Extracranial carotid stenosis: evidence based review

Estenose de carótida extracraniana: revisão baseada em evidências

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ABSTRACT
Extracranial cerebrovascular disease is one of the most important causes of death and disability worldwide and its treatment is based on clinical and surgical strategies, the latter being performed by conventional or endovascular techniques. The management of stenosis of the carotid bifurcation is mainly aimed at preventing stroke and has been the subject of extensive investigation. The role of clinical treatment has been re-emphasized, but carotid endarterectomy remains the first-line treatment for symptomatic patients with 50% to 99% stenosis and for asymptomatic patients with 60% to 99% stenosis. Stent angioplasty is reserved for symptomatic patients with stenosis of 50% to 99% and at high risk for open surgery due to anatomical or clinical reasons. Currently, the endovascular procedure is not recommended for asymptomatic patients who are able to undergo conventional surgical treatment. Brazil presents a trend similar to that of other countries in North America and Europe, keeping endarterectomy as the main indication for the treatment of carotid stenosis and reserving the endovascular procedure for cases in which there are contraindications for the first intervention. However, we must improve our results by reducing complications, notably the overall mortality rate.

Keywords: Carotid Stenosis. Carotid Artery Diseases. Endarterectomy. Carotid. Angioplasty, Balloon. Stents.

INTRODUCTION
In the last decades, Brazil has changed its profile of morbidity and mortality, and chronic diseases have been among the main causes of death and disability. Stroke is among the most relevant chronic diseases and is one of the main reasons for hospitalization and death, causing disability in the vast majority of patients, be it total or partial. Apart from this, only the presence of carotid stenosis would already be related to significant cognitive decline. In addition, stroke is the third leading cause of death in the United States and Europe, losing only for coronary artery disease and cancer. In Brazil, cerebrovascular diseases registered 160,621 hospitalizations in 2009, according to public data from the Unified Health System, Ministry of Health. The mortality rate was 51.8 per 100,000 inhabitants and the age group older than 80 years was responsible for almost 35% of the 99,174 deaths. According to Lessa et al., about 250,000 strokes occur each year in Brazil, of which 85% are ischemic in nature. The ischemic etiology, with the participation of extracranial carotid stenosis in its etiopathogeny, is present in at least 80% of cases, also in countries of North America and Europe.

Similar to the USA, in Brazil the proportional mortality rate for cerebrovascular diseases has decreased in the last 32 years. However, the absolute number of deaths due to cerebrovascular diseases in Brazil has remained relatively constant, around 21 thousand deaths per year between 2008 and 2013. This rate means about one death every 25 minutes over the five-year period. Such behavior may be influenced by the change in the structure of the national age pyramid, with the population aging and consequent increase in the life expectancy of the Brazilian of around 30 years, that is, from 45.5 years to 75.5 years in the period from 1945 to 2015.

Globally, cerebrovascular disease accounts for more than five million deaths per year (1 in 10) and approximately 3% of total health expenditure. In the European Union, about 21 billion euros were spent in 2003 with care for cerebral ischemia. From 2005 to 2050, the estimated cost of stroke to the US economy is estimated at $ 2.2 trillion. In the face of a global scale health problem, with significant associated costs,
there is a need for advances in stroke prevention and consequences.

Given the relevance of the theme, we carried out this review to compile the highest quality evidence about it. The aim is to discuss the current therapeutic options for extracranial carotid artery stenosis.

**METHODS**

We performed an electronic search using the DeCS terms (Health Sciences Keywords) in Portuguese (Carotid Stenosis, Carotid Artery Diseases, Carotid Endarterectomy, Balloon Angioplasty and Stents) in the LILACS (Latin American and Caribbean Literature In Health Sciences) and IBECS (Spanish Bibliographic Index of Health Sciences) databases, both through the electronic site (lilacs.bvsalud.org). We also performed a search with the MeSH (Medical Subject Headings) terms or their English correspondents (Carotid Stenosis, Carotid Artery Diseases, Endarterectomy, Carotid, Angioplasty, Balloon, Stents) in the Medline database via Pubmed (https://www.ncbi.nlm.nih.gov/pubmed/) and in the Cochrane database (http://www.cochranelibrary.com/). We stratified the results of these searches according to the Oxford levels of evidence\(^\text{11,12}\) to prioritize the highest quality levels for each clinical question (incidence, treatment, etc.). Finally, we search the DATASUS\(^\text{9}\) publicly accessible website for mortality data according to the International Classification of Diseases, Tenth Edition, ICD-10, for the cerebrovascular disease group, and for endarterectomy and stent angioplasty procedures. We tabulated the findings per year and gender, and we converted the information on financial data into US dollars according to the average annual Brazilian currency quotation.

**Clinical condition**

Extracranial carotid stenosis requiring surgical correction may occur in two different scenarios: in the asymptomatic population\(^\text{7}\) and in the symptomatic one\(^\text{5}\). In the latter case, the symptoms most related to carotid injury are stroke, transient ischemic attack (TIA), and the fleeting amaurosis in ipsilateral brain territories\(^\text{3,5}\).

Asymptomatic carotid stenosis can be divided into: 1) lesions with hemodynamic impairment (stenosis greater than 50%); and 2) ulcerated/irregular lesions, with increased risk of embolization, regardless of hemodynamic changes. Such asymptomatic stenoses are the potential cause of future strokes and can be identified with noninvasive tests\(^\text{13}\). However, natural history is not linear, displaying variable and controversial forms.

Some prospective, randomized studies have been conducted to determine the efficacy of carotid endarterectomy in asymptomatic patients. The European clinical trial CASANOVA did not show benefits of endarterectomy versus clinical treatment but, unfortunately, in its evaluation it presented serious methodological problems\(^\text{14}\). The Asymptomatic Carotid Atherosclerosis Study (ACAS) is the largest study ever performed for completely asymptomatic carotid lesions. It presents evidence that the surgical treatment of asymptomatic lesions with stenosis superior to 60% by arteriography is better than only the clinical treatment, with decrease in morbidity and mortality in the surgical group. More recently, another European clinical trial, the Asymptomatic Carotid Surgery Trial (ACST)\(^\text{16}\) included 3,120 patients with more than 60% stenosis (NASCET method\(^\text{17}\)). According to this study, asymptomatic patients under 75 years of age, males and stenosis superior to 60% are indications for surgery. The benefit is unclear for patients over 75 years and for women\(^\text{16}\).

As for TIA, which is defined as a neurological impairment not lasting for more than 24 hours, many affected patients never get to the hospital, so inpatient studies are not a true reflection of the disease.

The best studies in this regard are conducted in specific communities, such as Rochester, Minnesota, USA\(^\text{18,19}\). In this population, the incidence of TIA was 31 patients per 100,000 inhabitants per year at all ages, with an increase in incidence related to advanced age. TIA was also seen more frequently in men than in women of the same age group: 1.3 men for each woman. In those studies\(^\text{18,19}\), the predisposing factors for stroke after TIA were age, transient ischemia, hypertension and heart disease.
However, there are conflicting data when studying the natural history of TIA, mainly due to the lack of definition of the baseline damage to the study population. If the individuals studied have predominantly critical lesions with ulcerated plaques, they probably have subsequent stroke rates greater than individuals with less severe lesions do. Currently, TIA are classified as small strokes, with lesions better identified by more accurate imaging methods\textsuperscript{20}. Grigg et al.\textsuperscript{21} correlated TIA with heart attacks and cerebral atrophy. Therefore, TIA should be seen not as a benign disease, but as a sign that something worse may be coming. Thus, the ideal would be to approach carotid lesions before permanent clinical damage. However, only about 15% of patients with stroke had a previous TIA, a scenario that highlights the role of screening of asymptomatic carotid lesions\textsuperscript{3}.

**Indications for treatment**

Characterization of cerebrovascular ischemic signs and symptoms is important in determining treatment and prognosis. Most patients with extracranial carotid artery stenosis are asymptomatic and have their diagnosis through the identification of lesions on imaging tests such as vascular echography with Doppler\textsuperscript{22}.

Indications for treatment are made after imaging of the carotid bifurcation, which may be (1) for the neurologically symptomatic patient or (2) for the neurologically asymptomatic patient. Image acquisition of the cervical carotid artery is recommended in all patients with symptoms of ischemia in the carotid territory. In addition, there are two basic indications for the screening of asymptomatic patients: 1) patients with evidence of clinically significant peripheral vascular disease, regardless of age, and 2) potential high-risk groups, who may benefit from screening for asymptomatic stenosis. It is important to note that screening is not recommended in the presence of an isolated cervical murmur without other risk factors. Potential high-risk groups include: 1) patients with peripheral arterial disease, regardless of age; or 2) patients 65 years of age or older who have one or more of the following risk factors: carotid artery disease, smoking or hypercholesterolemia. In general, the more risk factors are present, the greater the benefit of screening\textsuperscript{3}. A Brazilian study found a prevalence of 84% of carotid stenosis in patients who already had peripheral arterial disease. In this same sample, carotid stenosis greater than 50% was present in 40% of patients and stenosis greater than 70% in 17% of them\textsuperscript{22}.

The treatment of extracranial carotid stenosis is usually composed of two strategies: clinical or surgical. The latter is performed by conventional or endovascular techniques. Conventional surgical treatment is commonly performed by carotid endarterectomy (CEA), and the endovascular, by carotid angioplasty with stent (CAS). The management of carotid bifurcation stenosis is particularly performed for the prevention of stroke and has been the subject of extensive research.

The greatest predictor of risk of a future stroke is the presence of recent ipsilateral neurological symptoms and not only the degree of carotid stenosis. The NASCET and ECST studies have shown that the risk of stroke is greater in the first month after an initial event and this neurological risk approaches the same risk of an asymptomatic patient six months after an event\textsuperscript{17,23}.

The role of clinical treatment has been re-emphasized for the treatment of carotid disease\textsuperscript{3}. A national reference document prepared by the Brazilian Society of Angiology and Vascular Surgery is in the production phase and should also highlight the importance of the best medical practice (BMP)\textsuperscript{24}. This BMP includes control of hypertension, smoking, reduction of cholesterol levels and use of antiplatelet agents.

In clinical decision-making for treatment, the systematic review is considered the best scientific evidence available because it refers to all the best randomized clinical trials on a particular subject\textsuperscript{25}. A Cochrane systematic review\textsuperscript{5} on CEA for symptomatic carotid stenosis with 35,000 patient-years of follow-up (included NASCET\textsuperscript{17}, ECST\textsuperscript{23} and VACSP\textsuperscript{26}) reported that the benefit of surgery was greater in men, in patients aged 75 years or older, and in randomized
patients within two weeks of their last ischemic event. This benefit fell rapidly with increasing the interval after the onset of ischemia. CEA was of some benefit between 50% and 69% of symptomatic stenosis and highly beneficial for stenosis between 70% and 99% without subocclusion. The benefits in patients with carotid subocclusion were marginal in the short term and uncertain in the long one. These results are generalizable only for patients operated by surgeons with low complication rates (less than 7% risk for stroke and death). The benefits of endarterectomy depend not only on the degree of carotid stenosis, but may also vary according to other factors, including the time between the neurological event and the CEA.

The Committee of the American Society for Vascular Surgery recommends CEA as the first-line treatment for symptomatic patients with stenosis between 50% and 99% and for asymptomatic patients with stenosis between 60% and 99%. The risk of perioperative stroke and death in asymptomatic patients should be less than 3% to ensure benefit for the patient. CAS should be reserved for symptomatic patients with stenosis of 50% to 99% and high risk for CEA due to anatomical or clinical reasons. CAS is not recommended for asymptomatic patients who can undergo conventional surgical treatment. Asymptomatic patients at high risk for intervention or less than three years of life expectancy should be considered for clinical treatment (BMP) as the first line therapy.

Another Cochrane systematic review with a total of 5,223 patients included in three randomized controlled trials (ACAS, ACST and VA) found that, despite a perioperative stroke rate or death of 3%, CEA reduced the risk of ipsilateral stroke and any cerebral ischemic event by about 30% over three years in asymptomatic patients with carotid artery stenosis (greater than 50% in the VA and greater than 60% in the ACAS and ACST trials). However, the absolute risk reduction was small (approximately 1% per year during the first few years of follow-up in the two largest and most recent trials), but could be larger if there was a longer follow-up.

Similar to these global results, the Brazilian view is more careful, especially concerning the results for asymptomatic patients. It is believed that CEA and CAS should be done only in reference centers with minimal perioperative risks (<3% for asymptomatic individuals and <7% for symptomatic ones). This would ensure better patient outcomes. Until some time ago, in Brazil and other major world centers, CAS was believed to be a good therapeutic option for asymptomatic patients. However, it is now known that CAS has limited indications for symptomatic patients, and is not currently recommended for asymptomatic patients that can undergo CEA.

**Surgical results**

Few operations are as studied in scientific circles as CEA. In 2005, 135,701 carotid interventions were performed in the USA. Of these, 122,986 (92%) were in asymptomatic patients (91% CEA and 9% CAS), while in the UK only 20% were in asymptomatic individuals. The main paradox of this intervention is the fact that it is intended to prevent long-term stroke, but in the course of its execution, it may be directly responsible for the occurrence of the same event in a small proportion of patients. Therefore, the intervention is justified only if the morbidity and mortality associated with it are significantly lower than one can expect with the clinical treatment alone.

The endovascular Balloon transluminal angioplasty and stent insertion may be a useful alternative to carotid endarterectomy in the treatment of atherosclerotic carotid artery stenosis. Bonati et al. published a Cochrane systematic review in 2012 that evaluated the benefits and risks of CAS in comparison with CEA or with clinical treatment alone in patients with symptomatic or asymptomatic carotid stenosis. They used 16 randomized clinical trials involving 7,572 patients. CAS was associated with a greater risk than the CEA for the outcomes death, myocardial infarction or any stroke, occurring between randomization and 30 days after treatment, in patients with symptomatic carotid stenosis and...
standard surgical risk. The rate of death or disabling/major stroke did not differ significantly between treatments. In patients with asymptomatic carotid stenosis, the effects of treatment on primary safety and on combined safety and efficacy results were similar to symptomatic patients, but differences between treatments were not statistically significant. They concluded that endovascular treatment is associated with an increased risk of perioperative stroke or death compared with endarterectomy. However, this excess risk seems to be limited to patients older than 70 years. The long-term efficacy of endovascular treatment and the risk of restenosis are unclear and require longer follow-up of existing studies. Further studies are needed to determine the best treatment for asymptomatic carotid stenosis.

The Brazilian gross procedure-related mortality rate from 2008 to 2013 was 2.42% for CEA and 2.14% for CAS, according to DATASUS data. See figure 1 for the evolution of mortality by type of surgery per year. These results differ from the reality found in places such as USA, Canada and Europe. The risk of perioperative mortality in the CREST study ranged from 0.3% for CEA and 0.7% for CAS. In Brazil, not only are the mortality rates for both types of treatment higher, but also the inequalities in the risk of death between the two surgical modalities are not reproduced.

**Economic aspects**

In Brazil, from 2008 to 2013, there was an absolute number of 7,461 CEA and 783 CAS performed. Expenses for all procedures were US$ 10,533,233.41 for CEA and US$ 1,648,300.65 for CAS. The average cost and length of stay for the procedure was US$ 1,357.09 / nine days for CEA and US$ 2,086.57 / five days for CAS, but the professional who performed the surgery received only an average of 23.61% (US$ 333.14) and 13.03% (US$ 273.31) of this amount, respectively. See figure 2 for the annual evolution of the average costs in this period, by type of surgery. We verified that 36.2% (US$ 645,570.10) of the total spent in each surgical procedure corresponds to the cost of the intensive care unit after CEA and 11% (US$ 30,645.78) after CAS. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), conducted in the USA, showed that the initial cost with CAS is higher, costing an average of US$ 1,025 more per patient when compared with CEA, which corroborates Brazilian data.

The reimbursement to the Unified Health System (SUS) in Brazil, created by article 32 of Law 9,656/1998 and regulated by the norms of the National Health Agency, is the legal obligation of private health insurance providers in order to restore the expenses of the SUS with any beneficiaries of services that are covered by private plans. However, the public health services do not obtain financial return in some of these cases, reducing
available resources and impairing the service to the user in general. According to DATASUS\(^9\), each CAS in 2014 was reimbursed at US$ 1,213, while only one stent in this same region at the same time cost about US$ 3,428.

We should also remember that the direct cost of treatment is not the only one impacting the patient’s life, his/her family and society as a whole, especially regarding stroke, which is the leading cause of disability in the world. There are also the costs with complementary treatments or for assistance to the patients with some sequelae\(^4\).

**DISCUSSION**

Brazil has a trend similar to that of other countries in North America and Europe in some respects, maintaining CEA as the main indication for the treatment of carotid stenosis, CAS being reserved for cases in which there are contraindications for the first intervention. However, national results still need to be improved, including complications related to the surgical procedure. Perhaps the execution of these procedures in centers of reference, preferably or even exclusively, favors better results\(^38,39\).

The causes of perioperative complications in carotid revascularization depend on a series of factors such as previous clinical conditions, intensive support and the surgical technique\(^40,41\). The postoperative carotid thrombosis, or the thromboembolism initiated at the site of the arteriotomy, remains a cause of perioperative stroke and is often related to technical defects in the arterial reconstruction procedure. In the endovascular technique, this is minimized by the routine use of protective brain mechanisms, such as filters, reverse flow systems or shunts, and by post-procedure angiographic control in the same intervention\(^30\). Other devices have been used to improve surgical outcomes of large vascular centers around the world. Cerebral electroencephalography, transcranial Doppler, cerebral electromagnetic flow measurement, and revascularization (either CEA or CAS) with local anesthesia and awaken patient for serial neurological examination are some of the techniques used\(^41\). An attractive alternative has been intraoperative imaging in carotid endarterectomy, as it is usually done in the endovascular technique\(^38,40,41\). However, catheter angiography and digital subtraction add risks and costs that would otherwise not exist in the classical endarterectomy technique, such as contrast nephrotoxicity, surgical intervention (arterial puncture), and the use of ionizing radiation\(^38,40,41\). Thus, in endarterectomy, mapping with vascular Doppler echography seems to play a relevant role, since it would avoid these additional risks. This intraoperative control in endarterectomy is not a routine of all services and its real effects are being discussed\(^38-41\).

Despite the overall reduction in the proportional mortality rate for age of cerebrovascular diseases, stroke continues to be the leading cause of disability in the modern world and a major cause of death. Its outcomes represent a great socioeconomic commitment to the patient, family members and the population in general. Efforts to prevent baseline illness should be accompanied by a medical team committed to improving their treatment outcomes in order to provide the best in medical evidence and care to their patients.
REFERENCES


Received in: 26/01/2016
Accepted for publication: 20/03/2017
Conflict of interest: none.
Source of funding: none.

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