions have been raised.

First of all, it seems that at least 10% of patients were not on intensive medical therapy at the time of intervention. It was recently shown that with intensive medical treatment, the risk of stroke is low enough that the benefit of carotid revascularization for asymptomatic disease is questionable, especially in patients with stenosis less than 80%, representing 38% of the patients included in the trial.[1, 8] Also, the incidence of aspirin resistance and carriage of the CYP2C19 was not considered in the trial, which varies significantly among western and eastern populations.[9] Of interest, out of the 3625 patients included in the trial, only one patient was from the US and only 21 from Asia (China and Japan). We wondered if the authors had any thoughts about the generalizability of the trial results since patients with potentially different genetic backgrounds and managed in different practice environments were not included in the trial.

Moreover, it is unclear in the methodology of the trial whether patients were randomized for characteristics such as aortic arch disease, common carotid disease, history of neck radiation, presence of high carotid bifurcation lesions, life expectancy and sonographic features of unstable or ulcerated plaques that are common clinical factors that guide decision-management of carotid disease, favouring one modality over the other or even supporting intensive medical management alone. This is of paramount importance since the trial's main inclusion and the randomization criterion was if the doctor and patient were both substantially uncertain which procedure to prefer.

Finally, we were wondering how the results of the present trial align with the emerging literature, mainly from US, about the role of transcrotid artery revascularization in patients with asymptomatic, severe carotid artery disease (>80% stenosis), that has a lower risk of postprocedural stroke or death compared to transfemoral CAS.[10]

To sum up, the search for meaning, who of asymptomatic carotid patients may be included in the “high risk of stroke” is ongoing. Despite the recently published ACST-2 trial study, some queries exist on whether patients with ACS and intensive medical therapy still benefit from revascularization. To address this question, the currently ongoing randomised trial (CREST 2) has recruited ACS patients, and the results are waiting.

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