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ASYMPTOMATIC CAROTID DISEASE: WHAT IS THE BEST APPROACH?

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Nobody comes from nothing;
some are lucky enough to come descend from fighters.

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RESUMO

A aterosclerose da porção extra-craniana das artérias coronárias internas é um mecanismo comum de acidente vascular cerebral, sendo responsável por 10 a 20 % de todos os acidentes vasculares cerebrais isquémicos. O impacto da doença carotídea assintomática está a revelar-se significativamente maior, especialmente no contexto do envelhecimento populacional. A abordagem adequada desta patologia é ainda um assunto controverso e com espaço para incertezas, dada a falta de estudos randomizados atuais de grande dimensão. Dados recentes revelaram taxas de incidência de enfarte cerebral baixas em pacientes apenas medicados com o melhor tratamento médico disponível, o que promove o debate acerca da pertinência e condições ideais para a revascularização carotídea nos pacientes assintomáticos. Esta revisão tem como objetivos resumir a evidência científica mais atualizada acerca deste tópico, bem como as *guidelines* e recomendações atuais para a abordagem da doença carotídea assintomática.

ABSTRACT

Extracranial internal carotid artery atherosclerosis is a common mechanism for stroke, being responsible for 10-20% of all ischemic strokes. The burden of asymptomatic carotid disease is becoming significantly greater especially in the set of an aging population. Adequate management is still a matter of controversy and uncertainty, given the lack of recent large randomized clinical trials comparing all different possible approaches. Recent data showing low stroke rates on best medical treatment alone promotes debate over the pertinence and optimal setting for carotid revascularization in asymptomatic patients. This review aims to summarize the most up-to-date evidence, current guidelines, and recommendations for the interventional management of asymptomatic carotid disease.

Keywords:

Asymptomatic carotid disease; Carotid endarterectomy; Carotid stenting; Medical treatment

LIST OF ABBREVIATIONS

AANN	American Association of Neuroscience Nurses
AANS	American Association of Neurological Surgeons
ACAS	Asymptomatic Carotid Atherosclerotic Study
ACCF	American College of Cardiology Foundation
ACR	American College of Radiology
ACS	Asymptomatic carotid stenosis
ACD	Asymptomatic carotid disease
ACST-1	Asymptomatic Carotid Surgery Trial
ACST-2	Asymptomatic Carotid Surgery Trial-2
ACT-I	Asymptomatic Carotid Trial I
AHA	American Heart Association
ASA	American Stroke Association
ASNR	American Society of Neuroradiology
BMT	Best medical treatment
BP	Blood pressure
CAAD	Carotid artery atherosclerotic disease
CAS	Carotid artery stenting
CEA	Carotid endarterectomy
CNS	Congress of Neurological Surgeons
CoR	Class of recommendation
CREST-2	Carotid Revascularization and Medical Management Asymptomatic Carotid Stenosis Study
CREST	Carotid Revascularization Endarterectomy versus Stenting
CTA	Computed tomography angiography
ECST-2	European Carotid Surgery Trial 2
ECVD	Extracranial carotid or vertebral disease
LDL	Low-density lipoprotein
LoE	Level of evidence
MI	Myocardial infarction
MRI	Magnetic resonance imaging
RCTs	Randomized controlled trials
SAIP	Society of Atherosclerosis Imaging and Prevention
SCAI	Society for Cardiovascular Angiography and Interventions
SIR	American Society of Neuroradiology
SNIS	Society of Interventional Radiology
SPACE-2	Stent Protected Angioplasty versus Carotid Endarterectomy-2
SVM	Society for Vascular Medicine
SVS	Society for Vascular Surgery
TCD	Transcranial Doppler ultrasound

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Stroke poses a significant burden on healthcare and is the second largest cause of death both globally and in Europe.[1] Extracranial internal carotid artery atherosclerotic disease (CAAD) is a common stroke mechanism[2] responsible for 10-20% of all strokes.[3] Individuals with asymptomatic carotid stenosis (ACS) have an annual absolute stroke risk of over 3%, and more than 50% relative compared to those without CAAD.[3]

ACS is defined by the presence of luminal carotid narrowing in the absence of previous neurological symptoms or evidence of silent brain infarction on cross-sectional imaging in the preceding 6 months.[3, 4] The risk of stroke increases with the severity of the luminal narrowing: patients with moderate stenosis (<50%) have a risk of stroke <1% per year, while patients with >80% stenosis have an annual risk of up to 5%.[4] The burden of ACS is becoming significantly greater, which can be explained by an aging population with a high prevalence of vascular risk factors including hypertension, diabetes, hypercholesterolemia, and cigarette smoking.[5]

The adequate management of ACS is a matter of controversy and uncertainty, given the lack of recent large randomized clinical trials comparing all different possible approaches. For many decades now, carotid artery interventions, such as carotid endarterectomy (CEA) and carotid artery stenting (CAS) have been used to reduce the risk of stroke in individuals with carotid stenosis.[3] However, in the United States, up to 90% of all carotid interventions performed in asymptomatic patients are ultimately unnecessary and potentially harmful.[6] In 2018, Balucani *et al* conducted a survey regarding the management of carotid stenosis across European and North American experts.[7] A big difference in current clinical practice was observed: CAS for asymptomatic carotid stenosis was mostly never recommended in Europe.[7]

The annual rate of stroke among medically treated asymptomatic patients has declined over the past 20 years, regardless of the severity of stenosis at baseline.[8] Existing clinical trials supporting adequate management of ACS, such as the Asymptomatic Carotid Atherosclerotic Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST-1), are being questioned as to their validity nowadays,[9] as since these trials were conducted medical therapy has improved significantly. Therefore, a question has been raised as to whether invasive treatment of extracranial carotid stenosis remains an effective way to reduce the risk of stroke in ACS patients compared to medical treatment alone.[10]

This review aims to summarize the most up-to-date evidence, current guidelines, and recommendations for the interventional management of ACS.

MATERIALS AND METHODS

Our research leading question was defined using the problem, interventions, comparisons and outcomes strategy. This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (i.e. PRISMA). Our aim was to identify the current literature body of class I evidence comparing surgical interventions, namely CEA and CAS, and medical treatment in the management of patients with ACS.

A systematic search on PubMed database was performed, using the following keywords: “asymptomatic carotid disease”, “carotid endarterectomy”, “carotid stenting” and “medical treatment”. The search was restricted to papers published in English language between January 2010 and January 2019. The literature considered for eligibility purposes included systematic reviews, meta-analyses and multicentre randomized controlled trials (RCTs) that included 100 or more patients with long-term follow-up (> 1 year). With regard to best medical treatment (BMT), cohort studies and state-of-the-art reviews were also considered. Guidelines identified through this search were considered if they were S3-guidelines, i.e. developed by a full formalized, systematic process conducing to evidence- and consensus-based guidelines

After applying the selection criteria, as described in Figure 1, 28 articles were included in our review.

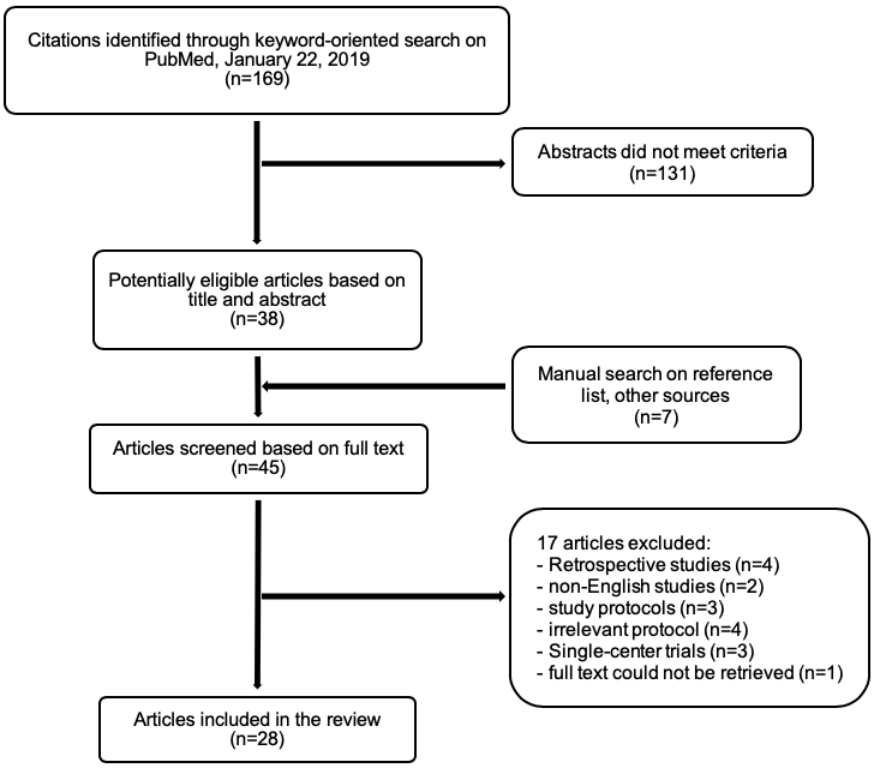

Figure 1. PRISMA flow chart of study selection.

BEST MEDICAL TREATMENT

There are no recent randomized controlled trials focusing only on BMT. Evidence on this topic was extracted from meta-analyses, systematic reviews, and prospective cohort studies.

Patients with ACS are at increased risk of ipsilateral carotid territory ischemic stroke and of acute coronary events and vascular death.[11] Therefore, all patients with ACS require intensive medical treatment for atherosclerosis.

In recent years, it has been suggested that the risk of stroke associated with BMT is lower than the previously reported.[11, 12] With the purpose of investigating temporal changes in the incidence rate of cerebrovascular events, mortality and cardiovascular events among patients with ACS receiving medical therapy alone, Hadar *et al* described in their meta-analysis that the summary incidence rate of ipsilateral stroke was significantly lower in recent studies (with the last recruitment year between 2000 and 2010) when compared to studies that completed recruitment prior to 2000 (1.0 vs 2.3 events per 100 person-years, respectively).[13] A systematic review reported a decline of 1% per decade in the rate of recurrent stroke in the last 5 decades.[14] Recent years have been marked by changes in diagnosis, better availability of effective medical therapies and risk factor modifications that have resulted in the substantial decline in vascular events rates in ACS patients.[13] Data from the Oxford Vascular Study (OXVASC) reported that the annual average risk of ipsilateral stroke in ACS patients on BMT alone is now 0.3%.[11]

The basic principles of medical therapy include lifestyle modifications, antiplatelet therapy, hypertension and diabetes control, and lipid-lowering therapy with statins.[15] Aspirin is the first-line option among antiplatelets, whereas statins may have beneficial effects on plaque morphology and attenuate the underlying inflammatory response of vulnerable plaques.[13]

A healthy lifestyle is key for reducing the risk of stroke. Smoking is a known modifiable risk factor for carotid artery stenosis,[16] increasing the risk of stroke by six-fold.[12] It is essential that physicians educate patients to quit smoking and to avoid smoking environments, given that even secondhand smoke nearly doubles the cardiovascular risk.[12] A healthy diet, particularly the Mediterranean diet[12, 17], and physical activity are essential to reduce cardiovascular risk.

In a prospective, population-based cohort study of 101 patients, the average annual risk of ipsilateral stroke and/or TIA in patients with ACS of ≥50% on intensive medical therapy was very low (average annual risk of ipsilateral stroke of 0,34% [95% CI, 0.01 to 0.187] and average annual risk of ipsilateral TIA of 1,78% [95% CI, 0.58 to 4.16]).[11] Almost all patients were on antithrombotic therapy, statins, and anti-hypertensive drugs, and were under close follow-up for ischemic events for 5 years, highlighting the potential implications in routine clinical practice of intensive medical

therapy. However, this cohort study did not discriminate the antithrombotic or blood pressure-lowering agents used.

Spence JD *et al* observed that high-dose statins (e.g. 80 mg of atorvastatin or 40 mg of rosuvastatin) were significantly associated with a decline in lipid levels and plaque progression.[17] A subgroup analysis in a meta-analysis also showed that studies with a higher proportion of patients (≥25%) taking statins had significantly lower incidence rates of ipsilateral events (P = .009).[13]

Regarding antithrombotic therapy, a systematic review concluded that evidence supported the use of aspirin in the range of 75 mg to 150 mg, and no evidence supported the use of dual antiplatelets.[16] Hadar *et al* also observed that studies with a higher proportion of patients using antithrombotic drugs (≥50% vs. < 50%) resulted in significantly lower incidence rates of ipsilateral stroke (P=.009) and ipsilateral stroke or TIA (P=.001).[13] Hypertension is the most important modifiable risk factor for stroke[18] and cardiovascular death.[19] Blood pressure (BP) goal levels must be inferior to 140/90 mmHg for nondiabetic patients; in diabetic patients BP control should be tighter, aiming for a systolic BP inferior to 130 mmHg.[16] Each 20 mmHg elevation in systolic BP and 10 mmHg elevation in diastolic BP is associated with a doubling risk of death by stroke, heart disease, or other vascular diseases.[19] Nevertheless, low BP levels (<110/70 mmHg) are equally associated with increased risk of cardiovascular events.[18, 19] Low-dose thiazides and angiotensin-converting enzyme inhibitors were shown to be the most effective anti-hypertensive drugs in reducing all-cause mortality and morbidity.[16]

Diabetes is a major cardiovascular risk factor, with an increasingly high prevalence,[19] leading to a 2- to 5-fold increase in the risk of stroke.[20] However, evidence shows that low glycated hemoglobin levels have no significant impact on stroke incidence.[16]

REVASCULARIZATION VERSUS BEST MEDICAL TREATMENT

One of the major questions regarding the best approach to patients with ACS consists of deciding what the best strategy is: revascularization (CEA or CAS), or best medical treatment. Table 2 summarizes the characteristics of the largest RCTs conducted that focused on studying the topic of revascularization versus medical treatment in ACS patients. ACAS and ACST-1 trials, that finished recruiting patients more than 25 and 15 years ago respectively, showed that patients with ACS > 60% would benefit from surgical intervention, given that the risk of stroke or death was significantly lower in the surgical groups.[21, 22]

ACST-1 randomized asymptomatic patients to either immediate CEA or to indefinitely deferred CEA.[21] The trial protocol did not specify medical management, but records of the medical therapy were done. Recently, data regarding long-term outcomes was published. The authors found that long-term medical therapy in both groups did not differ significantly.[23] Although the use of antithrombotic drugs (mainly aspirin) did not show significant variation between 1995 and 2005, a marked increase in anti-hypertensive and lipid-lowering drugs within that decade was patent,[23] reflecting recent changes in medical approaches. Moreover, long-term outcomes showed that successful CEA for asymptomatic patients < 75 years significantly reduces the 10-year stroke risk (p=.0009), and at 10 years follow-up the benefit was significant for both men and women.[23] Two meta-analyses of RCTs comparing CEA to CAS or BMT have also observed that CEA is superior to BMT in reducing long-term mortality and stroke risks.[24, 25] However, the evidence is concordant regarding the 30-day superiority of medical treatment compared to surgical or endovascular intervention,[24, 25] as would be expected given the well-reported risks of revascularization procedures.

Benefit from surgery depends on achieving a low operative risk, and there is some evidence that the operative risk in routine clinical practice is higher than in large randomized trials.[11] Benefit from surgery may now be lower than anticipated[20] and the potential long-term benefits of CEA are seriously limited in patients that have < 10 years of life expectancy.[23] There are no published RCTs directly comparing CAS to BMT alone. Both the Carotid Revascularization and Medical Management Asymptomatic Carotid Stenosis Study (CREST-2)[26] and the Stent Protected Angioplasty versus Carotid Endarterectomy-2 (SPACE-2)[27] are large ongoing RCTs that include one arm comparing CAS plus BMT to BMT alone; results are expected in the upcoming years.

Researchers are now starting to focus on developing methods to identify high-risk asymptomatic patients who could benefit more from revascularization, through detection of microemboli on transcranial Doppler,[17] or plaque characteristic.[28]

Nevertheless, most data comparing surgery to medical treatment is based on older studies; thus, generalization to current practice must be undertaken critically. The issue of whether any form of revascularization is beneficial for asymptomatic patients in comparison to BMT using current regimens is consequently an essential question that ongoing trials such as ECST-2, CREST-2 and SPACE-2 aim to clarify.[29]

Table 1. **Randomized clinical trials comparing BMT and revascularization.**

Trial	Year of Publication	Study Location	Recruitment Period	Participants, n	Follow-up time (years)	Degree of stenosis	Protocol	Long-term outcomes				Important Conclusions
								Definition	CEA	MT	p value	
ACAS[22]	1995	USA and Canada	1987 - 1993	1659	Median 2,7	≥60%	Randomization for MT only, or CEA plus MT	5-year risk of ipsilateral stroke and any perioperative stroke or death	5,1%	11,0%	.004	Prophylactic carotid endarterectomy was effective for patients in good health who had a stenosis ≥60%, if conducted by surgeons with surgical morbidity and mortality < 3%
ACST-1[21, 23]	2004	UK/Europe	1993 - 2003	3120	Mean 3,4	≥60%	Randomization for immediate CEA or indefinite deferral of CEA; all patients under MT	5-year risk of any stroke or perioperative death	6,9%	10,9%	.0001	Significant stroke risk reduction after CEA. No difference in benefit for stenosis > 70% and stenosis < 80-90%
	2010				Median 9			10-year risk of any stroke or perioperative death	13,4%	17,9%	.0009	Successful CEA for ACS in patients < 75 years reduces 10-year stroke risk.
SPACE-2[27]	2016	Austria, Germany, Switzerland	2009 - 2014	513	5	70-99%	Randomization 1:1 to one of two parallel studies: SPACE-2 A (BMT alone versus CEA plus BMT) or SPACE-2 B (BMT alone versus CAS plus BMT)	Pending				No 30-day postprocedural deaths or strokes in patients randomized to BMT.
ECST-2 (unpublished data)[30]	not yet published	UK/Europe	2012 - ongoing	Planned: 2000	Planned: minimum 5, maximum 10	>50%	Randomization of symptomatic and asymptomatic patients for immediate revascularization (CEA or CAS) with BMT, or BMT alone	Pending				Main hypothesis: patients who have clinical characteristics that predict a 5-year risk of future ipsilateral stroke of <20% when treated with modern BMT alone will not benefit from early revascularization in addition to BMT
CREST-2[26, 31]	not yet published	USA and Canada	2014 - ongoing	Planned: 1240 in each trial (total: 2480)	4	≥70%	2 parallel RCTs: 1) Randomization to CEA plus BMT, or BMT alone; 2) Randomization to CAS plus BMT, or BMT alone	Pending				The aim is to test whether CEA or CAS plus BMT is superior to BMT alone in asymptomatic patients with high-grade stenosis.

BMT: best medical treatment; CEA: carotid endarterectomy; CAS: carotid artery stenting; MT: medical treatment; RCTs: randomized clinical trials; USA: United States of America; UK: United Kingdom

CAROTID ENDARTERECTOMY VERSUS CAROTID STENTING

Advances in medical treatment have changed the approach to ACS; nonetheless, patients with significant/severe (50-99%) stenosis may still require invasive treatment.[32] In the 1990s CAS became an alternative to CEA.[33] There is substantial uncertainty regarding which revascularization procedure is the optimal choice for patients with ACS. Since the beginning of the twenty-first century, there have been a few multicentered RCTs aiming to clarify this matter. Table 2 describes the main characteristics and outcomes of these trials.

The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), a large multicentered RCT published in 2010, compared CEA to CAS in symptomatic and asymptomatic patients.[34] No significant differences were found in periprocedural or 4-year-follow-up outcomes in asymptomatic patients,[34] but it failed as it was not powered enough to discern whether the two procedures could be faced as equivalent or not in ACS.[35] SPACE-2, which included only ACS patients, despite the early cessation of recruitment, also reported low 30-day rates of death and stroke both for endarterectomy and stenting.[27] More recently, the Asymptomatic Carotid Trial I (ACT-I), the only completed and published trial restricted to asymptomatic patients,[36] reported that stenting was noninferior to endarterectomy regarding the composite endpoint of death, stroke, or myocardial infarction (MI) within 30 days after the procedure or ipsilateral stroke within 1 year.[35] Strong evidence from several meta-analyses suggests however that the risk of periprocedural stroke or death is in fact significantly higher after CAS.[33, 36, 37] while no differences in the periprocedural ipsilateral stroke rate with CAS or CEA.[33, 37]

ACT-I found no statistically significant differences in the rates of cranial nerve injury, overall events, freedom from clinically-driven target lesion revascularizations at 6 months, and estimated 5-year survival rates at between the stenting group and the endarterectomy group.[35] However, meta-analyses articles found that the risk of periprocedural cranial nerve palsy was significantly lower after stenting.[36, 37] With regard to periprocedural MI rate, data suggest that CEA and CAS do not differ significantly[32, 33, 36] but Kakkos *et al* reported a nonsignificant trend for a lower periprocedural MI rate for CAS.[37] Despite the findings that CEA increases the rate of cranial nerve palsy and did not show to be beneficial to MI risk, Moresoli *et al* concluded that CEA may be a safer treatment option than stenting for patients with ACS.[36]

Regarding the long-term outcomes of both procedures, the evidence is not yet solid. Recently, the authors of CREST published the long-term results of the trial, reporting that the 10-year rates of death or stroke did not differ significantly between CAS and CEA(p=.51); there were

no significant treatment differences according to symptomatic status (*p*=.59).[38] Maresoli *et al* could not rule out clinical significant benefits of either procedure regarding the long-term rate of stroke.[36]

An ongoing trial, the Asymptomatic Carotid Surgery Trial-2 (ACST-2) is currently the largest trial ever conducted to compare carotid endarterectomy to stenting in patients with ACS.[39] By March 2016, 2125 patients with ACS had already been randomized to one of the procedures.[39] Early results published in 2013, reporting to 691 patients with at least 30 days' follow-up, indicated a 30-day stroke rate of 2.9% and a 1.0% immediate risk of disabling stroke and death.[40], but did not discriminate between the two types of procedures.

CREST and ACT-I had a similar approach concerning medical therapy: patients that were randomized to CEA were on aspirin only, and patients that underwent CAS were prescribed aspirin and clopidogrel, in the pre- and post-procedural periods.[34, 35] ACST-2 protocol does not specify the medical treatment, but it will be analyzed.[40]

It is expected that ACST-2 will strongly contribute to the decision process of procedure choice in asymptomatic patients that are considered eligible for revascularization.

Table 2. **Randomized clinical trials comparing CEA and CAS.**

Trial	Year of publication	Study Location	Recruitment Period	Participants, n	Follow-up time (years)	Degree of stenosis	Protocol	Procedural hazards				Long-term outcomes				Important Conclusions
								Definition	CEA	CAS	p value	Definition	CEA	CAS	p value	
SAPPHIRE[41, 42] (*subgroup*)	2004	USA	2000-2002	237	3	80%-99%	Randomization 1:1 to CAS plus clopidogrel 75mg daily, or to CEA; aspirin 81 or 325mg to all patients	30-day cumulative incidence of death, stroke or MI	10.2%	5.4%	.20	Death, stroke or MI within 30 days after intervention, or death or ipsilateral stroke between 31 days and 1 year, or death or ipsilateral stroke between 1 and 3 years of follow-up	29.2%	21.4%	not reported	CAS with the use of emboli-protection device showed to be non-inferior to CEA. No conclusion regarding ACS.
								Death, stroke or MI within 30 days after intervention, or death or ipsilateral stroke between 31 days and 1 year	21.5%	9.9%	.02					
CREST[34, 38] (*subgroup*)	2010	USA and Canada	2000 - 2008	1181	Median 7.4	≥60% on angiography; ≥70% on ultrasonography; ≥80% on CTA/MRI if stenosis of 50 to 69% on ultrasonography	Randomization 1:1 to CAS plus clopidogrel 75mg twice daily, or to CEA; aspirin 325mg to all patients	30-day stroke, MI, or death, or postprocedural ipsilateral stroke	3.6%	3.5%	.96	Any stroke, MI, or death during the periprocedural period or ipsilateral stroke within 4 years of randomization	4.9%	5.6%	.56	No significant differences in outcomes between CAS and CEA in ACS.
												Any stroke, MI, or death during the periprocedural period or ipsilateral stroke within 10 years of randomization, in symptomatic and asymptomatic patients	9.9%	11.8%	.51	The 10-year risk did not differ significantly between the two groups.
ACT-I[35]	2016	USA	2005 - 2013	1453	Up to 5	70-99%	Randomization 3:1 to CAS plus clopidogrel daily, or to CEA; aspirin 325mg to all patients	30-day incidence of stroke, death of MI	2.6%	3.3%	.60	Rate of freedom from any stroke (ipsilateral or contralateral) through 5 years	94.7%	93.1%	.44	No significant differences in long-term outcomes between the two study groups. (p value refers to non-inferiority of CAS)

SPACE-2[27]	2016	Austria, Germany, Switzerland	2009 - 2014	513	5	70-99%	Randomization 1:1 to one of two parallel studies: SPACE-2 A (BMT alone versus CEA plus BMT) or SPACE-2 B (BMT alone versus CAS plus BMT)	Death or stroke within 30 days after the procedure	1.97%	2.54%	non-applicable	*Pending*	Small sample size and low stroke and death rates allowed for very wide confidence intervals. No direct comparisons can be made between CEA and CAS outcomes.
ACST-2[39, 40]	not yet published	UK and worldwide	2008 - ongoing	Planned: 2000	At least 5 years	non-specified/any	Randomization 1:1 to CEA or CAS	MI, stroke, and death within the first month after randomization, for CEA and CAS (published interim results, 2013)	3,5%		non-applicable	*Pending*	ACST-2 did not discriminate between CEA and CAS. CEA and CAS have a 1.0% immediate risk of disabling stroke and death. No new results were published in the 2017 update.

BMT: Best medical treatment; CEA: carotid endarterectomy; CAS: carotid artery stenting; MI: myocardial infarction; USA: United States of America; UK: United Kingdom.

GUIDELINES AND RECOMMENDATIONS

We identified four relevant documents formulating high-quality guidelines and recommendations for the treatment of ACS. The main conclusions of these reports are summarized in Table 3.

Secondary prevention in asymptomatic patients includes several approaches, including risk factor control, antiplatelet therapy, lipid-lowering drugs, management of hypertension, appropriate management of diabetic patients, diet and exercise, and revascularization in selected patients.[20, 43] Adherence to BMT is a topic that was never evaluated in RCTs, despite having a role in achieving optimal stroke prevention outcomes. Assistant physicians should be alert for predictors of poor compliance, such as psychological problems, medication side-effects or missed appointments,[43] which is more prone to happen in asymptomatic patients.

Given the lack of strong evidence, several recommendations are based on consensus. Antiplatelet therapy in asymptomatic patients is a conflicting matter, with no adequately powered controlled studies favoring the efficacy of this therapy in the prevention of stroke in asymptomatic patients.[20] There are concerns that inappropriate therapy might increase the risk of major bleeding events without reducing the risk of stroke.[43]

Regarding revascularization, the class of recommendations is not very strong. CEA is mostly recommended for low and average surgical risk patients (which are not clearly defined in the literature), as long as the perioperative complication rate is < 3%.[44] Stenting may be considered in patients regarded as “high-risk-for-surgery”,[43, 44] which include asymptomatic patients with severe stenosis (70-99%) and one or more of the following: clinically significant cardiac disease (congestive heart failure [HF], abnormal stress test, or need for open-heart surgery); severe chronic lung disease; contralateral carotid occlusion; previous radical neck surgery; cervical radiation therapy; recurrent stenosis after CEA; and age >80 years.[43] Other comorbidities that increase the surgical risk and that may compromise the effectiveness of revascularization include left main or multivessel coronary artery disease, MI within 4 weeks, and class III or IV angina pectoris.[20]

Importantly, management of patients with ACS should involve a multidisciplinary team, including neurologists/stroke physicians, vascular surgeons, interventional radiologists,[43] and anesthesiologists, attending to the experience of the center and the operator.[45]

Table 3. **Guidelines and Recommendations of management of ACS**

Topic	Guidelines of the European Society of Vascular Surgery, 2018[43] (CoR; LoE)	Guidelines of the ASA/ACCF/AHA/AANN/ AANS/ACR/ASNR/CNS/ SAIP/SCAI/SIR/SNIS/SVM/SVS, 2011[20] (CoR; LoE)	German-Austrian Guidelines[44] (CoR; LoE)	Italian Stroke Organization Guidelines[45] (CoR; LoE)
Best medical treatment	A healthy diet, smoking cessation, and physical activity are recommended for all patients with ACD. (I; B)	Patients with ECVD should be advised to quit smoking and offered smoking cessation interventions. (I; B)	Patients with atherosclerotic carotid stenosis should undergo comprehensive risk factor modification, including smoking cessation, normalization of body weight, and adequate exercise, as well as anti-hypertensive medication, lipid-lowering drugs, and treatment of diabetes mellitus. (NA; NA)	Best medical treatment alone should be considered if survival is estimated to be shorter than that presumably obtained by carotid endarterectomy, such as in the case of patients > 80 years and in insulin-dependent diabetes patients, serious cardiopathy or bronchopathy, or chronic renal insufficiency receiving dialysis. (IIb; NA)
	Low-dose aspirin (75-325 mg) is recommended in patients with ACS for prevention of late MI or other cardiovascular events. (I; A) Clopidogrel 75 mg daily should be considered in ACS patients if aspirin intolerant. (IIa; C)	The benefit of antiplatelet therapy has not been established for prevention of stroke in ACD. (I; A) Antiplatelet agents are recommended rather than oral anticoagulants for patients with ECVD without ischemic symptoms. (I; C)		
	Statin therapy is recommended for long-term prevention of stroke, MI and other cardiovascular events in patients with ACD. (I; A)	Treatment with a statin is recommended for all patients with ECVD to reduce LDL cholesterol below 100 mg/dL. (I; B)	Patients with an asymptomatic carotid stenosis of <60% would benefit more from conservative treatment. (good clinical practice; NA)	
	Antihypertensive treatment is recommended for patients with hypertension and ACS to maintain long-term BP <140/90 mmHg. (I; A)	Antihypertensive treatment is recommended for patients with hypertension and asymptomatic ECVD to maintain BP <140/90 mmHg. (I; A)		
	In diabetic patients with ACS, strict glycemic control is recommended. (I; C) The target BP in diabetic patients should be <140/85 mmHg. (I; B)	Diet, exercise, and glucose-lowering drugs can be useful for patients with diabetes mellitus and ECVD. (IIa; A)		
Revascularization	In "average surgical risk" patients with an asymptomatic 60-99% stenosis, **CEA** should be considered in the presence of ≥1 imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,* provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years. (IIa; B)	Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors, and should include a thorough discussion of the risks and benefits of the procedure, with an understanding of the patient's preferences. (I; C)	CEA should be considered for patients with 60-99% ACS because it lowers those patients' risk of stroke by a small but statistically significant amount. (NA; A)	CEA should be considered for asymptomatic patients with ACS ≥70% if survival is expected to be 3 years or more and if the periprocedural risk of complications (death or any type of stroke) is <3%. (IIb; NA)
	In "average surgical risk" patients with an asymptomatic 60-99% stenosis in the presence of ≥1 imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,* **CAS** may be an alternative to CEA, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years. (IIb; B)	It is reasonable to perform a CEA in asymptomatic patients with >70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low. (IIa; A)	CEA is of benefit to patients with ACS only if it can be performed with a complication rate of <3%. (NA; A)	
	CAS may be considered in selected asymptomatic patients who have been deemed by the multidisciplinary team to be "high-risk for surgery" and who have an ACS 60-99% in the presence of ≥1 imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,* provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years. (IIb; B)	Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone is not well established. (IIb; B)	The benefit of CEA in patients with ACD is mainly in men and persons with a life expectancy of at least 5 years. (NA; A)	CEA should be considered for the treatment of ACS in patients deemed "at risk" from medical therapy alone if at least one of the following is encountered: previous brain infarction; vulnerable, ulcerated, or rapidly growing plaque; pre-occlusive stenosis; and 70-80% stenosis in the presence of contralateral carotid occlusion or signs of ipsilateral microemboli at TCD. (IIb; NA)
		In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, the effectiveness of revascularization versus medical therapy alone is not well established. (IIb; B)	Asymptomatic patients who are at very high cardiovascular risk would not benefit at all from revascularization. (NA; C)	

*Imaging/clinical criteria that might confer an increased risk of stroke on BMT include silent infarction on CTA, stenosis progression, large plaque area, large juxta-luminal black area, plaque echolucent, intra-plaque hemorrhage on MRI, impaired cerebrovascular reserve, spontaneous embolization on transcranial doppler, and history of contralateral transient ischemic attack.

AANN = American Association of Neuroscience Nurses; AANS = American Association of Neurological Surgeons; ACCF = American College of Cardiology Foundation; ACR = American College of Radiology; ACS = asymptomatic carotid stenosis; ACD = asymptomatic carotid disease AHA = American Heart Association; ASA = American Stroke Association; ASNR = American Society of Neuroradiology; BP = blood pressure; CNS = Congress of Neurological Surgeons; CoR = Class of Recommendation; CTA = computed tomography angiography; ECVD = extracranial carotid or vertebral disease; LDL = low-density lipoprotein; LoE = Level of Evidence; MI = myocardial infarction; MRI magnetic resonance imaging; NA = not available; SAIP = Society of Atherosclerosis Imaging and Prevention; SCAI = Society for Cardiovascular Angiography and Interventions; SIR = Society of Interventional Radiology; SNIS = Society of NeuroInterventional Surgery; SVM = Society for Vascular Medicine; SVS = Society for Vascular Surgery; TCD = transcranial Doppler ultrasound.

CONCLUSION

Management of ACS is a topic of ongoing debate and research, given the impact of the disease in stroke incidence. Best medical treatment, including lifestyle modifications, statins, antiplatelet therapy and control of hypertension and diabetes, plays a central role in the approach of asymptomatic patients and must always be considered. In fact, stroke incidence was shown to be very low with current BMT.

Revascularization procedures, despite being widely performed in ACS patients, should only be considered in selected patients. Carotid endarterectomy has shown to be superior to BMT in preventing long-term ipsilateral stroke and death in asymptomatic patients. Carotid stenting, a more recent and less invasive procedure, is an alternative to CEA in high-risk-for-surgery patients, although evidence is not yet strong enough as to clearly define criteria for its selection as the procedure of choice. Consensus has not been reached on what is the best approach to ACS. Large ongoing multicenter randomized controlled trials (ACST-2, ECST-2, SPACE-2, and CREST-2), which include improved BMT regimens, are expected to be of great value in guiding management strategies in asymptomatic patients.

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Asymptomatic Carotid Disease. What is the best approach?

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