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MANAGEMENT OF A SYMPTOMATIC CAROTID ATHEROSCLEROTIC DISEASE- UPDATE BASED ON INTERNATIONAL GUIDELINES

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ABSTRACT

A significant proportion of all ischemic strokes is directly caused by atherosclerosis in the internal carotid artery. The diagnosis and management of patients experiencing ischaemic episodes lie at the intersection of neurology and vascular surgery. The text is largely based on the latest European Society for Vascular Surgery (ESVS) 2023 and AHA/ASA Guidelines 2021 recommendations at the time of publication, summarizing the management of symptomatic carotid artery stenosis.

KEYWORDS

Symptomatic Carotid Atherosclerotic Disease, Carotid Stenosis, Carotid Endarterectomy, Carotid Artery Stenting

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Introduction

The location most frequently affected by carotid atherosclerosis is the carotid bifurcation, usually with extension into the proximal internal carotid artery. Atherosclerosis of the internal carotid artery at the bifurcation accounts for 10 to 17 percent of all ischemic strokes. [1], [2]

According to ECST/NASCET, patients defined as symptomatic are those who have experienced at least one neurological incident, such as transient ischemic attacks (TIAs) characterized by focal neurologic dysfunction or transient monocular blindness, or one or more ischemic strokes, in the last 6 months. [3]

In patients with symptomatic stenosis, the most beneficial treatment should be selected based on general and neurological condition, age, gender, degree of stenosis, anatomy, and other relevant factors, using the best medical treatment or qualifying for the procedure of choice.

Diagnostics

Digital subtraction angiography (DSA), CT angiography, ultrasound, and MRI are used to estimate the extent of extracranial internal carotid artery lesions.

In DSA and CT angiography, the degree of internal carotid artery stenosis is described according to three scales - NASCET (The North American Symptomatic Carotid Endarterectomy Trial) and ECST (European Carotid Surgery Trial) and CC (The Common Carotid), which differ in their choice of parameters. The CC scale has tended to be used historically and is now based on the other scales. NASCET measures the residual lumen diameter in the most stenotic segment of the artery and compares it with the lumen diameter of the unaffected internal carotid artery segment distal to stenosis. [4] ECST measured the lumen diameter at the most stenotic portion of the vessel and compared it with the estimated diameter of the carotid bulb. [5]

The greatest stenosis usually forms in the carotid bulb, which is naturally wider than the distal segments of the artery. For this reason, the results calculated according to NASCET are usually lower than in ECST. A complication in ECST, which may affect the calculation result, is the need to estimate the estimated diameter of the carotid bulb. It can be assumed that 50% according to NASCET is the same as 65% stenosis according to ECST. [6]

In addition, it is now also possible to estimate the degree of stenosis using carotid duplex ultrasound (CDUS). The test involves measuring the blood flow velocity at the stenosis site and the unchanged segment proximal to the coronary plaque. CDUS is a recognized diagnostic method for detecting moderate and severe stenosis.

Based on angiography and CDUS, lesion severity is determined. It is considered mild if <50%, moderate while 50-69%, and severe when it is 70-99%, near occlusion when the stenosis is severe and a "string sign" and occlusion is seen on examination.

Qualification for the procedure

Treatment of symptomatic extracranial carotid atherosclerotic disease includes medical management and may or may not include carotid revascularization. The decision for surgical treatment is based on a calculus of the potential risks associated with the procedure and the achievable benefits. Patients are eligible for revascularisation surgery based on the degree of stenosis, sex, age, expected age of survival, and neurological status. [7]

Patients likely to benefit generally are called those with severe or moderate symptomatic stenosis in whom the potential benefits of stroke risk reduction outweigh the perioperative risk. The effect depends on the degree of stenosis. Men may be more beneficial than women. The procedure should be performed as soon as possible after a neurological incident. The most beneficial for patients is performing revascularisation within 2 weeks of symptom onset.

For patients with 50-69% stenosis having a life expectancy of more than 3 years, revascularisation may be beneficial but performed up to 2 weeks after the incident. Treatment at a later date has uncertain benefits to the patient. [8]

Patients unlikely to benefit from the procedure are those with less than 50% stenosis, in severe clinical condition, and patients with neurological deficits. [7] According to the European Society for Vascular Surgery (ESVS) 2023 guidelines, patients who have had a disabling stroke (modified Rankin score ≥ 3), or whose area of infarction exceeds one-third of the ipsilateral middle cerebral artery territory, or who have altered consciousness/drowsiness, carotid vascular interventions should be avoided. [8], [9], [10]

The CETC meta-analysis indicated that patients with a stenosis of 20-49%, treated only with pharmacological interventions will not gain benefit from surgical intervention, however, in this group, the risk of recurrent ipsilateral stroke is about 7.4% at 3 years. In the case of recurrent neurological incidents, they

should be diagnosed to exclude other conditions potentially causing their complaints, such as atrial fibrillation or antiphospholipid syndrome. If no other cause is revealed, it may be reasonable to consider CEA, but only following a detailed neurovascular workup and multidisciplinary team review. [8], [11]

For patients with total occlusion, any means of revascularisation is not an option.

- Gender

Eligibility and management are the same for both sexes, but the benefit of CEA differs. Women with the same degree of stenosis have a lower risk of stroke than men, while the perioperative risk is higher. For this reason, men benefit more from the procedure. Rothwell et al. have shown that carotid endarterectomy is beneficial in women with 70% or more symptomatic stenosis, but not in those with 50-69% stenosis. Short-term benefits are therefore greater for men, although ACST-1 reported that women gained benefits from CEA at 10 years the same way as men. [7], [12]

- Age

The current 2023 guidelines of ESVS are based on the ACST-1 meta-analysis from the 2010 year, in which published outcomes were stratified for ages <65, 65-74, and > 75 years. Excluding peri-operative risks, CEA patients aged < 65 years had a five-year risk of any stroke of 1.8% vs. 9.6% after the best medical treatment, which makes them the group that benefits most from the intervention. CEA patients aged 65- 74 years had a five-year risk of any stroke of 2.2% vs. 9.7% after pharmacotherapy, while CEA patients aged > 75 years had a 5.5% risk of any stroke at five years vs. 8.8%. Half of those aged > 75 who were randomized to CEA died in less than five years and once peri-operative risks (3.7%) were included, there was no evidence that CEA conferred benefit in patients aged > 75. years. [13]

However, the newest big Meta-Analysis of studies from 1980-2022 years done by Ya Yuan Rachel Leung et al. draws different conclusions. The study collected data on perioperative events after CEA, such as stroke, myocardial infarction, and death in patients with symptomatic carotid stenosis in older patients. According to the collected statistics, the risk of perioperative stroke was 2.04% in octogenarians (people over 80) and 1.85% in nonoctogenarians, and perioperative death was 1.09% in octogenarians and 0.53%. However, during the last 3 decades, perioperative stroke or death has decreased significantly in octogenarians 7.78% before the year 2000 to 2.80% after 2010, which leaves the question of subjecting elderly patients to CEA still open. In the study the 1- and 2-year mortality and postoperative stroke rates up to 5 years post-surgery were comparable between older and younger patients. As stroke risk increases with age when on medical therapy alone, the findings support selective intervention in symptomatic elderly patients, particularly those without major cardiac comorbidity and other significant burdens. [14]

Until now, amaurosis fugax has been considered synonymous with TIA, classifying the patient as recently symptomatic. However, in recent guidelines non-hemispheric symptoms defined as isolated syncope (blackout, drop attack), and presyncope (faintness) have been defined as having no evidence to benefit from carotid (or vertebral) interventions if not co-existing with focal symptoms such as limb clumsiness, aphasia or dysgraphia. Intervention in these patients may be beneficial if more stroke risk factors are present, but amaurosis fugax alone is no longer an independent indication for surgery. [15]

Procedure techniques

Carotid artery revascularization options include carotid endarterectomy (CEA) or carotid artery stenting (CAS). Both methods have their advantages and disadvantages. The technique chosen is ruled out for each patient, taking into account the clinical condition, degree of stenosis, plaque morphology, post-radiotherapy status, and subsequent anatomical presentation of the vessels. The appropriate timing of intervention is a crucial issue when discussing symptomatic ICA stenosis. Generally, except in selected patient groups, symptomatic patients with moderate to severe stenosis in whom a carotid intervention is considered appropriate, it is recommended that this be performed as soon as possible, preferably within 14 days of symptom onset.

- Endarterectomy

CEA is the method of first choice for most patients because of its safer profile. Studies from different centers mostly agree that CEA is associated with a lower risk of any stroke, death/any stroke, death/disabling stroke, and death/any stroke/MI versus CAS. [8], [16]

It is also the method of choice for patients undergoing surgery in the period immediately after a neurological event. According to Rantner et al. Randomised Controlled Trial comparing stenting with CEA

for symptomatic carotid artery stenosis, CAS was associated with a substantially higher periprocedural risk during the first 7 days after the onset of symptoms compared with patients undergoing CEA. In patients after CAS, the risk of death or stroke was 8.3% versus 1.3% after CEA. [17]

Another group for whom CEA has been proven as a safer are the elderly. The results of CAS versus CEA favor the second method in people >75 years of age because of the lower risk of perioperative complications.

It is recommended that in a given center the 30-day risk of stroke/death when performing CEA in patients reporting ipsilateral carotid territory symptoms of less than six months should be 6% or less. [8]

According to NASCET, although surgery is associated with a higher risk of perioperative stroke than in a patient with lesions on only one side, for individuals with closed or severely stenosed contralateral ICA CEA is the method of choice, still performing better than CAS.

- Stenting

Is an alternative method to CEA, although statistically with a higher risk of perioperative stroke complications, but more suitable for specific patient groups.

CAS is the preferred method in cases of severe pulmonary, cardiac, or other anaesthesia-related risk-increasing disease.

Another group benefiting from CAS are post-radiotherapy patients suffering from radiation-induced stenosis. The preference for the endovascular method is due to the alteration of the tissues by the romix and both the different characteristics of the lesion and the difficulty for the operator. [8], [18]

CAS is also a second-line method when the patient has experienced ischaemic symptoms during an attempted CEA and ICA clamping.

Vascular treatment of neurological emergencies

About 10 to 20% of patients undergoing i.v. Thrombolytic therapy (TT) has an underlying mild to severe internal carotid artery stenosis and may be candidates for CEA or CAS. Although the importance of the time elapsed between the incident and treatment is generally emphasized, intervention is postponed for patients undergoing thrombolysis. Because of the hematological changes that occur after thrombolysis, patients become more susceptible to intracranial bleeding and hematoma formation at the puncture or incision site. In an attempt to balance the risk of complications and reoccurrence of ischaemic incidents, different studies and guidelines set the optimal timing of the procedure differently. The UK National Vascular Registry reported no association between CEA timing after thrombolysis and procedural risks when according to the US National Inpatient Sample reports the risk of post-operative stroke and intracranial hemorrhage is comparable to those non-TT patients only after 7 days. [19], [20]

The official 2023 ESVS Recommendations introduced a new recommendation in patients with moderate to severe carotid stenosis to consider delaying surgery 6 days after TT. [8]

Because of their high risk, patients with extensive neurological lesions of more than 3 points on the Ranson scale should be stabilized and have neurological improvement before surgical intervention. Studies indicate that the preoperative extent of ischaemic lesions seen in imaging studies is an independent predictor of postoperative strokes. As was reported by Pini et al. in a series of 489 recently symptomatic patients undergoing CEA, an acute cerebral ischaemic lesion volume 4000mm³ on pre-operative CT was predictive of postoperative stroke, with a sensitivity of 75% and a specificity of 63%. [11]

In patients with crescendo TIA and progressive stroke, emergency CEA may be considered. A crescendo TIA is defined as the occurrence of multiple TIAs in a short period, a minimum of 2 within 24 hours or at least 3 incidents within a week with full recovery in between. [21]

In this patient group, the procedure is associated with a high risk of perioperative- 30-day stroke or death after CEA was 20% in patients with stroke in evolution and 11% in patients with crescendo TIAs. However, by selecting patients with small ischaemic areas and crescendo TIAs accordingly, the risk of death or stroke can be reduced to 2-8% in patients with small ischaemic lesions for stroke in evolution and 0-2% for crescendo TIAs. In this setting, emergency CEA seems a reasonable treatment, looking at the poor prognosis of these conditions. [22]

Based on these results, the ESVS recommends considering performing emergency CEA in patients with moderate to severe lesions from ICA presenting crescendo TIA within 24 h. [8], [21]

For patients after mechanical thrombectomy, there are no uniform guidelines as to the greater benefit of CAS or CEA. CAS seems to be the more preferred method in this situation, the 2021 German-Austrian

guidelines, advise that endovascular treatment with emergency stenting and thrombectomy is indicated. [23] According to the ESVS, in cases of acute ischaemic stroke undergoing intracranial mechanical thrombectomy with a 50-99% carotid stenosis and a small area of ipsilateral infarction, a combined procedure with CAS may be considered if the circle of Willis artery is not well developed or there is poor blood flow from the ipsilateral internal carotid artery. [8]

Best medical treatment

Patients who have experienced a TIA with an ABCD2 score of greater than 4 or a minor ischaemic stroke with A score of 3 or less on the National Institutes of Health Stroke Scale (NIHSS) and no persistent disabling neurological deficit with carotid artery stenosis should be given appropriate pharmacological treatment. The highest risk period for recurrent stroke is the first 7- 14 days after symptom onset. For this reason, the international guidelines strongly recommend antiplatelet therapy selected for further management. Best medical treatment should be instituted without delay within 24 hours after the incident after imaging studies have confirmed the absence of intracranial bleeding. [8]

It is recommended to extend DAPT 10-21 days after the incident, then switch to single antiplatelet therapy permanently, if there are no contraindications. The inclusion of DAPT should take into account the extent of the stroke, as it is not to be used for major strokes because of the increased risk of intracranial hemorrhage in these patients. [24]

- Patients after recent fibrinolysis or mechanical treatment of stroke

As with qualification for surgery, special consideration is given to the risk of intracranial hemorrhage during the initiation of anticoagulant and antiplatelet therapy.

For symptomatic patients undergoing thrombolysis, it is recommended that intravenous heparin and antiplatelet therapy be withheld for 24 hours after completion of thrombolysis, but antiplatelet therapy should then be commenced before any carotid intervention is undertaken.

For patients undergoing early carotid interventions after thrombolysis, active treatment of post-interventional hypertension is recommended to reduce the risks of parenchymal hemorrhage.

- Patients qualified for CEA

In the case of recently symptomatic carotid stenosis patients in whom CEA is being considered, it is recommended that a team consisting of a vascular surgeon, and a stroke neurologist, in cooperation with an anesthesiologist develop local protocols to specify preferred antiplatelet therapy. Delay in the procedure is important, and the inclusion of DAPT, depending on the type of anesthesia and the center, may be an obstacle to qualification for anesthesia. Each patient should receive appropriate antiplatelet pharmacotherapy in the perioperative and postoperative periods, with long-term monotherapy. In recently symptomatic patients with moderate to severe carotid stenosis awaiting CEA, deciding on monotherapy, 300-325 mg daily aspirin should be used for 14 days, then the dose reduced to 75-160 mg. Higher doses of aspirin >325 mg are not recommended in this group of patients.

- Patients qualified for stents

For recently symptomatic patients undergoing carotid stenting, combination antiplatelet therapy with aspirin (75-325 mg daily) and clopidogrel is recommended. Clopidogrel in a dose of 75 mg daily should be started at least three days before stenting or as a single 300 mg loading dose in urgent cases. Aspirin and clopidogrel should be continued for at least four weeks after stenting and then long-term antiplatelet monotherapy (preferably clopidogrel 75 mg daily) should be continued indefinitely.

- Not qualified for procedure

For recently symptomatic carotid stenosis patients who are not being considered for CEA or stenting and who are intolerant of, or allergic to, aspirin and clopidogrel, dipyridamole monotherapy or ticagrelor monotherapy is recommended. [8] The AMBDAP study revealed similar reductions in embolization on aspirin and dipyridamole versus aspirin and clopidogrel, although this now needs testing in large phase III trials. [25]

General Recommendations

Due to the pathophysiology of atherosclerotic plaque formation, it is currently recommended that every patient with symptomatic ICA stenosis, in addition to antiplatelet therapy, also receive lipid-lowering therapy as the long-term prevention of stroke, myocardial infarction, and other cardiovascular events. Patients should receive lipid-lowering therapy before vascular intervention, regardless of whether they are being prepared for CEA or CAS. In those who do not reach their lipid targets on maximum doses or maximum tolerated doses of statins, ezetimibe 10 mg daily is recommended. In cases where patients are intolerant of standard treatment, or not achieving target low-density lipoprotein levels on statins, with or without ezetimibe, additional or alternative treatment with PCSK9 inhibitors should be considered. [8] In addition to antiplatelet and lipid-lowering pharmacotherapy, it is important to take care of the patient's general condition and control other systemic diseases, such as hypertension and diabetes. In the Northern Manhattan Study, it was shown that diabetes mellitus (DM) patients are more likely to develop a stroke compared to the population without DM and 20% of DM patients will die after a stroke. [26] A very important element of comprehensive patient care is strict BP control.

A Cochrane review reported that the use of antihypertensive therapy in the form of an ACEI and/or a diuretic in patients with a history of stroke or TIA reduced the risk of recurrent stroke by 24%. [27]

Conclusions

The choice of procedure largely depends on the patient's medical condition. The first-choice method in most cases is CEA. CAS is the preferred method only in certain groups of patients due to a higher risk of perioperative stroke.

In each case, the patient should be looked at holistically, in addition to the ICA stenosis itself, also treating other systemic diseases and providing him with antiplatelet therapy and lipid-lowering.

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