UNIVERSITY OF NORTH DAKOTA
SCHOOL OF MEDICINE & HEALTH SCIENCES
DEPARTMENT OF SURGERY
JOURNAL CLUB

TO: Surgery Residents, Surgery Faculty at Altru, Sanford, & VA Medical Center and Medical students

FROM: Geralyn Lunski, Conference Coordinator - 777-2589

DATE: August 11, 2017

Meeting Information

Date: Tuesday, August 15, 2017

Time: **6**:00 PM

Locations: Sanford Clinic, Fargo, North Dakota and
Altru Hospital, Grand Forks, North Dakota

Rooms: Clinic B2, Sanford Health
SurgSimLab, Altru Hospital

Topic: Updates on the Carotid

Moderator: Brian Johnson, MD

ARTICLES: Attached.

Dinner will be provided by Merck in Fargo

Cerebrovascular Diseases

Recent Update on Carotid Endarterectomy versus Carotid Artery Stenting

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Key Words

Carotid artery stenosis · Carotid endarterectomy · Carotid artery stenting · Carotid artery interventions · Risk stratification

Abstract

Carotid artery stenosis (CS) is a major cause of ischemic stroke. Treatment of CS consists of best medical treatment and carotid revascularization (CR), including carotid endarterectomy (CEA) and carotid artery stenting (CAS). Both CR techniques have their own procedural risks. Therefore, selection of the appropriate treatment for patients with CS is relatively complicated. Many studies and guidelines have reported the efficacy of each treatment for both symptomatic and asymptomatic patients. However, the results are still controversial, especially concerning the efficacy and safety of CEA and CAS. In this paper, we review and discuss the current evidence and compare results from studies of CEA and CAS, including major randomized trials, meta-analyses and ongoing trials. Moreover, based on the current data, we propose a new comprehensive decision-making for the management of CS.

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Introduction

Carotid artery stenosis (CS) accounts for up to 20–25% of all ischemic strokes [1]. Treatment of this disease consists of the best medical treatment (BMT) and carotid revascularization (CR), including carotid endarterectomy (CEA) and carotid artery stenting (CAS).

CEA and CAS are recommended for symptomatic patients who have more than 50% stenosis or asymptomatic patients who have more than 70% stenosis [2]. Although CEA is the standard treatment and has been shown to benefit patients who have had indications of CS for a long time [3–5], it has some limitations because of patients' comorbidities, unfavorable neck anatomy and surgical complications. CAS, therefore, has been developed to increase safety and provide a minimally invasive procedure. However, there are also concerns associated with CAS because of its periprocedural complications, especially stroke.

Therefore, whether CS is optimally managed with CEA or CAS remains controversial. This review intends to draw a comparison between the results of CEA and CAS and describe a process for reasonable decision-making in choosing the appropriate treatment.

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Evidence Data of CEA vs. CAS

In recent years, there are numerous studies on CAS in comparison with CEA. Although most of the early studies on CAS yielded disappointing results, it has been argued that those trials had some pitfalls. Moreover, there were differences in the experience among interventionists in those trials, and various different stenting systems had been used.

Randomized Trials of CEA vs. CAS

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [6] was an early multicenter trial that showed no significant difference in the rates of disabling stroke or death between carotid balloon angioplasty and CEA in patients with CS (p = 0.8). However, this study was underpowered to measure the equality because the inclusion and exclusion criteria were not strict, and no embolic protection devices (EPD) were available at that time. Moreover, only 26% of patients in the endovascular treatment arm were provided with stents, which resulted in a high rate of re-stenosis and stroke at the 8-year follow-up [7].

In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy [8] trial conducted in North America, 334 high-risk patients were randomly treated with either CAS (with EPD) or CEA. This study favored CAS over CEA in a non-inferiority analysis (p = 0.004) whereas long-term results at 3 years were not different between the 2 treatment groups [9]. However, this study has been criticized for several reasons. First, it was terminated prematurely because of competing with nonrandomized stent registries, which may have decreased the power of the study. Second, most patients in this trial were asymptomatic. Finally, asymptomatic myocardial enzyme leakage was counted as myocardial infarction (MI).

Later, there were 3 large randomized trials conducted in Europe that reported similar results favoring CEA over CAS. First, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) [10] trial, a multicenter international study, which was terminated early because of slow enrollment and lack of funding, failed to prove the non-inferiority of CAS (p = 0.09). Second, the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) [11] study was a French multicenter, randomized study that included 527 patients. It was terminated prematurely because of a significantly higher rate of death or stroke in CAS than CEA (p = 0.01) at 30 days. The cumulative probabilities of event were also significantly higher in CAS (p = 0.04) at a 5-year follow-up, but they were not significant at a 10-year follow-up (p = 0.07) [12]. Lastly, the International Carotid Stenting Study (ICSS or CAVATAS-II) [13] enrolled 1,713 patients with >50% symptomatic CS from 50 centers worldwide. The 120-day rate of stroke, MI or death was significantly higher in CAS (p = 0.006). Furthermore, new ischemic lesions were found more frequently in CAS than in CEA [14]. Although the 5-year results of this study showed similarity in the incidence of fatal or disabling stroke between CAS and CEA, the cumulative risk of any stroke in CAS was significantly higher than in CEA (p < 0.001) [15]. However, the inferior efficacy of CAS compared with CEA remains inconclusive from the results of SPACE, EVA-3S and ICSS because there were some pitfalls in the study designs. First, EPDs were not required in any of these trials. Second, there was variation in the type of stent used in the studies (SPACE and EVA-3S). Third, dual antiplatelet therapy for CAS, which is beneficial to prevent thrombi on the stent, was not mandatory (EVA-3S, ICSS). Finally, the results from these trials implied that periprocedural complication rates relied on the experience of the interventionists. Calvet et al. [16] concluded that carotid stenting should only be performed at centers where interventionists can perform >6 CAS procedures every year.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) [17], a large, randomized, multicenter trial from North America, was published several months after ICSS. This trial included 2,502 patients who were both symptomatic and asymptomatic assigned to CAS or CEA. CAS was performed with only one stent type and EPD was mandatory whenever technically feasible. In addition, pre- and post-procedural antiplatelet therapies were required. The interventionists in this trial were trained and evaluated strictly in the lead-in phase. There was no difference in the rates of primary end point between CAS and CEA (p = 0.51). However, periprocedural stroke rate was higher in the CAS than in the CEA (p = 0.01), whereas the incidence of periprocedural MI was higher in the CEA (p = 0.03). In the subgroup analysis from CREST, symptomatic patients [18], women [19] and age >65 years [20] were factors associated with a higher rate of stroke and death rates in the CAS .

Although CREST is the largest study to date and showed an acceptable outcome for CAS compared with CEA, it has been criticized for several reasons. First, CREST originally enrolled only symptomatic patients,

Table 1. Results from large randomized trials of CEA vs. CAS

Name	Number	EPD use, %	Periprocedural* D/S		p value	Periprocedural D/S/MI		p value
			CEA, %	CAS, %		CEA, %	CAS, %	
CAVATAS [6], 2001	504	0	5.9	6.4	0.8	NA	NA	NA
SAPPHIRE [8], 2004	334	95.6	8.4	5.5	0.36	20.2	12.2	0.004
SPACE [10], 2006	1,200	27	6.3	6.8	0.09	NA	NA	NA
EVA-3S [11], 2008	527	91.9	3.9	9.6	0.01	NA	NA	NA
ICSS [13], 2010	1,713	72	4.7	8.5	0.001	5.2	8.5	0.006
CREST [17], 2010	2,502	96.1	2.3	4.4	0.005	6.8	7.2	0.51

D/S = Death or stroke; D/S/MI = death, stroke or MI; NA = not available.
* Periprocedural period was defined in most studies as the 30 days after the intervention.

but asymptomatic patients were included later because of slow enrollment, which is likely to have diluted the power on the divergence of the primary outcome between CAS and CEA in symptomatic patients. Second, it was debatable whether MI should have been included as the primary end point because it is not a treatment goal of CR. Moreover, CREST showed that MI had fewer adverse effects than stroke on the quality of life of patients at 1 year [17, 21]. Definition of MI in CREST was unusual and possibly overestimated. Despite fewer periprocedural MI in CAS, there were >2.5-fold more MI after CAS than CEA at 4 years. Worth noting, the 4-year MI rate was not a component of the primary end point. In addition, a greater proportion of late deaths were observed in CAS patients who had suffered a periprocedural MI [22]. Third, it is questionable to apply the results from CREST to routine practice because the interventionists in CREST were trained rigorously in the lead-in phase. Finally, the protocol specified the use of only RX Acculink stents and RX Accunet EPDs, which are big, open-cell design stents and large-pored filters, respectively, that can cause distal embolization. Summarized data from the studies described above are illustrated in table 1.

In the same year of CREST publication, the American Heart Association (AHA) and 13 other related societies [2] published guidelines stating that CAS is an alternative to CEA for symptomatic patients, although the data obviously reveal that CEA remains safer. Furthermore, these guidelines recommended that prophylactic CAS might be considered in highly selected asymptomatic patients, but they rated the level of evidence for this suggestion as class IIb. The background of these guidelines was mainly based on the results of CREST, which made it substantially different from the other guidelines, espe-

cially the guidelines from the Societies of Vascular Surgery [23]. On the contrary, the American Society for Vascular Surgery [24] published an update of their 2008 guidelines 2 months after the publication of AHA guidelines stating that their guidelines were more circumspect with regard to the role of CAS and a more supportive role of CEA. Kakisis et al. [25] reviewed the 2009 European Society for Vascular Surgery guidelines and also found that CEA is preferable to CAS for the majority of symptomatic patients. However, both guidelines of the vascular societies did not recommend CAS for asymptomatic patients.

Meta-Analysis of Randomized Trials

Recent meta-analyses [26–32], which included the latest large studies, seem to support the superiority of CEA over CAS in the periprocedural period whereas long-term results are inconclusive (table 2). The meta-analysis [29] published in 2011 showed that CAS, when compared with CEA, was associated with an increased risk of periprocedural outcomes of death, MI or stroke except for cranial nerve injury and MI. In addition, CAS was associated with 19% increase in the risk for the composite of periprocedural death, MI or stroke plus ipsilateral stroke in the intermediate to long-term outcomes. A meta-analysis of Vincent et al. [30] revealed that the higher cumulative incidence of stroke-related events throughout long-term follow-up was possibly caused by an increased risk during the periprocedural period. Interestingly, Zhang et al. [32] systematically reviewed the data comparing CAS with CEA in the treatment of CS and pooled the data to analyze the results in different aspects. This study concluded that CEA is superior to CAS with regard to the stroke or death rate within 30 days, especially from 2006 to 2015, in North America and Europe.

Table 2. List of meta-analyses of CEA vs. CAS

Name	Number of studies	Number	Periprocedural results (within 30 days)	Long-term results
Meier et al. [26], 2010	11	4,796	Lower risk of D/S for CEA	No difference up to 4 years
Liu et al. [27], 2012	13	7,501	Significantly higher risk of D/S for CAS	No difference up to 1 year
Bonati et al. [28], 2011	3	3,433	Higher risk of D/S for CAS	Higher 120-day risk of S/D for CAS
Bonati et al. [29], 2012*	16	7,572	Higher risk of D/S and D/S/MI for CAS	Higher 4-year risk of D/S for CAS
Bangalore et al. [30], 2011	13	7,477	CAS was associated with a significantly higher risk of D/S/MI and D/S	Higher risk of both D/S/MI and D/S for CAS (>40 months)
Vincent et al. [31], 2015	8	7,091	Significant higher risk of D/S for CAS	Risk of any long-term stroke was significantly higher with CAS (2–10 years)
Zhang et al. [32], 2015	35**	27,525	Higher D/S risk for CAS	Significant higher risk of D/S for CAS at 4- and 10-year but lower risk than CEA at 1-year follow-up

* Data from Cochrane database.
** Including 12 RCTs, 3 prospective controlled trials and 20 retrospective controlled trials.

The superiority was also observed at 4- and 10-year follow-up. On the contrary, the efficacy of CEA was inferior to that of CAS for the stroke or death rate at 1-year follow-up.

Ongoing Randomized Trials of Asymptomatic Carotid Stenosis

Regarding the lack of evidence in asymptomatic patients and the fact that medical therapy has been improved, large ongoing trials are being conducted to compare the efficacy between CR and BMT. Carotid Stenting vs. Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACTI) [33] was a multicenter, randomized trial of CAS vs. CEA for asymptomatic severe CS. This study was terminated because of slow recruitment. The results from 1,453 patients in this study showed a higher rate of stroke in CAS compared with CEA but it did not reach statistical significance.

Asymptomatic Carotid Surgery Trial-2 [34] is an ongoing trial planning to enroll 5,000 patients with asymptomatic severe CS and assign them randomly to CAS or CEA. The study has enrolled over 1,200 patients to date and has revealed a 1% rate of 30-day stroke, MI or death.

SPACE-2 [35], started in 2008, first began randomization with a 3-arm trial – BMT alone vs. CAS plus BMT vs. CEA plus BMT. Because of slow enrollment, the study design was revised into 2 parallel 2-arm trials in 2013: CEA plus BMT vs. BMT alone (SPACE-2A) and CAS plus BMT vs. BMT alone (SPACE-2B). However, the revision of the design did not affect the enrollment and the trial was halted after recruiting 513 patients. The 30-day rate of stroke or death was 2.54% in the CAS group and 1.97% in the CEA group whereas no patient in the BMT group had stroke or death.

Currently, CREST-2 is a large, multicenter, randomized trial, assigning patients to 2 parallel trials, similar to the SPACE-2. The primary end point is a 30-day rate of stroke or death and ipsilateral stroke at a 4-year follow-up. The study started to recruit patients in 2014 with a goal of 2,418 patients. It is notable that both SPACE-2 and CREST-2 are not directly comparing CAS with CEA.

Although the previous data showed the superiority of CEA over CAS in symptomatic patients and the results of asymptomatic patients are uncertain, it is remarkable that both CEA and CAS are associated with a risk of procedural complications. In addition, the advanced technology of CAS has been further developed and the CAS operators have gained more experience in the past few years. A consensus from Italy [36] recommended specific training to achieve basic competence and technical skill as the primary operator for performing CAS in order to improve the outcomes. Therefore, the debate between CEA

Table 3. High-risk features of CEA and CAS

High-risk CEA		High-risk CAS	
comorbidity	surgical anatomy	plaque morphology	vessel anatomy
– Severe coronary artery disease – Congestive heart failure – Recent MI within 6 weeks – Planned open heart surgery – Severe pulmonary disease – Renal failure – Age >80 years	– Previous CEA or neck surgery – Previous radiation – Bilateral stenosis – Contralateral carotid occlusion or laryngeal nerve palsy – Tracheostomy status	– Soft, lipid-rich plaque – Extensive plaque (>15 mm) plaque – Intraplaque hemorrhage – Thin fibrous cap – Heavy calcified plaque – Preocclusive lesion – Stenosis at the bifurcation involving both the ICA and ECA – Lesion located at a curve	– Aortoiliac tortuosity – Arch type II or III anatomy – Bovine configuration – Arch disease – Proximal or distal ICA tortuosity

and CAS is probably not as important as the question of how to select the best treatment without complications for each patient.

Decision-Making on Management of Carotid Stenosis

According to the latest guidelines [2, 24, 25], BMT is an essential part of the treatment for all patients with CS whereas symptomatic patients with more than 50% stenosis and highly selected patients with more than 60% asymptomatic stenosis should be considered for CR. In spite of disputable data from CAS and CEA, each of them is associated with their own high-risk features, which are summarized in table 3.

The risks of CEA depend on 2 main factors: patient status and surgical anatomy. CEA can be considered a high risk for patients with severe medical comorbidities, especially for those with severe cardiac diseases. Moreover, unfavorable surgical anatomy, leading to difficult cervical dissection during CEA, is also considered a high-risk CEA.

On the other hand, plaque morphology and vessel anatomy influence the outcomes of CAS. Distal embolization can occur during manipulation or crossing of the carotid plaque. According to the AHA grading system using MRI [37], type IV/V plaque (lipid or necrotic core) was defined as vulnerable whereas type VI plaque (intraplaque hemorrhage or fibrous cap rupture) was associated with a high risk of stroke. Moreover, heavily calcified, extensive (>15 mm) and preocclusive lesions increase the risk of periprocedural

stroke after CAS. Therefore, screening plagues with MRI can identify patients at high-risk from CAS [38]. The anatomy of vessels along the access route of CAS can complicate the procedure. Tortuosity of iliac artery, abdominal aorta or distal ICA, complexity of aortic arch or arch disease should be considered high-risk features.

However, the risks do not only depend on the procedure but also on the competency and experience of the surgeons. To achieve the best outcomes, therefore, the treatment should be selected on the basis of the procedure-related risk specific to each individual patient, as summarized in figure 1.

Regarding the management of asymptomatic CS, there is strong evidence comparing the efficacy between BMT and CR. However, evidence to date [39, 40] has shown that natural history of asymptomatic CS has improved significantly with modern BMT, and routinely treating asymptomatic patients with CR, considered by degree of stenosis, is not reliable. Annual stroke risk of CR was similar to modern BMT while there were periprocedural risks in CR but not in BMT. Therefore, selection of asymptomatic patients based on their respective 'high-risk features' (table 4) for CR would be reasonable and beneficial to prevent stroke [23, 39, 41, 42].

Conclusions

The management of CS is complicated and has been studied for a long time. Stroke prevention without complications is the main goal of successful treatment. Risk–benefit assessment should be discussed with individual

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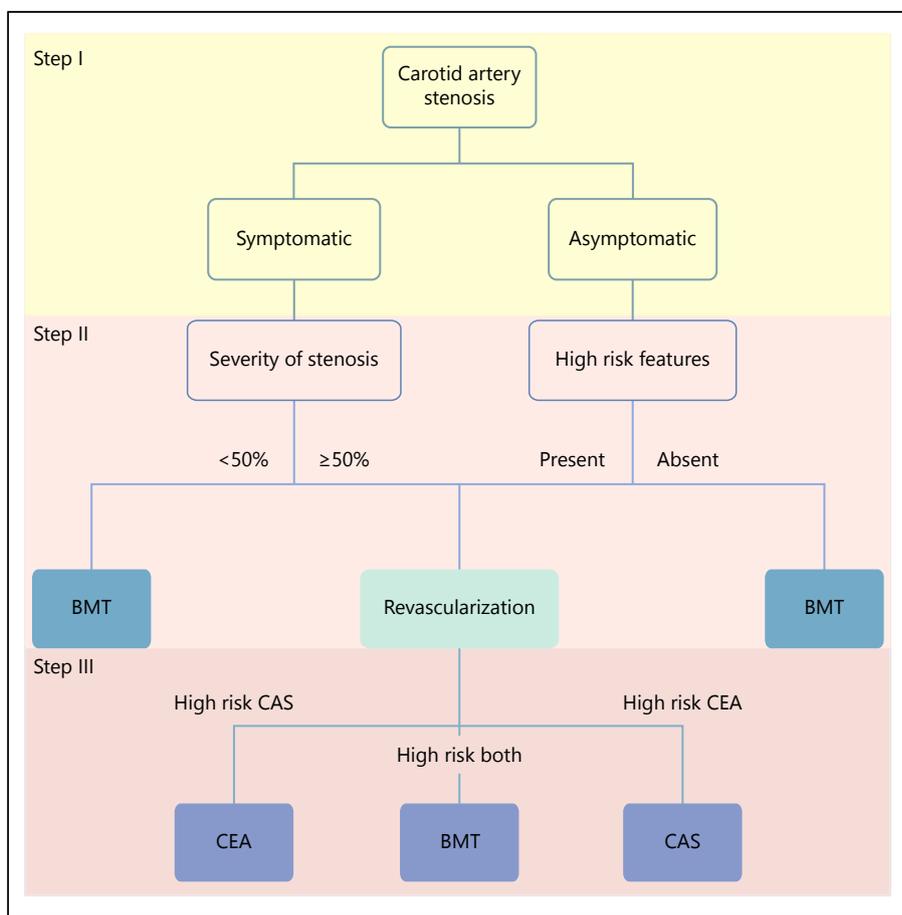
Fig. 1. Decision-making diagram of 3 steps for the management of CS. Step I – symptomatic status. Step II – choice of treatment based on severity of stenosis in symptomatic patients and high-risk features in asymptomatic patients. Step III – choice of revascularization based on procedural risk. It is important to additionally consider the surgeon's experience and other risk factors, especially in asymptomatic patients for selecting the treatment options.

Table 4. High-risk features of patients with asymptomatic carotid stenosis

Progression of stenosis
History of contralateral transient ischemic attack or stroke
Unfavorable plaque characteristic on ultrasound (irregularity, ulcerations, echolucency, gray-scale values and plaque area)
Intraplaque hemorrhage on MRI
Microemboli detected by transcranial Doppler ultrasound (TCD)
Silent infarcts on CT
Reduced cerebrovascular reserve

patients, and should be based on patient status, plaque characteristics and procedural risk, rather than on the argument between CEA and CAS. Although the data show CEA to be associated with fewer stroke events, there have been advancements in technology and training for CAS, resulting in comparable outcomes between the 2 procedures. Moreover, BMT, including antiplatelet drugs, antihypertensive agents and statins, has also been developed not only to stabilize atherosclerotic lesions but also to

break down the plaque. Ongoing trials are investigating the efficacy between new BMT and CR in asymptomatic patients.

Disclosure Statement

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REVIEWS

Current Diagnosis and Treatment of Carotid Atherosclerotic Disease

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ABSTRACT

Carotid atherosclerotic disease increases the risk for ischemic stroke and transient ischemic attack and challenges are presented when seeking the appropriate strategy of management. In this review, we will discuss the current diagnostic and treatment approaches of asymptomatic and symptomatic carotid stenosis. The definition of carotid plaques, staging of stenotic severity, and noninvasive tests including carotid duplex ultrasound, computed tomographic angiography, magnetic resonance angiography and transcranial Doppler will be summarized. Optimal management for asymptomatic and symptomatic carotid stenosis with medical therapy, carotid artery stenting or carotid endarterectomy has been controversial and should be judged in specific clinical settings. More clinical data are needed to better understand the correlation of different diagnostic measures and the disease progress and to optimize the treatment approach to improve patient outcomes.

KEY WORDS: Carotid atherosclerotic disease (CAD), stroke, intima-media thickness (IMT), asymptomatic carotid stenosis (ACS), symptomatic carotid stenosis (SCS), carotid duplex ultrasound (CDUS), computed tomographic angiography (CTA), magnetic resonance angiography (MRA) , transcranial Doppler (TCD), carotid artery stenting (CAS), carotid endarterectomy (CEA)

INTRODUCTION

Carotid atherosclerotic disease (CAD) refers to stenosis and occlusion of the carotid artery caused by atherosclerosis, where the carotid bifurcation and the proximal internal carotid artery (ICA) are most frequently affected. Progression of atheromatous plaques results in luminal narrowing and is often accompanied by plaque ulceration. Atherosclerosis progresses silently and the first symptom may be a stroke or transient ischemic attack (TIA), potentially devastating for patients. Overall prevalence of CAD differs from various studies. Data published from the

Cardiovascular Health Study in 1998 suggested an overall prevalence of severe asymptomatic carotid stenosis of 0.5% [1], whereas data published in 1992 showed that was 1.07% for women and 1.22% for men [2]. A meta-analysis published in 2012 [3] estimated the general prevalence of severe asymptomatic carotid stenosis between 0% to 3.1%. The prevalence of moderate asymptomatic carotid stenosis was 0.2% and 0% in males and females younger than 50 years of age, respectively, and 7.5% and 5.0% in males and females older than 80 years of age, respectively. Additionally, racial differences are suggested by data from Life Line Screening [4] as there is a higher prevalence of clinically significant carotid stenosis in Native Americans and Caucasians than African Americans and Asians. Based on the presence of symptoms, CAD can be divided into asymptomatic carotid stenosis (ACS) and symptomatic carotid stenosis (SCS). ACS refers to CAD without a history of recent ipsilateral carotid territory ischemic stroke or TIA, while SCS refers to CAD with emerging focal neurologic symptoms caused

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by ischemia of the ipsilateral carotid artery dominating region, including TIAs or non-disabling strokes [5]. Only symptoms occurring within the previous six months caused by carotid stenosis should be taken into consideration.

Risk factors for CAD are essentially the same as those for traditional coronary artery disease and the United States Preventive Services Task Force (USPSTF) has made recommendations for special screening of diseases of hypertension, diabetes mellitus, dyslipidemia and unhealthy lifestyle habits such as smoking, imbalanced diet or inadequate exercise [6]. Chronic hemodialysis program is another adverse factor as people with chronic kidney disease suffer a 5-10 fold higher risk of CAD than the general population [7].

In this review, we will briefly summarize the current techniques for diagnosing and evaluating carotid atherosclerotic disease, as well as up-to-date treatment of asymptomatic and symptomatic carotid stenosis.

1. DEFINITION AND EVALUATION

For patients with or without symptoms, evaluating the severity of CAD is always necessary to guide the appropriate therapy. Evaluation of the risk of perioperative cerebral ischemic events is especially important in the management of severe carotid artery stenosis [8]. While traditional non-invasive methods are widely used, newer technologies are being tested, such as using optical coherence tomography (OCT) to evaluate of the posterior part of the eye [9].

1.1 CAROTID PLAQUE

Advanced atherosclerotic plaques contain a fibrous cap and a necrotic lipid-rich core, infiltrated with inflammatory cells, sometimes with calcification, locally reflecting the severity of atherosclerosis. Carotid plaque morphology is classified as "smooth," "irregular," or "ulcerated" [10]. Patients with mild or moderate stable plaques may have no clinical symptoms and may never realize their existence, however, destabilization or rupture of plaques can lead to life-threatening events [11].

Carotid intima-media thickness (IMT) can increase significantly in patients with existing plaques [12] and was previously thought to reflect atherosclerotic burden, but large variations in histological measurements of IMT in late stage atherosclerotic disease challenge the validity of this assumption. Recent observations based on donor aortas also showed that IMT may not gradually increase as the atherosclerosis progresses, making the association between IMT and CAD less reliable [13].

The presence of carotid plaque was found to be a much stronger predictor of increased risk for coronary heart disease [14], stroke and cerebral infarction [15]. The European Mannheim consensus [16] and American Society of Echocardiography [17] define plaques as a focal wall thickening of > 50% (or 0.5mm) of the surrounding IMT, or an IMT of > 1.5 mm. In the Chinese Guidance of Ultrasound Examination in Stroke, a plaque is defined as a focal structural protrusion into the vessel lumen with an IMT > 1.5mm and thickening of > 50% (or 0.5mm) of the surrounding IMT [18]. The latter definition could be regarded as an improved version of the former.

Vulnerable carotid plaques are prone to rupture and thus need close observation and enhanced treatment. Several factors play a role in the formation of vulnerable plaques including age-associated changes [19], an increased hemoglobin A1c level [20], a decreased galectin-3 intra-plaque level [21] and the occurrence of neo-vessels within the plaque [22]. Contrast-enhanced ultrasonography find ulcerated plaques are more accurate for detecting disruption of fibrous cap and have a higher sensitivity (91.3%) compared to traditional ultrasonography [23]. A combination of quantitative change assessment by high-resolution magnetic resonance imaging and qualitative change assessment by Gray Scale Median analysis could also be used as a novel tool for detecting vulnerable plaques [24].

Quantification of carotid plaques is an important step of subclinical atherosclerosis assessment, which still lacks consensus for staging carotid plaque severity [25].

1.2 SEVERITY OF STENOSIS

Grading of severity of carotid artery stenosis ranges from mild (<50% stenosis), moderate (50% to 69% stenosis), severe (70% to 99% stenosis) to occlusion (100% stenosis). Traditional methods for quantitatively evaluating the severity of stenosis include the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method, the European Carotid Surgery Trial (ECST) method and the common carotid (CC) method. The first step in all the above methods is to measure the residual lumen diameter (RLD) at the most stenotic portion of the vessel. The difference among these methods is that NASCET method compares RLD with the lumen diameter in the normal ICA distal to the stenosis [26], the ECST method compares RLD with the estimated probable original diameter at the site of maximum stenosis [27] and the CC method compares RLD with the lumen diameter in the proximal common carotid artery [28]. Results of all three methods have a nearly linear relationship with each other and have similar prognostic values [28].

Conventional contrast angiography remains the gold standard to evaluate the severity of ICA stenosis. In current clinical

practice, noninvasive tests such as carotid duplex ultrasound (CDUS), computed tomographic angiography (CTA), magnetic resonance angiography (MRA) and transcranial Doppler (TCD) are sometimes preferred for their convenience and safety.

1.3 CAROTID DUPLEX ULTRASOUND

CDUS is a noninvasive, safe and relatively inexpensive technique for evaluating CAD by using B-mode and Doppler sonography to detect atherosclerotic obstruction of the carotid arteries [29]. CDUS measures focal increase in blood flow velocity to gauge the severity of the stenosis based on peak systolic velocity (PSV) and end-diastolic velocity (EDV). EDV is independently associated with future cardiovascular events where increases predict recanalization and neurological improvement from reperfusion therapy [30, 31]. Under criteria outlined by the Standards for Reporting of Diagnostic Accuracy (STARD), CDUS showed a sensitivity of 98% (95% CI: 97% to 100%) and a specificity of 88% (95% CI: 76% to 100%) in the identification of stenosis ≥50% with a PSV ≥130 cm/s, as well as a sensitivity of 90% (95% CI: 84% to 94%) and a specificity of 94% (95% CI: 88% to 97%) in the identification of stenosis ≥70% with a PSV ≥200 cm/s [32]. A simplified greyscale/mosaic ultrasound protocol was recently proposed to exclude significant severity, resulting in sensitivity, specificity, and negative predictive values to be 90%, 97%, 100%, respectively, for detection of stenosis >50% in the internal carotid artery [33].

A major limitation of CDUS is that the diagnostic accuracy relies heavily upon the experience and expertise of the ultrasound operators. In addition, different laboratories may use different measurement thresholds and the magnitude of the variation can have clinically importance [32, 34].

1.4 COMPUTED TOMOGRAPHIC ANGIOGRAPHY

CTA enables an anatomic depiction of the carotid artery lumen and measurement of RLD by three-dimensional reconstructions. CTA is a better option in situations where CDUS may fail such as the existence of severe calcification, inadequate neck length, or high bifurcation[35]. In the assessment of severe carotid artery stenosis, CTA correlates well with digital subtraction angiography (DSA), especially for detection of occlusions, with a high sensitivity and specificity of 97% and 99%, respectively [36]. Carotid CTA detects a complicated plaque reliably and provides the information of maximum soft plaque component thickness and the rim sign of adventitial calcification with internal soft plaque, of which the latter is highly predictive of carotid intra-plaque hemorrhage [37, 38]. CTA also predicts the risk of in-stent restenosis (ISR) with high volumes of plaque components of

<0 Hounsfield units (HU) [39]. Moreover, semiautomatic and automatic atherosclerotic plaque measurements using CTA showed overall diagnostic accuracy, however, confirmation by experienced radiologists is still necessary [40, 41].

Although there are benefits in using CTA, it requires a contrast agent and thus brings a higher risk for contrast-induced nephropathy to patients with impaired renal function, particularly those with concomitant diabetes or congestive heart failure.

1.5 MAGNETIC RESONANCE ANGIOGRAPHY

MRA is also an attractive noninvasive technique for the detection of stenosis and atherosclerosis. MRA was once thought to overestimate the degree and length of stenosis [42], but later findings showed comparable accuracy between three dimensional time-of-flight (TOF) MRA and DSA [43]. In a study published in 2001, MRA correctly identified 34 of 37 near-total and total occlusions [44] which confirmed the reliability of MRA in depicting occlusive carotid lesions. TOF MRA alone is accurate enough for the identification of severe stenosis and occlusions with sensitivities and specificities of 91.2% and 88.3% for severe ICA stenosis, respectively, and 94.5% and 99.3% for occlusions, respectively. Contrast enhancement (CE) MRA performs slightly better than TOF MRA, with sensitivities and specificities of 94.6% and 91.9% for severe stenosis, respectively, and 99.4% and 99.6% for occlusions, respectively [45]. A meta-analysis also concluded that CE MRA was more sensitive and specific than Doppler ultrasound, MRA and CTA for severe stenosis [46].

Compared with CDUS, MRA is less dependent on operators and produces an image of the artery of interest but cannot be performed when the patient is unable to lie supine for long periods of time, or has claustrophobia, a pacemaker, or ferromagnetic implants. MRA is also expensive to perform and time-consuming making it less practical.

1.6 TRANSCRANIAL DOPPLER

TCD noninvasively examines the major intracerebral arteries and assess real-time cerebral blood flow with physiological-flow related information. The American Academy of Neurology suggests that TCD is possibly useful in evaluating severe extracranial internal carotid artery stenosis or occlusion [47]. TCD can detect middle cerebral artery micro-emboli that arise from the heart or carotid artery in patients with severe carotid artery stenosis [48]. A meta-analysis found the post-test probabilities of a stroke after a positive and negative TCD were 7.1% (95% CI: 5% to 10.1%) and 1.2% (95% CI: 0.6 to 2.5%), respectively [49]. Utilizing cerebrovascular reserve capacity (CVRC) measurements, a hemodynamic parameter obtained with TCD-

inhalation CO2 tests, TCD may further add value for evaluating the brain's tolerance of ischemia with high availability and low cost. A significant difference in CVRC between asymptomatic and symptomatic patients and a close correlation between CVRC and the existence of symptoms suggest that CVRC could be an early mark-index to stage the risk of stroke and to guide further therapy [50]. The advantages of low cost, wide availability and bedside operability make TCD an attractive technique for detecting acute ischemia or intracranial stenosis and sonothrombolysis [51].

2. MANAGEMENT OF ASYMPTOMATIC CAROTID STENOSIS

Current management for patients with ACS include medical therapy for all patients and revascularization (CEA or CAS) reserved for select patients. Recent data suggested that the annual rate of stroke in medically treated patients with an ACS had fallen below 1% [52], which is lower than the risk of endarterectomy or carotid stenting, making routine revascularization unjustifiable for asymptomatic carotid stenosis except in the few patients at high risk of ipsilateral stroke.

2.1 CAROTID ENDARTERECTOMY
Randomized controlled trials in the 1990s had established CEA as a beneficial approach for selected patients with ACS. According to the Veterans Affairs Cooperative Study Group (VACS) trial in 1993, CEA reduced the overall incidence of ipsilateral neurologic events in male patients with ACS but did not have a significant influence on the combined incidence of stroke and death [53]. The Asymptomatic Carotid Atherosclerosis Study (ACAS) during 1987 to 1993 found that CEA decreased the aggregate risk for stroke or death over 5 years from 11.0% (with medical treatment only) to 5.1% [54]. The Asymptomatic Carotid Surgery Trial (ACST) during 1992 to 2003 also found out that immediate CEA had significant benefits compared with indefinite deferral of any CEA [55].

Perioperative complications including stroke and myocardial infarction limit the use of CEA. In the ACAS trial, candidates for surgery were required to have a perioperative complication rate of <3% [56]. Similarly, the ACST reported a 3.1% perioperative complication rate [55]. Therefore, CEA is not recommended for patients with ACS unless the risk of perioperative events (stroke and death) is <3%, otherwise the benefit from surgery would be negated [57, 58].

2.2 CAROTID ARTERY STENTING

In the prospective CREST trial, the rate of poor outcome in patients ≥ 70 years of age was higher with CAS than with CEA [59], but CAS with a device to capture and remove emboli is still an effective alternative to CEA in patients at average or high risk for surgical complications.

A recent 5-year follow-up to the Asymptomatic Carotid Trial I (ACT I) showed that there were no significant differences between the stenting group and endarterectomy group in the rate of stroke or death within 30 days after procedure (2.9% vs 1.7%, P = 0.33) or cumulative 5-year rate of stroke-free survival (93.1% vs 94.7%, P = 0.44) [60]. This trial included severe ACS patients ≤79 years of age. The results were also supported by the 10-year follow-up from the CREST trial [61] where no significant difference was found in the rate of the primary composite endpoint between the CAS group (11.8%, 95% Cl) and CEA group (9.9%, 95% CI), in which 47.2% of the patients were with ACS.

Compared with CEA restoration of chemoreceptor function, CAS may not acquire the same autonomic function as CEA [62]. Specifically, the complication rate may be greater with unfavorable aortic arch or carotid bifurcation anatomic features for CAS, in addition to the hazards of advanced age [63].

2.3 INTENSIVE MEDICAL THERAPY VS REVASCULARIZATION THERAPY
Current advances in medical therapy has narrowed the gap between medical and surgical treatment of CAD for reducing cardiovascular risk, as evident by the 91% reduction in stroke and 87% reduction in myocardial infarction by intensive medical therapy alone [64, 65]. With the relative risk reduction for the outcome of perioperative death or any stroke over 5 years of 30% to 50% and the absolute risk reduction of 4% to 5.9%, revascularization seems less attractive [66]. The early benefit of aggressive medical management in SAMMPRIS trial also lends support to the use of intensive medical treatment in high-risk patients with ACS and intracranial stenosis [67]. A Russian trial had showed that compared with medical therapy, CEA and medical treatment reduced the risk of death and cerebrovascular events in patients with 70% to 79% carotid stenosis, however this study had a small-sample and was a non-randomized trial [68]. More studies such as the SPACE-2 trial are still in need to clearly define the best treatment strategy, i.e., the addition of CEA and CAS in the background of medical therapy or medical therapy alone in patients with asymptomatic carotid stenosis [69].

Currently intensive medical treatment mainly consists of statin therapy, antiplatelet therapy, control of risk factors such as hypertension and diabetes and lifestyle changes [70].

Statins reverse the progression of carotid plaques and significantly reduce the risk of stroke by 15.6% for each 10% reduction in low-density lipoprotein cholesterol (LDL-C), and confers a definite 24% reduction in major vascular events and a 30% relative risk reduction of stroke over 20 years [71-73]. Additionally, the IDEAL study showed that compared with usual-dose statins, high-dose statins reduced the risk of composite secondary end events and nonfatal acute myocardial infarction [74]. It is thus recommended in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol that patients with a high 10-year risk for cardiovascular events should receive a high dose of statin [75]. Non-statin lipid-lowering drug like fibrates, ezetimibe and newly approved proprotein convertase subtilisin/kexin type 9 (PCSK9) may also be considered in patients intolerable to statins or with familial hypercholesterolemia, though their value has not been firmly established.

Antiplatelet therapy can reduce the incidence of the combined outcome of any serious vascular event including non-fatal myocardial infarction, stroke and death by 25% among high risk patients[76]. Aspirin, $P2Y_{12}$ inhibitor or cilostazol is protective in patients at increased risk of occlusive vascular events derived from ACS. Though there was limited evidence of efficacy, aspirin was recommended in the 2014 AHA/ASA Guidelines for the primary prevention of stroke in ACS patients[77]. Dual antiplatelet therapy (DAPT) in the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial showed early benefits of DAPT therapy in minor ischemic stroke or transient ischemic attack (TIA) by reducing the risk of subsequent stroke to 32% without increasing hemorrhage[78]. However, dual antiplatelet therapy may not benefit all patients with acute stroke or with ACS, unless the patient has concomitant symptomatic coronary artery disease, severe peripheral artery disease or recent coronary stenting[76, 79-81].

Hypertension is the most important modifiable risk factor for preventing stroke. Control of hypertension has been shown to reduce the incidence of stroke by 30% to 40% [82]. Optimal blood pressure (BP) targets remain unclear as most guidelines generally recommend a systolic BP of <140 mmHg and diastolic BP of <90 mmHg. For individuals with an older age, a more stringent goal would be beneficial in reducing major cardiovascular events, including stroke [83, 84]. However, in patients with severe carotid stenosis, cautious measures should be taken to avoid aggressive reductions in BP due to the possibility of insufficient brain perfusion. Though reduction of BP is presumed to be more important than the choice of a specific drug, some studies have suggested that angiotensin converting enzyme inhibitors (ACEI) offer more benefits than beta-blockers for the same drop in BP,

possibly due to their other physiological effects [81, 82]. Last but not least, lifestyle modifications consisting of smoking cessation, limited alcohol consumption, weight control, regular aerobic exercise, and a healthy diet, should be encouraged in patients with ACS. Smoking increases the overall risk of stroke by 150%, making its cessation mandatory [85]. Light alcohol consumption may decrease the risk of cardiovascular events while heavy alcohol consumption has been linked to a higher risk [86]. The Mediterranean diet supplemented with extra-virgin olive oil or nuts is recommended for people at high risk of cardiovascular events as it contains a broad combination of antioxidants [87, 88].

2.4 SUGGEST APPROACH TO ACS

For patients with ACS, intensive medical treatment alone may be effective enough and revascularizaition should be reserved for selected patients whose life expectancy is ≥5 years, stenosis at baseline or progression is >80% and perioperative risks including stroke and death is <3%. As for patients at high risk of revascularization or less than 5 years life expectancy, intensive medical treatment alone may be more suitable [89].

In choosing revascularization strategies, CAS is preferred in patients who have become recently symptomatic (<2 weeks), are older than 75 years of age, have a tortuous or heavily calcified aortas, and have long or heavily calcified lesions, while CEA is more suitable in those with contralateral carotid occlusions, recurrent carotid stenosis and significant cardiac and lung diseases [63]. Suggested management approach for ACS is shown in figure 1.

3. MANAGEMENT OF SYMPTOMATIC CAROTID STENOSIS

The optimal treatment of symptomatic carotid stenosis is less controversial for symptomatic patients than asymptomatic patients and revascularization is still supported and favored over medical therapy alone for moderate to severe symptomatic patients[89].

3.1 CAROTID ENDARTERECTOMY

CEA was developed in 1954 as a surgical option for stroke prevention in patients with SCS and its prophylactic application rose dramatically even without strong evidence of benefits until the mid-1980s. Following this, randomized controlled trials throughout the United States, Canada and Europe established CEA as safe and effective for reducing the risk of ischemic stroke in patients with SCS [5, 27, 90].
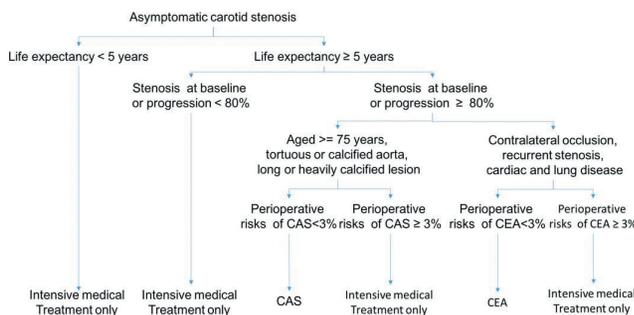
Figure 1. Management approach for asymptomatic carotid stenosis

CAS should be considered in those with life expectancy no less than 5 years and with stenosis at baseline or progression no less than 80%; and those who are older than 75 years of age with a tortuous or heavily calcified lesions. CEA as an alternative to CAS should be considered in those with contralateral carotid occlusions, recurrent carotid stenosis and significant cardiac and lung diseases.
CAS=carotid artery stenosis, CEA=carotid endarterectomy.

For symptomatic patients with severe carotid stenosis, the NASCET trial [26] showed an absolute reduction of 17% in the risk of ipsilateral stroke at two years (P<0.001), with perioperative morbidity and mortality quite acceptable at a rate of 2.1% for major stroke and 0.6% for death. In the 3-year follow-up of the ECST trial [90], risk of ipsilateral stroke was 2.8% in CEA-treated patients compared with 16.8% in medically treated patients. Patients with moderate SCS benefited less from CEA, with the risks of any ipsilateral ischemic stroke of 15.7% with CEA and 22.2% with medical therapy (P=0.045) in 5-year follow-up [91]. A synthesis of randomized controlled trials concluded that CEA is highly beneficial for patients with 70% to 99% stenosis and of marginal benefit for patients with 50% to 69% symptomatic stenosis, while no benefit was observed in patients with less than 50% stenosis [92].

3.2 CAROTID ARTERY STENTING

Carotid angioplasty and stenting is a more recent revascularization procedure utilized to treat patients at high surgical risk for CEA. The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) and Carotid Revascularization Endarterectomy versus Stent Trial (CREST) trials generally found that CAS and CEA had the similar rates of perioperative events [93-95]. CAS, however, is associated with a higher procedural risk of stroke and lower risk of myocardial infarction

than CEA in patients with SCS [96]. A seven-year follow-up of EVA-3S study showed both techniques were associated with low and similar long-term risks of recurrent ipsilateral stroke beyond the procedural period while CEA did have a lower risk of stroke during the procedural period [97]. Long-term results of CREST reported no significant differences between CAS and CEA in the risk of perioperative stroke, myocardial infarction or postoperative ipsilateral stroke in 10 years [61]. It is important to note that age has a huge impact on perioperative risk when choosing between CEA or CAS. The CAS-versus CEA perioperative hazard ratio (HR) was determined to be 1.61 (95% CI: 0.90 to 2.88) for patients aged 65-69 years and 2.09 (95% CI: 1.32 to 3.32) for patients aged 70-74 years [98]. It is in agreement with current recommendations that CEA should be preferred over CAS in patients older than 70 years.

In conclusion, CEA remains the standard revascularization option for patients of severe SCS (>70% stenosis) with perioperative stroke and death rate lower than 6%, while CAS may be better for patients with certain high risk feature, including high cervical lesions above C2, previous cervical irradiation or post-CEA restenosis. The value of CAS as an equivalent alternative to CEA is still questionable, calling for more trials in the future. Presently, application of CAS should be selective and must be done by experienced operators at experienced centers [99].

3.3 TIMING OF REVASCULARIZATION

The timing of revascularization in patients with SCS remains controversial. Post-hoc analysis from NASCET and ECST trials suggest that the greatest benefit is obtained when performing CEA within two weeks after a stroke event, with an absolute risk reduction (ARR) in perioperative stroke of 30.2%. ARR fell to 18% and 11% when delaying surgery to 2-4 weeks and 4-12 weeks, respectively [100]. The decline in benefit of CEA over time was more rapid in women than in men [101]. On the other hand, pooled data suggested revascularization performed within the first 48 hours of a carotid stroke had a higher risk of perioperative stroke, especially in those with stroke as index event (8.0%; 95% CI: 4.6% to 12.5%) [102]. Hyper-perfusion following CEA may be responsible as it induces reperfusion injury and increases the risk of intracerebral hemorrhage and thrombus translocation [103]. A recent summary and meta-analysis on early carotid intervention showed similar risks in perioperative stroke when revascularization is performed within 15 or 7 days after an index event for CEA (3.4% vs 3.3%, within 15 days and 7 days, respectively) or CAS (4.6% vs 4.6, within 15 days and 7 days, respectively). It suggested that carotid revascularization can be safely performed earlier (0–7 days) than

current recommendations [102]. Currently, there is an ongoing randomized controlled trial examining the timing of cerebral revascularization, and its results may have further implications in the future [104].

3.4 SUGGESTED APPROACH TO SCS

Optimal treatment strategies for SCS should be based upon intensive medical therapy as it is for ACS and should balance the risk and benefit from both revascularization approaches [77, 105-107]. For patients with <50% stenosis, medical therapy should be implemented with no need of CEA and CAS. For patients with SCS and severe stenosis of 70%-99%, CEA is recommended when the perioperative events (stroke/death) rate is <6%. CEA should be considered in patients with stenosis of 50%-69%. CAS is indicated as an alternative when its perioperative events rate is <6% and should be favored in patients with severe cardiac disease, history of irradiation, stenosis distal to the second cervical vertebra and previous ipsilateral CEA. In addition, patient age should be taken into consideration when choosing between CEA and CAS. Once decided, revascularization should be performed within two weeks, but not in the first 48 hours after stroke or TIA. Suggested management approach for SCS is shown in figure 2.

4. SUMMARY

Patients with carotid atherosclerotic disease remain at high risk for adverse cardiovascular events, especially stroke and myocardial infarction. Significant development and standardized implementation of recent medical therapy has dramatically driven down the rates of stroke among patients with asymptomatic carotid stenosis. However, more studies are still required to better stratify patients with high-risk profiles that would benefit from more invasive therapies. Also unclear is the decision on which revascularization method a patient should receive. More advanced devices and techniques are being developed to further overcome the procedural complications in patients undergoing endarterectomy or carotid artery stenting. We are looking forward to more clinical trials to amend the current treatment standards for a better management of carotid atherosclerotic disease.
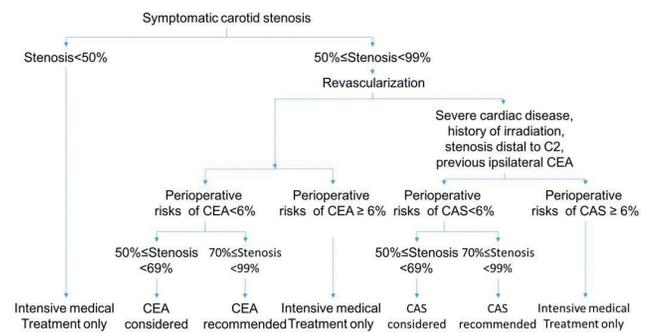
ACKNOWLEDGMENT

Figure 2. Management approach for symptomatic carotid stenosis

CEA should be considered in SCS with stenosis between 50% and 99% and with perioperative risks no more than 6%. The CAS as an alternative to CEA should be considered in those with severe cardiac disease, history of irradiation, stenosis distal to the second cervical vertebra and previous ipsilateral CEA; and those whose perioperative risks is less than 6%. CAS=carotid artery stenosis, CEA=carotid endarterectomy.

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