Section A-Research paper

Brief Insight about Internal Carotid Artery (ICA) Stenosis and Management

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Abstract

Background: 30% to 60% of all cerebral infarcts. The distribution and severity of atherosclerotic cerebrovascular diseases varies among the patients of different ethnic origins. In Egypt, extracranial carotid atherosclerosis is not common. the majority of ischemic patients enrolled in the study had non-significant extracranial carotid stenosis while in the western countries, the majority of symptomatic patients have significant extracranial carotid Stenosis. Carotid artery stenosis corresponds to 15%-20% of overall ischemic strokes for both symptomatic and asymptomatic (silent) strokes. Carotid artery disease can be characterized as symptomatic if associated with stroke or TIA or as asymptomatic in the absence of such symptoms. Asymptomatic carotid stenosis (ACS) is commonly defined as a ≥ 50% atherosclerotic narrowing of the extracranial internal carotid artery in the absence of retinal or cerebral ischemia in the preceding 6 months. Extracranial atherosclerotic disease (ECAD) can be managed with optimal medical therapy (OMT), carotid endarterectomy (CEA), and carotid artery stenting (CAS). Treatment options largely depend on the presence of symptoms, severity of stenosis, individual factors, efficacy and risk of complications

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Keywords: Internal Carotid Artery, Stenosis, management

Introduction

Atherosclerosis of the large cerebral arteries accounts for 30% to 60% of all cerebral infarcts. The distribution and severity of atherosclerotic cerebrovascular diseases varies among the patients of different ethnic origins. In Egypt, extracranial carotid atherosclerosis is not common. This is seen clearly from the results done by **Zakaria et al, in (1)in his study,** showing that the majority of ischemic patients enrolled in the study had non-significant extracranial carotid stenosis while in the western countries, the majority of symptomatic patients have significant extracranial carotid Stenosis.

The result of this study was very similar to the results of a previous one done also by **Zakaria et al, in (1),** performed at the stroke unit of the Ain shams University hospital on 148 patients and showed that 77% had non-significant extracranial carotid stenosis. Thus, the distribution of atherosclerosis in the carotid artery may be different among the Egyptian population, similar to the black Americans, who also show minimal lesions in the extracranial parts of the internal carotid artery **(1).** Another study done by **Abd Allah F. et al, in (2)**, revealed also that extracranial atherosclerotic carotid disease is rare among Egyptians.

In Western countries, extracranial carotid atherosclerosis accounts for 30% to 40% of cases of ischemic cerebrovascular diseases. Asian populations have been reported to have a lower prevalence of extracranial carotid and vertebral artery disease in comparison with Caucasian populations ***(3).***

Carotid artery stenosis corresponds to 15%-20% of overall ischemic strokes for both symptomatic and asymptomatic (silent) strokes. Carotid artery disease can be characterized as symptomatic if associated with stroke or TIA or as asymptomatic in the absence of such symptoms. Asymptomatic carotid stenosis (ACS) is commonly defined as a ≥ 50% atherosclerotic narrowing of the extracranial internal carotid artery in the absence of retinal or cerebral ischemia in the preceding 6 months ***(4).***

The estimated 2 years risk of stroke in symptomatic patients is 22% with 50%-69% stenosis and 26% with 70%-99% stenosis while in asymptomatic patients, the estimated 5 years risk is 7.8% with <50% stenosis vs 18.5% in 75%-95% stenosis ***(5).***

A number of studies have demonstrated that asymptomatic carotid artery stenosis patients had significantly poorer performance in executive function and memory, indicating that "asymptomatic" carotid stenosis might not be truly asymptomatic, while Symptomatic carotid disease is associated with a high risk of recurrent cerebral ischemia ***(5).***

Currently, embolization is considered the most common mechanism causing ischemic strokes from atherosclerotic lesions in the carotid bulb. Thrombosis and low flow are other possible mechanisms ***(3).***

Prevalence of moderate ACS varies from < 1 to 7.5%, whereas the prevalence of severe ACS (≥ 70% stenosis) ranges from 0 to 3.1%. Risk for ACS increases with age and cigarette smoking status, and is slightly higher in men than in women. Additionally, the risk of developing carotid artery stenosis increases in individuals with a higher prevalence of cardiovascular related diseases such as diabetes mellitus, smoking, dyslipidemia, and hypertension. These conditions are also associated with increased risk for cerebrovascular events including ischemic and hemorrhagic stroke, as well as vascular dementia and Alzheimer's disease. Even at sub-clinical levels, however, cardiovascular risk factors including ACS, are associated with alterations in brain structure, and neurocognitive dysfunction ***(6).***

Treatment of Extracranial Atherosclerotic Stenosis

Extracranial atherosclerotic disease (ECAD) can be managed with optimal medical therapy (OMT), carotid endarterectomy (CEA), and carotid artery stenting (CAS). Treatment options largely depend on the presence of symptoms, severity of stenosis, individual factors, efficacy and risk of complications ***(7).***

A) Medical Management.

Patients with ECAD can benefit from OMT consisting of antiplatelet agents, stains, and risk factor control.

Statin

Statins have been routinely used in RCTs and clinical settings. A meta-analysis of 26 studies reported efficacy of statin with a dose-dependent protective effect ***(8).***

Antiplatelet

Although the benefit of single antiplatelet agent for stroke prevention in asymptomatic carotid stenosis has not been confirmed by randomized controlled trials (RCTs), current guidelines recommend lifelong low-dose aspirin as part of OMT to reduce the risk of stroke and other cardiovascular events**.** Dual antiplatelet therapy has been recommended during the periprocedural period and for at least 1month after CAS ***(6).***

Risk factor control

Hypertension is an important risk factor for ECAD, and the goal of blood pressure (BP) in non-diabetic patients with asymptomatic carotid stenosis is recommended below 140/90mm Hg. Patients with

concomitant diabetes are at particularly increased risk of cerebrovascular events, for whom a diastolic BP ≤85mm Hg has been recommended by the latest European Society of Cardiology guidelines ***(7).***

B) Interventional management.

Previous studies have shown up to 26% risk of ipsilateral ischemic stroke over 2 years in patients with symptomatic severe carotid artery stenosis despite OMT. It is therefore pivotal to consider more effective intervention. Interventional management consisting mainly of carotid endarterectomy (CEA) and carotid artery stenting (CAS) has been shown to decrease the stroke rate in patients with carotid artery stenosis

Carotid endarterectomy

ECST (European Carotid Surgery Trial) and NASCET (North American Symptomatic Carotid Endarterectomy Trial) trials have demonstrated significant benefit of surgical intervention over medical treatment for secondary stroke prevention in patients with ipsilateral 50%–99% symptomatic carotid artery stenosis, with maximal efficacy in patients with 70%–99%carotid stenosis ***(9).***

Of note, pooled analysis of these trials showed no benefit of CEA for patients with 0%–49%stenosis. For asymptomatic carotid stenosis, ACAS (Asymptomatic Carotid Atherosclerosis Study) and ACST-1 (Asymptomatic Carotid Surgery Trial) established the benefit of CEA over medical therapy alone in patients with 60%–99%carotid stenosis ***(10).***

However, both studies started before the era of modern OMT, the widespread use of which has reduced the annual stroke rate significantly since the 1990s. In ACST-1, for example, the percentage of statin use has increased from 10% in the early period of recruitment to 80% by the end of follow-up. As such, it may be reasonable to consider OMT first for some patients who were considered surgical candidates in the past ***(7).***

CEA versus CAS

CEA was first described in 1975 by De Bakey and has since become a conventional treatment for severe ECAD. As an alternative to CEA, CAS emerged in 1989 and has proven to be effective and safe for carotid artery stenosis. A number of RCTs have been done to compare the two interventional therapies. Most studies have shown a higher rate of periprocedural stroke from CAS and a higher incidence of myocardial infarction (MI) with CEA. Similar findings have also been reported by a Cochrane review of 7572 patients, including 16 trials in 2012, and a meta-analysis of 6526 patients from 5 RCTs in 2017. Similar long-term outcomes, including the rate of ipsilateral ischemic stroke or death with CAS and CEA, have been reported by most of the studies. CEA is preferable to CAS in patients over 70 years old ***(7).***

Current guidelines

In general, current guidelines recommend OMT as an essential treatment for all patients with carotid artery stenosis, whereas symptomatic patients with >50% stenosis and asymptomatic patients with >60% stenosis be considered for additional interventional management if the estimated periprocedural complication rate is <3%.The choice between CEA and CAS should be made after considering demographics (e.g., age and gender), anatomic, clinical (e.g., contralateral TIA/stroke) and imaging (ipsilateral silent infarction, stenosis progression, spontaneous embolization on transcranial Doppler, impaired cerebral vascular reserve, large plaques and so on) features ***(7).***

Extracranial atherosclerotic disease and cognitive impairment:

The notion that carotid disease and impairments in blood flow can have consequences on cognitive functions was initially postulated in the early 1950s by Fisher ***(11).*** Since then, several studies have identified associations between cognitive deficits and carotid occlusions, although cognitive impairment can also occur as the result of cerebral emboli, small vessel disease, white matter lesions and silent cerebral infarction. ***(12).***

In terms of cerebral blood flow, blood flow was measured by **Tatemichi et al., (13)** in a 55-year-old man with bilateral internal carotid artery occlusions presenting with a subacute onset of severe behavioral and cognitive changes. Quantitative cerebral blood flow (CBF) and positron emission tomography studies showed a 40% to 50% reduction in blood flow and metabolism. After extracranial–intracranial bypass, the patient demonstrated neuropsychological improvement accompanied by significant increases in CBF and metabolism.

Yamauchi et al, (14) revealed that cerebral hypometabolism and perfusion measured by oxygen-15 positron emission tomography (PET O15) have been associated with cognitive impairments and atrophy of corpus callosum in carotid artery disease.

In terms of White Matter Lesions, carotid stenosis leads to significant hypoperfusion in the penetrating arteries arising from the proximal segments of the circle of Willis and only affects the distal penetrating arteries to a lesser extent. It was detected that the degree of carotid stenosis in a population with high grade occlusion (70–99%), appeared to be positively correlated with the total white matter hyperintensity (WMH) lesion burden**.** Furthermore, a study of patients with recent acute lacunar infarcts , found that the extent of carotid disease was associated with a particular increase in periventricular WMH ***(15).***

In a larger case series, 25 patients with unilateral carotid occlusion and poor neuropsychological performance underwent extracranial–intracranial bypass. Cognitive improvement was associated with increased CBF, increased cerebrovascular reactivity (CVR), and decreased oxygen extraction fraction **(16).**

Hypoperfusion of functional neurons may lead to hypofunctional neurons. Prolonged hypoperfusion can lead to neuronal infarction. After that, increasing cerebral blood flow, causes no change in cerebral metabolic rate of oxygen (CMRO2) with no cognitive improvement thus the interval between hypofunctional neurons and neuronal infarction "is the time to do the revascularization, which can influence cognition ***(16).***

The Trømso study compared 189 patients with carotid stenosis to 201 healthy controls. Patients with carotid disease had significantly lower scores on tests of attention, psychomotor speed, memory, and motor function than controls, with an association between degree of stenosis and cognitive dysfunction ***(17).***

Ruitenberg et al. **(18)** identified CBF as a risk factor that precedes atrophy of amygdala and hippocampal structures. Compared to subjects with reduced CBF, individuals with greater cerebrovascular reactivity (CVR) were more likely to have larger amygdala and hippocampal volumes and less likely to show cognitive decline over a 6.5-year follow-up period.

In good agreement with the previous findings, **Romero et al. (19)** identified that carotid atherosclerosis was correlated with measures of brain ischemia and cognitive impairments.

Furthermore ***Marshall et al.*** **(16).** showed that unilateral cerebral hypoperfusion and hemispheric hemodynamic failure with increased OEF were associated with cognitive impairments in patients with symptomatic carotid artery disease. Increased ipsilateral OEF (≥ 1.13) as measured by PET was associated with cognitive dysfunction in 43 patients with symptomatic carotid artery occlusions, compared to those who were without these PET changes. This association held even for patients who had TIA but no stroke.

Balestrini et al. in (20) showed that severe unilateral carotid stenosis was associated with increased rates of cognitive deterioration during a 3-year follow-up in 210 patients with asymptomatic carotid artery disease. At follow- up, patients with severe unilateral ACS were more likely to show cognitive deterioration compared to controls.

Comparably, another three-year follow-up study examined cognitive performances in 159 patients with asymptomatic bilateral carotid stenosis (70 to 99%). Patients with bilaterally impaired CVR at baseline

had the most rapid cognitive decline as assessed by the change in the Mini-Mental State Examination (MMSE) at 36 months ***(21).***

Haratz et al. (22) tested the association between impaired CVR and cognitive scores. Hemodynamic dysfunction ipsilateral to the stenosis negatively correlated with lower global cognitive scores and poorer executive function in 98 patients with impaired CVR. The critical association between hemodynamic dysfunction and cognitive impairment supports the plausibility that hypoperfusion mediated cognitive impairments might be reversible.

Similarly, in the Framingham Offspring Study, participants (n = 1975) without dementia or history of stroke were assessed with carotid ultrasound, MRI, and neuropsychological tests. Carotid stenosis was associated with reduced cognitive performance and indices of cerebral ischemia on MRI ***(23).***

Tao et al. (24) showed that silent infarction and cerebral hypoperfusion are the main mechanisms in the development of cognitive decline in asymptomatic carotid artery stenosis patients, indicating that cognition may be improved by reducing silent infarction and restoring CBF. In his study, he showed increased in regional CBF mainly in the left frontal gyrus, anterior cingulate, left occipital gyrus, and left cerebellum after CAS. Since frontal gyrus and anterior cingulate consisted of regions that mediated memory and executive function, increased CBF in these regions may contribute to the cognitive improvement after CAS.

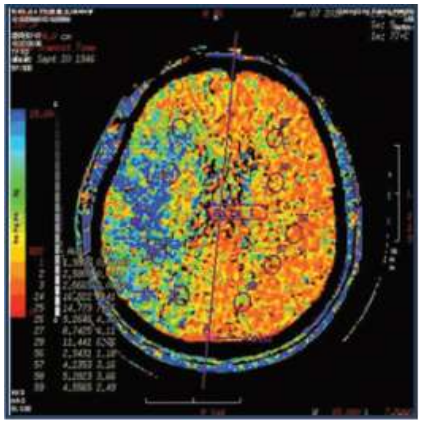

Figure 1: Brain perfusion computed tomograph showed hemisphere hypoperfusion due to ipsilateral severe right carotid stenosis

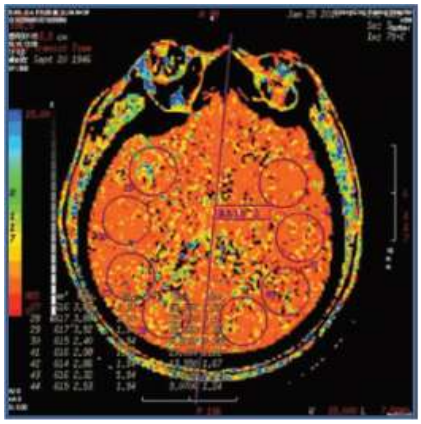

Figure 2: Three weeks after right carotid stenting, ipsilateral hemisphere perfusion was improved.

Marshall et al. **(16).** investigated the association between regional cortical blood flow and regional cortical thickness in patients with asymptomatic unilateral high-grade internal carotid artery disease without strok. He found that cortex was thinner on the side of occlusion in motor cortex where the blood flow was significantly lower.

The association between cortical blood flow and cortical thickness in carotid arterial territory with greater thinning on the side of the carotid occlusion suggests that altered cerebral hemodynamics is a factor in cortical thinning. Because cortical thinning has been associated with cognitive impairment in several disease states, it is possible that cognitive impairment reported in high grade carotid artery disease may be

driven by the hemodynamic effects of atherosclerotic arterial stiffness, and by chronic low cerebral blood flow on the side of high grade carotid stenosis, a notion which has support in animal models of chronic hypoperfusion **(16).**

Due to the persistent autoregulatory processes by which the brain works to maintain homeostatic balance, there is tantalizing evidence that restoration of anterograde blood flow can reverse hypoxia-induced changes, and restore cognitive function ***(6).***

However, whether cognitive impairment could be ameliorated following protracted periods of ischemia remains an open question. Speculation regarding the reversibility of cognitive dysfunction in people with carotid stenosis became one catalyst for revascularization interventions ***(6).***

Cognition Following Revascularization in Asymptomatic Patients with ECAS

Research that compares the effect of carotid endarterectomy (CEA) and carotid artery stenting (CAS) on cognitive performance has included both symptomatic and asymptomatic patients, and yielded evidence to suggest that subclinical cognitive impairments may indeed be modifiable. However, no significant differences between procedures have emerged. ***Lunn et al. (25)*** reviewed 28 studies and found that 57% reported cognitive improvements following CEA, whereas the remaining 43% reported cognitive decline or no change.

Increasingly, research has been aimed at exploring whether asymptomatic carotid disease increases the risk for cognitive decline. The preponderance of the evidence supports associations between unilateral carotid atherosclerotic stenosis or occlusion and cognitive decline in the absence of physical signs and symptoms. Eleven studies were identified and are summarized below.

Fearn et al.(26) used ultrasonography to measure CVR in 159 asymptomatic CEA patients. Cognitive tests were administered before and after revascularization. At 2 months postoperatively, memory, attention, and accuracy had improved in CEA patients, with the greatest improvements found in patients with impaired CVR at baseline.

Borroni et al. (27) evaluated 78 patients with severe carotid stenosis who underwent CEA. Uniquely, the authors divided participants into two groups based on baseline cognitive results: those with no cognitive impairment (CON), and a group who showed mild vascular cognitive impairment (mVCI). Cognitive testing was conducted 1 week before and 3 months after revascularization. At the 90-day follow-up, it was found that 100% of the mVCI group maintained (40%) or improved cognitive function (60%).

Bossema et al. (28) compared 56 patients with severe ACS scheduled for CEA, with 46 healthy control subjects. Baseline cognitive assessments indicated reduced performance on attention, verbal and visual memory, planning of motor behavior and psychomotor skills, and executive functions for CEA patients compared to the healthy controls. The patient group was reassessed again at 3 and 12 months. Significant improvements were reported for verbal memory, executive functioning, and planning speed for CEA patients.

Tiemann et al. (29) found that preoperative cognitive performance improved significantly in 22 patients with ACS after CAS. Baseline group means of cognitive z scores (i.e., statistical comparisons to a normative population with a normal distribution) did not reveal cognitive deficits; however, single-subject cognitive deficits were recorded for 81% of patients in one or more cognitive domains. Mean z-scores at 6-week follow-up revealed significant improvements in verbal memory, and verbal memory span.

Feliziani et al. (30) enrolled 46 severe ACS patients ≥ 65 years of age. Twenty-four patients received CAS and 22 received CEA, based on clinical characteristics. Cognitive function was assessed prior to revascularization, at 90 days, and again 12 months after intervention. For all cognitive assessments, no significant differences were observed between groups at any time point. Cognitive performance over time did not differ between groups, and similar results were reported for performance over time within groups. The authors concluded that carotid revascularization, regardless of procedure, does not alter cognitive functions acutely or chronically in either CEA or CAS patient groups.

Grunwald et al. (31) compared 41 patients with ACS who underwent CAS, and a group of seven healthy controls. Both groups underwent cognitive testing (cognitive speed and memory function tests) 1 day pre- and 3 months post-intervention. At follow-up, a significant improvement in cognitive speed, but not memory function, was observed in the CAS group, whereas no difference in either domain was found both group.

In a non-randomized prospective study with patients with severe ACS undergoing CEA (n = 25) or CAS (n = 21), individuals underwent cognitive testing 1 to 3 days before revascularization, and again at 4 to 6 months. Cognitive tests included TMT-A & -B, Processing Speed Index, Boston Naming Test, Working Memory Index, Controlled Oral Word Association Test, and Hopkins Verbal Learning Test. A composite score was generated for each patient at baseline and follow-up, and change scores between the two time points were used as the primary outcome. A secondary analysis compared change scores for each individual test. Results showed overall improvements in cognitive functions. Compared to baseline, composite change scores improved for both CEA and CAS groups at follow-up; however, non-significant differences emerged between the two groups. In addition, scores for the individual cognitive function domains improved for each test except for Working Memory Index, which was decreased in 80% of CEA patients, but showed improvement in the CAS group. Conversely, improvements were reported for each cognitive test except for Processing Speed Index, which decreased in 18/21 CAS patients ***(23).***

Chen et al. (32) compared 34 patients with severe ACS, who underwent CT perfusion scans to measure CBV, CBF, and a cognitive assessment at baseline and 3 months post procedurally. Following stenting, patients were subdivided into three groups: Group 1 (G1), 6 patients, included those with ipsilateral ischemia and failed stenting procedure; Group 2 (G2), 17 patients, included those with ipsilateral ischemia and successful CAS; while Group 3 (G3), 11 patients, included those with no ischemia (as indicated by CT perfusion) and successful CAS. Ischemia was reversed in 94% of patients in G2 in contrast to patients in G1 or G3 in which there were no perfusion changes. Furthermore, cognitive changes were reported for patients only in G2. Specifically, scores on ADAS Cog Alzheimer's measure, MMSE, and Color Trail Making A were all improved after revascularization. Additionally, there was a trend toward improvement in Color Trail Making B. No significant changes across any test parameters were observed in G1 or G3. Overall, the results from this study provided a strong demonstration of improved cognition following CAS related to the improvement in cerebral hemodynamics.

In a small study of 22 patients (CEA, n = 10) and (CAS, n = 12) with ACS, Picchetto et al. assessed the effect of revascularization on cognition. Cognitive assessments were conducted 1 to 3 days before, and 3 months after CEA or CAS, and included: Wisconsin Card Sorting Test, and the Mental Deterioration Battery (Rey AVLT immediate and delayed recall, copying drawings, phonological verbal fluency). Post-intervention performance was significantly improved on the Rey AVLT immediate recall and phonological verbal fluency. CEA or CAS of the left carotid correlated with improved performance on verbal fluency, prompting the authors to conclude that the side of occlusion accounted for most of the observed

improvements in these two domains, especially because the two tests are measures of highly lateralized verbal abilities ***(33).***

Ortega et al. (34) conducted a prospective study with 25 patients with ACS scheduled to undergo CAS with flow reversal. Cognitive function was assessed immediately prior to CAS, and again 6 months after surgery. Mean overall cognitive scores were reduced in several domains at baseline. Post-procedurally, significant improvements in mean global cognitive scores ($p = .002$) and information processing ($p = .018$) were observed. Mild but insignificant improvements in visuospatial function, memory, executive functions, language, and attention were reported.

A study by ***Kougias et al. (35)*** replicated previous findings. Fifty-five ACS patients, 28 (CEA), and 27 (CAS), with underlying cardiovascular risk factors (coronary artery disease or congestive heart failure was present in 78% of CEA patients and 51% of CAS patients, respectively) underwent domain specific cognitive testing (memory, processing speed, executive functioning, visual spatial skills, attention) at baseline, 6 weeks, and again at 6 months. Compared with CEA, cognitive processing speed was superior in the CAS group at 6 weeks. Executive functioning and motor function were also superior in the CAS group at 6 months. Tests of attention, memory, and visual-spatial skills were similar between CAS and CEA patients at 6 weeks and 6 months. While this study showed recovery of cognitive function, the improvements were mainly limited to the CAS group.

Taken together, these studies provide converging evidence supporting revascularization as a way to reverse of cognitive decline in many patients with ACS. The evidence provides additional support for the hypothesis that restoration of cerebral blood flow is sufficient to facilitate cognitive recovery. Overall, most revascularization studies that reviewed confirm cognitive changes after revascularization ***(6).***

Future direction

Due to significant advances in medical therapy, risk reduction and endovascular technology in recent years, there is renewed discussion regarding the superiority of CEA over CAS and interventional management over the best medical therapy, especially in asymptomatic carotid stenosis. Several studies are being conducted to address these issues. Asymptomatic carotid surgery Trial-2 (ACST-2) is an RCT comparing immediate and long-term safety and efficacy of CEA versus CAS in a patient with severe asymptomatic stenosis. The primary endpoint is 30-day MI, stroke and death, with subgroup analysis emphasizing health economic aspects including procedural and stroke-related healthcare costs and quality of life. This study is recruiting patients from over 20 countries currently with 3600 patients by the end of 2019 ***(6).***

Carotid revascularization and medical management for asymptomatic carotid stenosis trial-2 (CREST-2) is an undergoing three-arm RCT to compare current OMT, OMT plus CEA, and OMT plus CAS for asymptomatic severe carotid stenosis, which enables a direct comparison of CAS and CEA. The primary endpoint is any stroke/death within 44 days after randomization or ipsilateral ischemic stroke within 4 years. This study is estimated to be completed by 2020***(7).***

The European Carotid Surgery Trial-2 (ECST-2) is an international RCT aimed to investigate the optimal treatment in patients with symptomatic or asymptomatic moderate or severe carotid stenosis at low or intermediate risk of stroke, in which patients will be randomized to OMT versus CAS or CEA. The

primary endpoint is any stoke at any time or non-stroke death within 30 days after surgery. This trial is currently recruiting participants and estimated to be completed by 2022 ***(7).***

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