Why Selective Screening for Asymptomatic Carotid Stenosis is Currently Appropriate: A Special Report

Abstract

Introduction: Two of the main reasons recent guidelines do not recommend routine population-wide screening programs for asymptomatic carotid artery stenosis (AsxCS) is that screening could lead to an increase of carotid revascularization procedures and that such mass screening programs may not be cost-effective. Nevertheless, selective screening for AsxCS could have several benefits. This article presents the rationale for such a program.

Areas covered: The benefits of selective screening for AsxCS include early recognition of AsxCS allowing timely initiation of preventive measures to reduce future myocardial infarction (MI), stroke, cardiac death and cardiovascular (CV) event rates.

Expert Opinion: Mass screening programs for AsxCS are neither clinically effective nor cost-effective. Nevertheless, targeted screening of populations at high risk for AsxCS provides an opportunity to identify these individuals earlier rather than later and to initiate a number of lifestyle measures, risk factor modifications and intensive medical therapy in order to prevent future strokes and CV events. For patients at 'higher risk of stroke' on best medical treatment, a prophylactic carotid intervention may be considered.

Keywords: asymptomatic carotid atherosclerosis, carotid plaque burden, carotid stenosis, guidelines, screening, stroke

Article highlights:

- Population-wide screening for asymptomatic carotid stenosis by duplex ultrasound is neither clinically-efficient nor cost-effective.
- Current international guidelines (e.g., the 2022 Society for Vascular Surgery and the 2023 European Society for Vascular Surgery guidelines) do not recommend population-wide screening programs for asymptomatic carotid stenosis.
- Selective screening of 'high-risk' patient subgroups may be beneficial for the timely identification of individuals with ≥50% asymptomatic carotid stenosis.
- Early identification of individuals with asymptomatic carotid stenosis may lead to prompt initiation of preventive measures to reduce the high myocardial infarction and cardiovascular event rates, including stroke, in these patients.
- For patients at 'higher risk of stroke' on best medical treatment, a prophylactic carotid intervention may be considered.

1. Introduction

The purpose of screening programs is to identify individuals in the general population who are at higher than average risk of developing a certain disease, so that treatment can be offered earlier [1]. Such early identification of a disease may lead to better health outcomes for many of the screened individuals [1]. In their landmark publication, which marked the beginning of the era of modern screening, Wilson and Jungner stated 10 principles that should be used to assess whether screening for a particular condition or disease is helpful to improve public health care (**Figure 1**) [1]. These principles form the basis for the discussion about the benefits, harm, costs and ethics of screening programs [1].

Several national screening programs have been introduced in healthcare in the last 5 decades. For instance, the Centers for Disease Control and Prevention in the United States support screening for breast, cervical, colorectal and lung cancers [2]. In the UK, similar screening programs are available for breast, cervical and colorectal cancers (but not for lung cancer) [3]. The United States Preventive Services Task Force (USPSTF) recommended 1-time screening for abdominal aortic aneurysms with ultrasonography in men aged 65-75 years who have ever smoked (B recommendation) [4] – but recommended against screening for asymptomatic carotid artery stenosis (AsxCS) in the general population (D recommendation) [5].

The objective of this article was to critically review the available evidence, with the purpose of discussing the pros and cons of population-wide *vs.* selective screening for AsxCS. The rationale supporting selective screening for AsxCS is outlined and discussed.

2. Why did the USPSTF recommend against population-wide screening for AsxCS?

Several arguments were presented in the USPSTF document to support the recommendation against population-wide screening for AsxCS [5], namely:

i) There have been no population-based screening trials for AsxCS,

ii) The optimal treatment for clinically significant AsxCS remains uncertain,

iii) The prevalence of stroke attributable to AsxCS in the general population is low, and

iv) The benefit of surgery compared with medical therapy in older trials is small, while there is potential for small to moderate surgical harm.

As a result of its low cost, non-invasive nature and availability, duplex ultrasonography is the examination of choice for the detection of AsxCS [5]. Nevertheless, a possible drawback of duplex ultrasound when used in mass screening programs is its relatively high number of false-positive results [5]. A false-positive result is the overestimation of carotid stenosis due to increased velocities as a result of e.g., carotid tortuosity/kinking [5]. Those who argue against the usefulness of screening programs for AsxCS support that due to the high number of false positive ultrasound scans, several patients might be offered an unnecessary operation and suffer a perioperative stroke during the carotid procedure [5]. However, a false-positive duplex result relates to the severity of stenosis, not to the presence of a substantial plaque at the carotid bifurcation, which should be managed with aggressive medical therapy. Carotid plaque area/carotid plaque burden are more accurate predictors of future cardiovascular (CV) disease (CVD) risk than carotid intima-media thickness [6].

The low yield of screening and the uncertainty about the efficacy of carotid revascularization procedures in AsxCS patients are additional arguments that have been used by those who refute screening for AsxCS [5]. The conclusion reached was that the evidence supporting a benefit of screening for AsxCS in terms of reducing the incidence of stroke or mortality is currently lacking [5].

3. What is the rationale supporting selective screening for AsxCS?

A recent international, multispecialty expert-based document presented the rationale supporting selective (instead of population-wide) screening for AsxCS [7, 8]. It was clarified that the detection of AsxCS by selectively screening high-risk individuals should be seen as an opportunity for the timely identification of asymptomatic patients at high risk for future stroke, myocardial infarction (MI) and CV events. Such a timely identification of AsxCS patients should be followed by prompt initiation of lifestyle measures (e.g., weight loss, quitting smoking, initiation of regular exercise and a healthy diet), vascular risk factor control (e.g., blood glucose control, management of hyperlipidemias/dyslipidemias and hypertension, etc.) and intensive medical therapy (antiplatelets, antihypertensives and statins). The purpose of these preventive and pharmacological measures is to reduce the high CVD risk seen in these individuals, rather than to select patients for a prophylactic carotid endarterectomy (CEA)/carotid artery stenting (CAS) [7, 8]. By identifying AsxCS patients, it is possible not only to provide risk factor control and best medical treatment to these individuals, but also to monitor the progression of AsxCS [7, 8].

There is evidence that AsxCS may progress despite the implementation of intensive medical therapy. According to the 2023 European Society for Vascular Surgery (ESVS) Carotid Guidelines [9], progression of AsxCS is associated with a nearly 5-fold higher risk of stroke (odds ratio [OR] 4.7; 95% CI confidence interval [CI] 2.3-9.6; p<0.01). In a single-center study (n=900 carotid arteries; 794 patients), patients with moderate (50-69%) AsxCS were prescribed optimal medical treatment (aspirin + statin treatment aiming at low-density lipoprotein cholesterol [LDL-C] levels <100 mg/dl) and were followed-up with duplex ultrasound for a mean 3.6 (range: 0.3-6.7) years [10]. The 5-year freedom from progression to severe (70-99%) stenosis was 61.2 ± 2.1%, with no benefit from optimal medical treatment compared with control (60.1 ± 3.7% *vs.* 61.6 ± 2.6%, respectively; p=0.33) [10]. Carotid plaque progression occurred in 262 arteries and 36 of these (13.7%) developed symptoms [10]. The average time to plaque progression was 32 months (range: 2-79 months). Of the entire cohort, 90 patients (11.3%) developed ipsilateral neurologic symptoms during follow-up, 58% of which were strokes [10]. These results were verified in an independent study that included 258 patients (282 carotid arteries) with moderate (50-69%) AsxCS [11]. During a mean follow-up of 2.6 ± 0.10 years, disease progression to severe stenosis occurred in 25.2% (n=71) [11]. Although the incidence of ipsilateral stroke (2.13%; n=6) and transient ischemic attack (TIA; 0.71%; n=2) were low, it can be argued that with a longer follow-up period, these incidents could increase substantially.

By identifying AsxCS patients with selective screening, it is possible to improve carotid plaque stabilizing therapies and to identify patients for the much needed randomized trials. Recent evidence also suggests that patients with severe AsxCS may

have cognitive dysfunction [12]. A 2023 systematic review (n=49 studies) assessing the evidence supporting an association between AsxCS and impaired cognitive function demonstrated that the evidence supports an association between AsxCS and progressive cognitive deterioration [13]. Patients with severe AsxCS often demonstrate progressive cognitive decline in several aspects of cognitive function, including global cognition, memory and executive function [13]. The mechanisms involved in the cognitive decline associated with AsxCS include cerebral hypoperfusion and silent cerebral embolization [13]. Therefore, early identification of AsxCS patients may have an effect on prevention/reversal of the progressive cognitive deterioration often seen in these patients.

The 2022 Society for Vascular Surgery (SVS) guidelines covered the issue of carotid screening in a separate Clinical Practice Guidelines document [14]. A strong (Grade I; Level of Evidence: B) recommendation was provided against routine screening for AsxCS in individuals without cerebrovascular symptoms or significant risk factors for carotid artery disease [14]. Nevertheless, in selected asymptomatic patients who are at increased risk for AsxCS, the SVS Guidelines provided a weaker (Grade 2; Level of Evidence: B) recommendation for AsxCS screening. These high-risk groups included patients with lower extremity peripheral arterial disease (PAD), those undergoing coronary artery bypass surgery, individuals ≥55 years of age with ≥2 atherosclerotic CVD risk factors or active smoking, patients with diabetes mellitus, hypertension or coronary artery disease and individuals with clinically occult cerebral infarction noted on brain imaging studies [14].

According to the 2023 European Society for Vascular Surgery (ESVS) guidelines for the management of patients with carotid artery stenosis [9], mass screening for AsxCS is

not indicated. However, the 2023 ESVS guidelines provided a weaker recommendation for selectively screening individuals with 2 or more vascular risk factors for the presence of AsxCS with the purpose of optimization of medical treatment and risk factors (Class IIb; Level of Evidence: B) [9]. However, patients at 'higher risk of stroke' on best medical treatment may be candidates for a prophylactic CEA or CAS [9]. These recommendations may not apply to elderly (e.g., >80 years) female AsxCS patients, as there is no solid evidence that CEA confers benefit in asymptomatic female patients and in patients aged >75 years [9]. However, selected patients aged >75 years with a predicted life expectancy of >5 years and at least one clinical/imaging feature that may make them "higher risk of stroke on BMT" might benefit from intervention [9].

For a population screening program to be cost-efficient, it should yield a >20% identification rate of a disease [15]. It has been demonstrated that only around 2.0% of the general population present with moderate (less than 50%) AsxCS, and only 0.5% of the population demonstrate severe (70% or more) AsxCS [16]. Such a low prevalence is not able to justify mass screening programs for AsxCS with ultrasound. On the other hand, there have been attempts to describe risk scores and risk models able to predict AsxCS and thus to justify targeted screening programs of high-risk individuals [17-20]. Using data from nearly 600,000 patients attending vascular screening clinics in the United States and the United Kingdom, it was demonstrated that the most accurate risk scores and risk models included a number of characteristics such as patient age and gender, high blood pressure, blood glucose and cholesterol levels, MI, diabetes, history of stroke/transient ischemic attack episode and patient height [21]. It was demonstrated that

selective screening of the 2 highest deciles could identify >50% of patients with ≥50% AsxCS [21].

The same group has recently introduced a novel risk score called the Prevalence of Asymptomatic Carotid Artery Stenosis (PACAS) risk score [22]. This risk score was developed in a large contemporary screened population of nearly 600,000 participants with the purpose of reducing the number of individuals needed to screen (NNS) by targeted screening of those at highest risk of AsxCS. Once again, male sex, older age (≥70 years), current smoking coronary heart disease, diabetes mellitus and history of stroke or TIA were identified as predictors of AsxCS [22]. By selectively screening those individuals at the highest decile of predicted risk the authors were able to identify >40% of patients with ≥50% AsxCS and >50% of those with ≥70% AsxCS [22].

Patients with PAD are amongst the highest yield subset of individuals testing positive for >50% AsxCS upon screening, with >20% of patients with intermittent claudication testing positive for >50% AsxCS [23, 24]. In a screening program in Western New York including 1334 unselected individuals voluntarily attending the screening sessions, the prevalence of >50% AsxCS was 18% (n=239) [25]. Age >65 years (OR: 4.1; 95% CI: 2.6-6.7), current smoking (OR: 2.0; 95% CI: 1.2-3.5), CAD (OR: 2.4; 95% CI: 1.5-3.9) and hypercholesterolemia (OR: 1.9; 95% CI: 1.2-2.9) were significantly associated with >50% AsxCS [25]. A risk score was developed based on the presence or not of these variables and patients were categorized as high-, intermediate- and low-risk based on their risk score [25]. Individuals in the high-risk group had a post-test probability for >50% AsxCS of 35%, whereas those in the intermediate- and low-risk groups had a post-test probability of 20% and 7%, respectively [25]. It was concluded that risk stratification

of individuals based on routinely available information may help select a small group of individuals with a high probability of significant AsxCS [25].

A cross-sectional analysis of 396,869 individuals undergoing screening for AsxCS and atrial fibrillation in vascular screening clinics in the U.S. and the U.K. between 2008 and 2013 identified 6,174 patients with ≥50% AsxCS (1.6%) [26]. Selective screening for AsxCS in participants with a predicted 10-year CVD risk of ≥20% showed a prevalence of ≥50% AsxCS of 3.7% with an NNS of 27 (compared with an NNS of 64 if all participants had been screened) [26]. Thus, based on the above-discussed compelling evidence [21-26], selective screening for AsxCS should be implemented to (1) reduce CVD risk and (2) decrease CV events.

4. Duplex Ultrasound as the Ideal Method of Screening for Carotid Stenosis in Asymptomatic Patients

When considering the Wilson and Junger principles of screening, duplex ultrasound is clearly the ideal screening tool for detecting significant AsxCS in appropriately selected patients with advanced atherosclerotic risk [1]. Specifically, carotid duplex creates no procedural-related medical risk to patients, has a low relative cost and has good sensitivity and specificity in detecting stenosis [27, 28]. Furthermore, duplex has the ability to identify plaque morphology features (such as low gray scale median) indicating higher lipid content with greater embolization potential [27]. A new standardized and reliable grading system for the risk of vulnerability of carotid plaques, the Plaque-Reporting and Data System (RADS) score has recently been published [29], which can be

used with ultrasound and quickly provides indications of the potential vulnerability of the carotid plaque.

Magnetic Resonance Imaging (MRI) is a suboptimal screening tool for AsxCS due to the pitfalls of over-estimating the degree of carotid stenosis, being a lengthy procedure and having a high cost [30]. Computed tomography angiography (CTA) has excellent accuracy in quantifying the extent of carotid stenosis. However, CTA has a relative high cost in combination with the risks of iodinated contrast and ionizing radiation, making it a poor screening tool, particularly given the relatively low incidence of significant AsxCS in even the higher risk atherosclerotic patient distribution [31].

Carotid ultrasound can readily identify atherosclerotic plaques, which are defined as focal wall thickening that is ≥50% greater than the surrounding vessel wall or as a focal protrusion of intima-media ≥1.5 mm into the lumen [32]. Among 6,524 participants aged 25-69 years in the Risk Evaluation For INfarct Estimates (REFINE)-Reykjavik study, the prevalence of minimal, moderate and severe carotid plaque was 35.0, 8.9 and 1.1%, respectively [33]. The presence of carotid plaque classifies cardiovascular risk as “high” or “very-high” according to the European Society of Cardiology Guidelines on CVD prevention in clinical practice [34]. Subjects with high or very high CV risk should receive appropriate risk factor modification, including statin treatment for LDL-C lowering [34, 35]. Addition of ezetimibe should also be considered since aggressive LDL-C lowering with a combination of high-dose statins plus ezetimibe improves outcomes compared with statin monotherapy alone [36].

Besides carotid ultrasonography, another application of Duplex ultrasound is in risk stratification of AsxCS patients by detection of microemboli using transcranial Doppler

[37-39]. Detection of microemboli by transcranial Doppler suggests an “unstable” carotid plaque and identifies asymptomatic individuals at high risk for a future stroke [37-39]. In addition, detection of carotid ulcers with 3-dimensional ultrasound is an additional tool for stroke risk stratification in AsxCS individuals [39]. Finally, another important application of carotid ultrasound is in following-up AsxCS patients to monitor plaque stability and/or stenosis progression.

A drawback of Duplex ultrasonography is that its utility is critically linked to the expertise and protocols of the person performing the study [40]. Peak systolic and end diastolic velocities of the common, internal and external carotid arteries are measured, as well as the peak systolic internal to common carotid artery ratio [40]. Measurement of the direction of flow and the velocities in the vertebral artery may also provide additional information about the severity of carotid stenosis/occlusion [40]. Despite its limitations, carotid ultrasonography may provide a quick evaluation of the carotid arteries and can be used as an inexpensive and non-invasive tool for screening for AsxCS.

In the future, the use of dedicated MRI plaque imaging to identify vulnerable plaque, likely to cause embolism and stroke, might provide an alternative or additional tool to select individual patients with AsxCS for revascularization in addition to intensive BMT [41].

5. Conclusions

Although population-wide screening for AsxCS is not recommended, there are several benefits associated with selective screening programs for AsxCS in ‘high-risk’ individuals. These benefits include the early identification of AsxCS patients for the

timely initiation of lifestyle measures, risk factor modification and intensive medical therapy to reduce the late CV morbidity, including stroke, and CV mortality rates of these patients. Besides prevention of cerebrovascular events and cardiovascular morbidity/mortality, selective carotid screening could prove useful in the early diagnosis and prevention of AsxCS-related vascular dementia.

6. Expert Opinion

Patients with AsxCS are at high risk for future stroke, MI and CVD death. Population-wide screening programs for the detection of AsxCS patients are neither clinically efficient nor cost-effective. Nevertheless, selective screening of high-risk patient subgroups may prove to be useful and should be viewed as an opportunity to identify individuals at high risk for atherosclerotic CVD and future CVD events.

The benefits from the timely identification of individuals with significant AsxCS include: i) the initiation of risk factor modification and lifestyle measures, as well as appropriate drug therapy for the reduction of future cerebrovascular and cardiovascular events and mortality, and ii) the identification of patients developing AsxCS-associated progressive cognitive decline.

Despite the advances in the constituents of best medical treatment and the progress in imaging techniques and vascular disease prevention measures, the number of strokes has remained largely unchanged in Europe and the United States over the last 20 years. Therefore, it is crucial that early preventive measures be established in order to observe a reduction in the number of strokes in the future. The purpose of selective screening is to optimize risk factor control and to initiate intensive medical therapy for the prevention of

future CVD events, including stroke. Furthermore, by utilizing selective screening it will be possible to identify individuals at future high stroke risk despite risk factor control and intensive medical treatment, and consider these individuals for a prophylactic carotid intervention to reduce the risk of a future cerebrovascular event. Future studies should identify specific patient subgroups that could benefit from such selective screening programs. In the meantime, we suggest selective screening using carotid duplex ultrasound of high-risk individuals (such as those with ≥2 vascular risk factors, lower extremity PAD, those undergoing coronary artery bypass surgery and individuals with clinically occult cerebral infarction noted on brain imaging studies), in line with the recommendations of the 2022 SVS [14] and the 2023 ESVS [9] Carotid Guidelines.

By adopting selective screening programs for AsxCS, it is expected that there will be a considerable reduction in the number of strokes in 10-15 years. In the future, development and validation of risk scores for the early detection of high-risk asymptomatic individuals with severe AsxCS may result in a reduction in number of strokes and CVD events.

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