ARTIGO DE REVISÃO REVIEW ARTICLE

MANAGEMENT OF THE CAROTID ARTERY STENOSIS IN ASYMPTOMATIC PATIENTS

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Abstract

Background: *An asymptomatic carotid stenosis (CS) is defined as a stable atherosclerotic luminal narrowing in patients with no history of ipsilateral cerebral or ocular ischemic events in the past six months. The bifurcation of the common carotid artery makes this area vulnerable to atherosclerosis due to the features of haemodynamic flow. The exact prevalence of asymptomatic patients with CS remains unknown and opinions on the treatment of these patients are controversial.*

Objective: *The authors aimed to review the evidence on the management of the asymptomatic CS and describe its clinical characteristics, diagnosis and treatment management.*

Methods: *A comprehensive review of the literature was carried out to collate data from relevant studies concerning patients with extracranial moderate to severe asymptomatic carotid stenosis. The data used was identified by a search using PubMed and Google Scholar with the keywords / MESH terms "carotid stenosis", in combination with the term "asymptomatic". For this study, the authors focused on publications in the past two decades, using English publications.*

Results: *A few studies have addressed the prevalence, natural course and/or prognostic impact of asymptomatic CS in patients under medical treatment or undergoing vascular surgery procedures. The prevalence of asymptomatic CS ranged from 0.3% to 4.5% in women and 0.5% to 5.7% in men - The risk of stroke/TIA in these patients was reported between 2% to 5% annually with a downward trend across time to 0.5% with current best medical therapy.*

Conclusion: *A great proportion of patients with asymptomatic CS should be submitted to conservative management with best medical therapy. However, selective surgical management should be considered if high risk features are present.*

INTRODUCTION

Our knowledge of the pathogenesis, clinical manifestations, diagnosis and best treatment of asymptomatic patients with carotid artery stenosis (CS) has evolved and changed in the last years. In this review, a detailed description of the epidemiology, pathogenesis, disease mechanisms and up-to-date diagnostic workup and management is presented.

The aim is to guide physicians through the supporting evidence and the potential efficacy of commonly prescribed regimens at preventing vascular events and pre-specified composite outcomes in patients with asymptomatic carotid stenosis.

METHODS

A comprehensive review of the literature was carried out to collate data from relevant studies in patients with extracranial moderate to severe asymptomatic stenosis.

The data used was identified by a search using PubMed and Google Scholar with the keywords / MESH terms "carotid stenosis", in combination with the term "asymptomatic". For this study, the authors focused on publications in the past two decades, using English language publications.

EPIDEMIOLOGY OF CAROTID ARTERY STENOSIS

In Europe, stroke is the second cause of mortality (1.1 million deaths/year) being the most frequent cause of death in Portugal.[1,2]

The prevalence of moderate/severe asymptomatic CS in the general population (moderate stenosis: > 50% to <69% of the lumen is narrowed; severe CS: ≥ 70%) ranged from 0.3% to 4.5% in women and 0.5% to 5.7% in men4. The annual risk of stroke for patients with severe asymptomatic carotid stenosis is approximately 2 to 5%.[5,6,7,8] It is also known that CS leads to 10% to 15% of all ischaemic strokes, so it is one of the preventable etiologic factors for stroke.[9,10,5]

PATHOLOGY AND PATHOPHYSIOLOGY OF CAROTID ARTERY STENOSIS

The presence of the carotid bifurcation makes this area vulnerable to atherosclerosis because of the features of haemodynamic flow (Figure 1).[11] The aetiology of carotid artery ischaemic stroke is mainly the result of an embolic event originating on the atherosclerotic plaque.[12]

The main structure of atherosclerotic plaques is formed by a lipid core with infiltration of inflammatory cells, coated with a fibrous capsule.[11]

Atherosclerotic plaques are present on the intima layer of arteries and are the result of a complex atheromatous process:

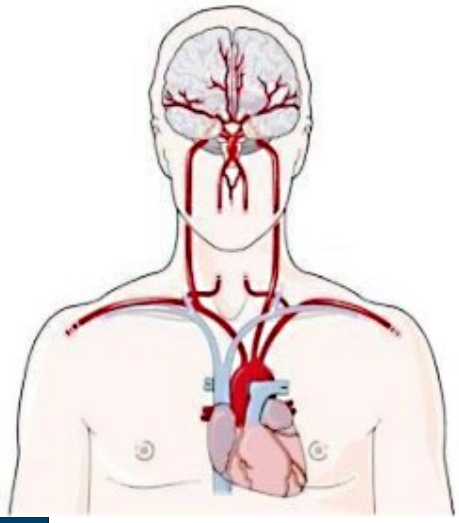

Figure 1 *Anatomy of carotid arteries. https://smart.servier.com/*

1. ↑increase in circulating LDL with vessel wall penetration.
2. Phagocytosis in the intima.
3. ↑ increase in vascularization.
4. ↑ increase in deposition of calcium and necrotic cells.
5. Fissures, ruptures and intra-plaque hemorrhages.
6. Ulceration and/or release of the plaque.
7. Deposition of platelets, clot formation, thrombosis and occlusion of the vessel (Figure 2).[13,9]

With the progression of atherosclerosis, the rupture of an atherosclerotic plaque is more likely, with thrombus formation resulting in arterial occlusion or embolism.[11] These thrombotic plaques are more often observed in patients with stroke (66.9%) *versus* TIA (36.1%) and asymptomatic patients (26.8%).[14] Initially, this occlusion can be temporary resulting in transient ischemic attack (TIA), which has similar symptoms to stroke and frequently lasts less than 24 hours.[11]

Regarding molecular pathways, initiation and progression of atherosclerosis are due to reactive oxygen

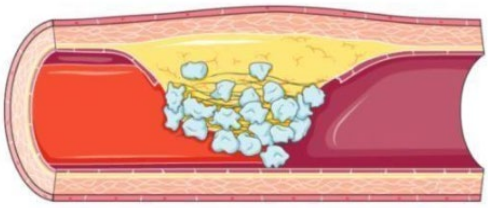

Figure 2 *Atherothrombosis. https://smart.servier.com/*

species (ROS.)[15,16,11] ROS increase the expression of cell adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1) and ELAMs (endothelial leukocyte adhesion molecule).[17,18] These molecules allow monocyte adhesion to endothelial cells. First, mild oxidation of low-density lipoprotein cholesterol (LDL-C) forms MM-LDL (minimally modified LDL) and then severe oxidation of MM-LDL forms oxidized LDL (OX-LDL). This increases Monocyte chemo-attractant protein-1 (MCP-1) due to stimulation of endothelial and smooth muscle cells. OX-LDL allows the differentiation of monocytes to macrophages which is promoted by MCSF (monocyte colony stimulating factor).[19] The new formed macrophages overexpress receptors for OX-LDL and produce foam cells which is the early stage of atherosclerosis.[20] Moreover, this mechanism also contributes to the instability of the atherosclerotic plaque which leads to thrombosis (Figure 3).[21]

This environment increases the expression of growth-regulating molecules PDGF (platelet-derived growth factor), bFGF (basic fibroblast growth factor), TGF-α and TGF-β and cytokines, such as IL-1 and TNF-α, which stimulate the synthesis of connective tissue and matrix. Progression of atherosclerosis is due to these mechanisms.[22]

CLINICAL PRESENTATION: UNSTABLE AND STABLE ATHEROSCLEROTIC PLAQUES

Unstable/vulnerable atherosclerotic plaques are characterized by extensive inflammation and accumulation of macrophages. Unstable plaques are more prone to rupture, leading to thrombotic and/or embolic events.[23] Unstable plaques are characterized by a thin fibrous capsule, less smooth muscle cells, more inflammatory cells and a vast lipid and necrotic core.[24] Hemodynamic stroke, in which the blood flow to the brain is temporarily suspended and then restored due to hemodynamic fluctuation, is a very rare event.

The majority of atherosclerotic plaques are stable and produce no symptoms, however, when the plaque increases considerably in size, the carotid artery lumen becomes markedly narrowed. An asymptomatic CS is

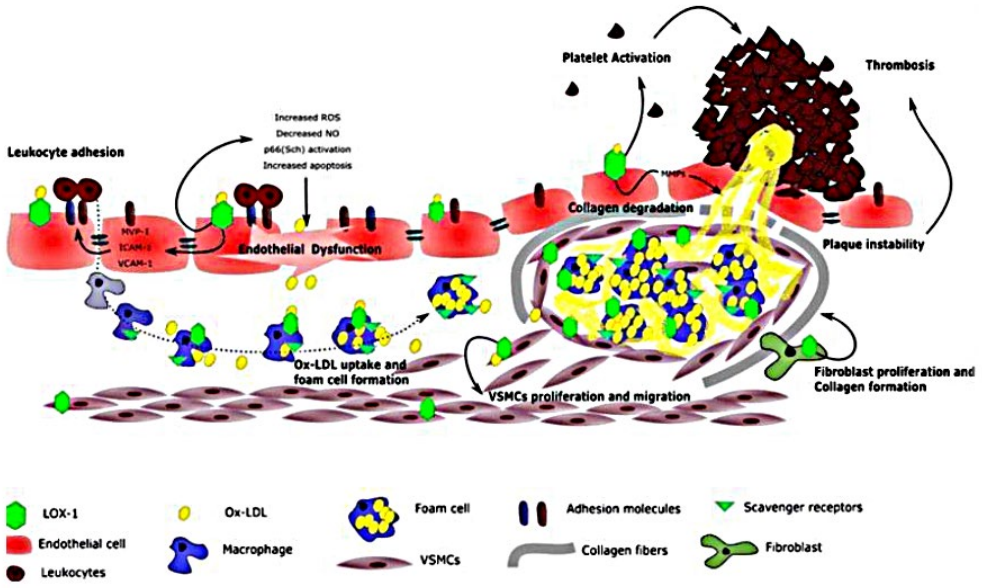

Figure 3

Molecular mechanism of atherosclerosis and posterior thrombosis.[21] Mehta AJKVKPPL. Oxidative Stress in Atherosclerosis. Genet Genomics. 2017.

present when a stable atherosclerotic plaque is detected in patients with no history in the past six months of ipsilateral cerebral or ocular ischemic events.[25]

It is known that CS is responsible for approximately 50% of TIAs.[26] The risk of having a stroke in the first month after TIAs is over 20%.[27]

RISK FACTORS

Risk factors for CS are similar to other cardiovascular diseases: dyslipidemia, hypertension, diabetes mellitus, advanced glycation end products (AGEs), obesity, cigarette smoking, lack of exercise, age, and C-reactive protein.[28,11]

Studies done by De Weerd M *et al.*, referred to cigarette smoking as the main risk factor for CS increasing the prevalence of CS in more than 50%.[29] Despite these various risk factors, the prevalence of severe CS is higher in patients with diabetes (Figure 4).[4]

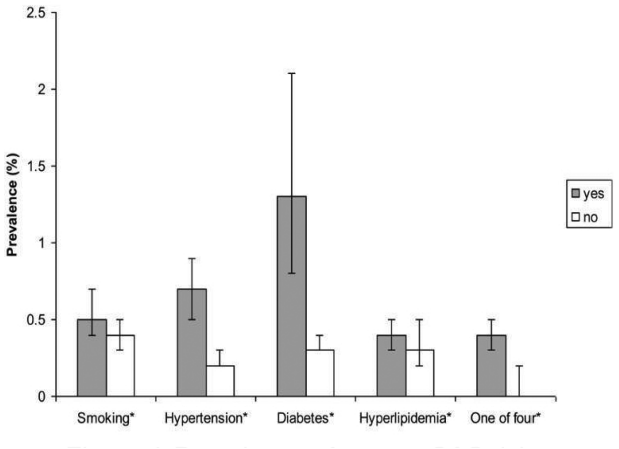

Figure 4

Prevalence of severe CAS risk factors.[4] M. de Weerd, J.P. Greving, B. Hedblad, M.W. Lorenz, E.B. Mathiesen, D.H. O'Leary, M. Rosvall, M. Sitzer, E. Buskens and MLB. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke. 2010;41:1294-1297.

1. Dyslipidemia

Hypercholesterolemia leads to atherosclerosis due to the generation of ROS.[30] However, LDL-C is the major responsible for the development of atherosclerosis due to the effect of LDL and OX-LDL on endothelial NADPH-oxidase, leading to ROS production.[31] A meta-analysis, including 165 792 patients, of randomised trials of statins in association with other preventive measures, demonstrated a 21.1% reduction in relative risk for stroke (95% CI 6.3-33.5, p=0.009). This is possible due to reduction of LDL serum levels and the stabilization of the atherosclerotic plaque.[32] High Triglyceride levels (TG) are also a risk factor for atherosclerosis although contributing less.[33] TG can lead to formation of small dense LDL, can reduce HDL levels and increase inflammatory particles, such as ROS.[11]

2. Hypertension

Hypertension also contributes to atherosclerosis by similar mechanisms: unbalance of oxidative stress / antioxidants with resulting increase of ROS, increase of proinflammatory cytokines (IL-1β, IL-6, and TNF-α), chemokines and cell adhesion molecules (ICAM-1, sE-selectin, and sP-selectin).[34,35]

It is well known that inflammation leads to atherosclerosis and one of the best markers of this association is the C Reactive Protein (CRP) 36. Kitiyakara C *et al.* refers that increase of ROS precedes the progression of hypertension.[37]

3. Cigarette smoking

The prevalence of symptomatic CS is 4.4% in never-smokers *versus* 7.3% in former smokers *versus*

9.5% in current smokers. Furthermore, studies refer that smoking 20 pack-years has a significant correlation. Nevertheless with lower amounts of cigarette smoke, no significant association was found.[38] So, similar to other risk factors, cigarette smoking contributes to atherosclerosis by increasing expression of ROS, vascular cell adhesion molecules and proinflammatory cytokines.[39] Serum levels of Advanced Glycation End-products are also increased in cigarette smokers and their interaction with their receptor (RAGE) increases the production of ROS, activates NF-kB and vascular cell adhesion molecules and proinflammatory cytokines.[40,41]

4. Diabetes

Hyperglycemia promotes atherosclerosis due to diverse mechanisms such as oxidative stress, AGEs, and protein kinase C. Oxidative stress leads to atherosclerosis mainly due to mitochondrial mechanisms in which hyperglycemia metabolism leads to reduction of NADPH and activation of NADPH-oxidase which contributes to oxidative stress.[42,43] Finally, hyperglycemia leads to activation of diacylglycerol (DAG) which promotes the development of atherosclerosis by activating the pathway of Protein Kinase C.[44]

5. Age

The prevalence of CS under 60 years is 0.5% *versus* <5% above 80 years old. Men under 75 years old have more chance of having CS than women of the same age. Although, after 75 years of age women have more chance of having CS than men.[11] The mechanism involved is probably due to an increase of inflammatory markers that naturally increase with aging.

6. Obesity

Obesity is considered an independent risk factor for CS although being also a risk factor for diabetes, hypertension and insulin resistance and some interaction between risk factors is an issue.[45,46]

7. C-Reactive Protein

High sensitivity CRP is a proinflammatory protein that increases the production of ROS over activation of neutrophils. So, this marker is correlated with higher risk of stroke.[47] Other mechanisms include increased expression of vascular cell adhesion molecules and foam cell formation.[48]

CLASSIFICATION AND DIAGNOSIS IN CS

The majority of plaques responsible for ischemic events are moderate, however there are some high-grade plaques which increase the probability of having a stroke. Most atherosclerotic plaques are stable/asymptomatic,[49] however, Anxin Wang *et al*, concluded that in patients with metabolic syndrome, the prevalence of unstable plaques is higher than the prevalence of stable plaques.[50]

It is of the most relevance in patients with asymptomatic carotid stenosis to determine the clinical and ultrasonographic plaque predictors of progression or regression of the stenosis. In a study, 1 121 patients with asymptomatic carotid stenosis were submitted to several clinical and ultrasound assessments during 6 months and 8 years (respectively). Regression was observed in 43 patients (3.8%) and progression in 222 (19.8%). No changes were observed in 856 patients (76.4%). Independent predictors of long-term stability were: younger age, more severe degrees of stenosis, absence of white areas in the atherosclerotic plaque and patients under lipid lowering therapy.[51] Independent predictors of progression were: high serum levels of creatinine, male gender, patients not under lipid lowering therapy, less severe degrees of stenosis and larger plaque area.[51]

However, the translation to clinical practice is hampered by the low frequency of progression (only 19.8% of the patients) and the low associated stroke rate (only 30% of the 30 strokes were in the progression group).[51]

The classification of CS can be determined mainly by two methods: NASCET (*North American Symptomatic Carotid Endarterectomy Trial*) and ECST (*European Carotid Surgery Trial*). The NASCET method grades stenosis by comparison of the local luminal narrowing and the diameter of the distal internal carotid artery while ECST is based on local grade degree of stenosis.[52] Despite the existence of these two methods, the most accepted and widespread is the NASCET method, although ECST can be used as well.[52]

Despite this, the 2018 *Guidelines* of ESVS don't recommend population screening for asymptomatic patients with CS (Class III, Level C). Furthermore, *The Society for Vascular Surgery* recommends that this routine screening should only be done in patients with multiple risk factors.[53]

TREATMENT INDICATIONS FOR ASYMPTOMATIC CSS

Independently of asymptomatic or symptomatic patients with CS, the core treatment is based on control of cardiovascular risk factors. However, some of these risk factors are modifiable (CRP, diabetes, obesity, hypertension, smoking, dyslipidemia) but others are not manageable.[11]

Lifestyle changes are paramount in the delay of the progression of CS. The 2014 *Guidelines of American Heart Association* recommends: DASH diet (vegetables, fruits, fish) and/or Mediterranean diet (same but with addiction on olive oil), weight reduction (body mass index <25), regular physical exercise (at least 40 min 3/4 times a week), limited consumption of alcohol and sodium (salt restriction to 2–3 g/day of salt) and smoking cessation.[54,55,56,57,58]

Chiuve SE *et al.*, concluded that if all these lifestyle changes were adopted, the risk of stroke could be reduced by 80% among women.[59] de Lorgeril M *et. al.*, refer that with Mediterranean diet it is possible to reduce the probability of developing a stroke and/or myocardial infarction (≥60%), if secondary prevention is adopted.[60] However, if primary prevention is adopted, stroke can be reduced by 50%.[55]

The management of patients with asymptomatic CS has some debatable aspects due to the annual risk of stroke for patients with severe asymptomatic carotid stenosis being nowadays as low as 2%-5%.[5,6,7,8] Additional, evidence has shown a decrease in the risk of stroke over time and this might be due to improvements in medical therapy.[61]

For asymptomatic patients with CS < 60%, medical treatment alone is favored and for asymptomatic patients with CS > 60%, invasive treatment is considered.[62,63] To warrant that the intervention is superior to best medical treatment alone, recommendations state that the perioperative risk of stroke in asymptomatic patients with CS should be inferior to 3%.[64] Selected patients on best medical therapy, with clinical and/or imaging features that classify them as having higher probability of suffering a stroke, might benefit from surgical procedure. Moreover, the patients that in the present are being treated with best medical therapy and don't benefit from surgical procedure, should be followed with regular carotid ultrasonography.[53]

TREATMENT OF ASYMPTOMATIC PATIENTS WITH CS

1. Pharmacological agents:

These patients must be treated with intensive medical treatment which is meant to correct the risk factors mentioned previously in order to lower the probability of developing a stroke.[65]

1.1. Lipid lowering agents: The most recent *Guidelines from the ESVS* recommend high dose statin therapy for primary and secondary prevention. *Asymptomatic Carotid Surgery Trial* (ACST-1) presents results for 10-year risk of stroke/death for asymptomatic patients taking lipid lowering agents (statins) of 13,4% while in patients without taking statins, was 24.1%.[66] Atorvastatin and rosuvastatin are the two pharmacological agents with more evidence support in reducing LDL to less than 70 mg/dl and also decreasing the levels of CRP to less than 2 mg/l. These results support the use of statins as primary prevention for stroke. The major therapeutic target is to obtain, at least, 50% reduction of the initial value of LDL or reach the value of less than 1.8 mmol L−1 (70 mg dL−1).[53,67]

1.2. Antihypertensive agents: Law MR *et al.*, refers that a decrease in stroke risk is related to a decrease of systolic blood pressure.[68] Huo Y *et al.*, in 2015, found out that enalapril and folic acid (despite enalapril alone) can reduce the risk of developing a first stroke, so they concluded that enalapril is the pharmacological agent with more evidence on hard outcomes in asymptomatic patients with CS.[69] The major goal in non-diabetic patients is to reduce arterial blood pressure to 140/90 mm Hg or less while in diabetic patients is 140/80 mm Hg (*Guidelines of hypertension 2018*).[70] Besides this, if a procedure is to be undertaken, the perioperative goal is less than 180/90 mm Hg.[53]

1.3. Antiplatelet therapy: Inadequate antiplatelet therapy can lead to a greater risk of developing major bleeding events, while not decreasing stroke risk. So, the benefit versus harm has to be carefully measured in every single patient. Thus, the more recent evidence recommends monotherapy with aspirin (instead of dual therapy) as first option, while clopidogrel is reserved for patients who have contraindications to aspirin. The doses should be between 75-325 mg of aspirin (low-dose aspirin) and 75 mg of clopidogrel.[53]

2. Carotid Endarterectomy (CEA) - surgical procedure

In some patients, carotid endarterectomy may be considered. There are some clinical predictors that may help in the decision such as: age, gender, stenosis severity, progression of stenosis, plaque characteristics, presence of silent emboli and/or microemboli and cerebrovascular reserve.

2.1. Age: Earlier studies concluded that, despite the age of the patient, it was beneficial to undergo CEA because the risk of suffering a stroke in the next 5 years would be lower when compared with medical therapy. However, further investigation indicates that half of these patients with more than 75 years old, would be dead in the long term follow-up after intervention. After including the perioperative risks, it was concluded that the benefit of undergoing CEA in patients older than 75 years was lower.[66] However, in patients older than 75 years of age and with an average life expectancy beyond 5 years, CEA may be beneficial.[53]

2.2. Gender: Multiple studies were performed and concluded that the probability of suffering a stroke within 5 years is decreased by CEA in men but not in women. Women would benefit from CEA only after 10 years of follow-up. This controversial finding is explained by the inherent lower risk of suffering a stroke in women not submitted to CEA, so it is expected that the benefit needs more time in order to be apparent.[72,66]

2.3. Stenosis severity: Despite what happens in symptomatic patients, stenosis severity alone is not a predictor of future stroke in asymptomatic patients with CS.[63,73] Patients with 50-69% stenosis have a lower risk of suffering a stroke compared to patients with more than 70% stenosis (0.8% *vs.* 1.4%).74. So, to make the decision of doing CEA, stenosis severity should be conjugated with other clinical features and not considered alone.[75] Hobson R. W. *et al.*, refers that with the presence of low-grade CAS in asymptomatic patients, the best choice of treatment is intensive medical treatment.[65]

2.4. Progression of stenosis: In the ACST was found out that patients with stenosis that had developed in two grades, had four times more probability of suffering an ipsilateral neurologic event.[76]

2.5. Plaque characteristics: DUS can characterize atherosclerotic plaques by evaluating, for example, the presence of ulceration. This finding may be associated with a higher probability of developing a thromboembolic event. Furthermore, the risk is also higher if the plaque is echolucent and with more lipids than fibrotic components.[77,78] The gray-scale median (GSM) is a standardized measurement of overall plaque echogenicity/echolucency. Lower values (associated with more echolucent plaques) are associated with higher long-term incidence of cardiovascular events.[79] However, its application are prone to some subjectivity, precluding its widespread use.

2.6. Presence of silent emboli and/or microemboli: Features of the atherosclerotic plaque on computed tomography (CT) or magnetic resonance imaging (MRI) may be predictors of silent emboli. Transcranial Doppler (TCD) can be used to identify active microembolization. This could be relevant because their presence can possibly predict an ipsilateral stroke.[80,81]

2.7. Cerebrovascular reserve: A reduced cerebrovascular reserve occurs when an incomplete circle of Willis is present or when intracranial or contralateral occlusive disease is present. This situation reduces cerebral perfusion pressure and is detected by transcranial Doppler flow on cerebral vessels. According to Gupta A. *et al.*, there is a significant association with a reduced cerebrovascular reserve and stroke.

So, with the integration of these clinical features it is possible to select an high risk patient with asymptomatic CS benefitting from CEA.[83,84] According to recommendations of the *American Heart Association* (AHA), only this type of patient should be considered for CEA.

CONCLUSION

With current best medical therapy, asymptomatic patients with CS have an annual risk of ipsilateral stroke of approximately 0.5%.[85] Therefore, the main goal is to promote control of risk factors.[11]

Due to elevated mortality and morbidity associated with CS, over the years, the identification of high-risk asymptomatic patients with CS has become one of the major goals in vascular surgery. The timely identification leads to timely treatment and this will lead to a decrease in morbidity and mortality.[12]

The 2018 Guidelines of ESVS recommend that a multidisciplinary team (MDT) should be present and should be composed by neurologists and vascular surgeons. This will allow an optimal treatment in patients undergoing CEA.[53]

Selim M H *et al.*, referred that medical treatment is more cost-effective than CEA and approximately only 50% of the patients benefit from CEA.[86]

The role of carotid artery stenting (CAS) in asymptomatic patients has been a matter of controversy in the past but at the moment there are no clear indications for its use in this subset of patients with CS.[53] The management of asymptomatic patients with CS remains a challenge, but it is already known that medical and surgical treatment are developing faster and in the future stroke risk will continue to decrease.[87]

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