Recent Update on Carotid Endarterectomy versus Carotid Artery Stenting

Raywat Noiphithak^a Anusak Liengudom^b^aDivision of Neurosurgery, Department of Surgery, Thammasat University Hospital, Faculty of Medicine, Thammasat University, Pathumthani, and ^bDepartment of Neurosurgery, Prasat Neurological Institute, Bangkok, Thailand

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.

© 2016 S. Karger AG, Basel

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.

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
<ul style="list-style-type: none"> – Severe coronary artery disease – Congestive heart failure – Recent MI within 6 weeks – Planned open heart surgery – Severe pulmonary disease – Renal failure – Age >80 years 	<ul style="list-style-type: none"> – Previous CEA or neck surgery – Previous radiation – Bilateral stenosis – Contralateral carotid occlusion or laryngeal nerve palsy – Tracheostomy status 	<ul style="list-style-type: none"> – 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 	<ul style="list-style-type: none"> – 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 plaques 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

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

The authors did not receive any specific grant from funding agencies in the public, commercial or not-for-specific sectors.

References

- Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO: Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke* 1999;30:2513–2516.
- Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al: 2011 ASA/ACCF/AHA/AANN/AAAS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Developed in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. *Catheter Cardiovasc Interv* 2013;81:E76–E123.
- Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, et al: The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. *Stroke* 1999;30:1751–1758.
- European Carotid Surgery Trialists Collaborative Group: Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379–1387.
- Walker MD, Marler JR, Goldstein M, et al: Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421–1428.
- CAVATAS Investigators: Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;357:1729–1737.
- Ederle J, Bonati LH, Dobson J, Featherstone RL, Gaines PA, Beard JD, et al: Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol* 2009;8:898–907.
- Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al: Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;351:1493–1501.
- Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al: Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;358:1572–1579.
- SPACE Collaborative Group, Ringleb PA, Altenberg J, Brückmann H, Eckstein HH, Fraedrich G, et al: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006;368:1239–1247.
- Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al: Endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol* 2008;7:885–892.
- Mas JL, Arquizan C, Calvet D, Viguier A, Albucher JF, Piquet P, et al: Long-term follow-up study of endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis trial. *Stroke* 2014;45:2750–2756.
- International Carotid Stenting Study Investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, et al: Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 2010;375:985–997.
- Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al: New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol* 2010;9:353–362.
- Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, et al: Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet* 2015;385:529–538.
- Calvet D, Mas JL, Algra A, Becquemin JP, Bonati LH, Dobson J, et al: Carotid stenting: is there an operator effect? A pooled analysis from the carotid stenting trialists' collaboration. *Stroke* 2014;45:527–532.
- Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al: Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;363:11–23.
- Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, et al: Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Stroke* 2011;42:675–680.
- Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD 2nd, Gonzales NR, et al: Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol* 2011;10:530–537.
- Voeks JH, Howard G, Roubin GS, Malas MB, Cohen DJ, Sternbergh WC 3rd, et al: Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. *Stroke* 2011;42:3484–3490.
- Cohen DJ, Stalker JM, Wang K, Magnuson EA, Clark WM, Demaerschalk BM, et al: Health-related quality of life after carotid stenting versus carotid endarterectomy: results from CREST (Carotid Revascularization Endarterectomy versus Stenting Trial). *J Am Coll Cardiol* 2011;58:1557–1565.
- Blackshear JL, Cutlip DE, Roubin GS, Hill MD, Leimgruber PP, Begg RJ, et al: Myocardial infarction after carotid stenting and endarterectomy: results from the carotid revascularization endarterectomy versus stenting trial. *Circulation* 2011;123:2571–2578.
- Paraskevas KI, Mikhailidis DP, Veith FJ: Comparison of the five 2011 guidelines for the treatment of carotid stenosis. *J Vasc Surg* 2012;55:1504–1508.
- Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK, et al: Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg* 2011;54:e1–e31.
- Kakisis JD, Avgerinos ED, Antonopoulos CN, Giannakopoulos TG, Moulakakis K, Liapis CD: The European Society for Vascular Surgery guidelines for carotid intervention: an updated independent assessment and literature review. *Eur J Vasc Endovasc Surg* 2012;44:238–243.
- Meier P, Knapp G, Tamhane U, Chaturvedi S, Gurm HS: Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. *BMJ* 2010;340:c467.
- Liu ZJ, Fu WG, Guo ZY, Shen LG, Shi ZY, Li JH: Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis. *Ann Vasc Surg* 2012;26:576–590.
- Bonati LH, Fraedrich G: Carotid Stenting Trialists' Collaboration: Age modifies the relative risk of stenting versus endarterectomy for symptomatic carotid stenosis – a pooled analysis of EVA-3S, SPACE and ICSS. *Eur J Vasc Endovasc Surg* 2011;41:153–158.
- Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM: Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev* 2012;9:CD000515.
- Bangalore S, Kumar S, Wetterslev J, Bavry AA, Gluud C, Cutlip DE, et al: Carotid artery stenting vs carotid endarterectomy: meta-analysis and diversity-adjusted trial sequential analysis of randomized trials. *Arch Neurol* 2011;68:172–184.

- 31 Vincent S, Eberg M, Eisenberg MJ, Filion KB: Meta-analysis of randomized controlled trials comparing the long-term outcomes of carotid artery stenting versus endarterectomy. *Circ Cardiovasc Qual Outcomes* 2015;8(6 suppl 3):S99–S108.
- 32 Zhang L, Zhao Z, Ouyang Y, Bao J, Lu Q, Feng R, et al: Systematic review and meta-analysis of carotid artery stenting versus endarterectomy for carotid stenosis: a chronological and worldwide study. *Medicine (Baltimore)* 2015; 94:e1060.
- 33 Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al: Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med* 2016;374:1011–1020.
- 34 Bulbulia R, Halliday A: ACST-2 – an update. A large, simple randomised trial to compare carotid endarterectomy versus carotid artery stenting to prevent stroke in asymptomatic patients. *Gefasschirurgie* 2013;18:626–632.
- 35 Eckstein HH, Reiff T, Ringleb P, Jansen O, Mansmann U, Hacke W, et al: SPACE-2: a missed opportunity to compare carotid endarterectomy, carotid stenting, and best medical treatment in patients with asymptomatic carotid stenoses. *Eur J Vasc Endovasc Surg* 2016;51:761–765.
- 36 Cremonesi A, Setacci C, Bignamini A, Bolognese L, Briganti F, Di Sciascio G, et al: Carotid artery stenting: first consensus document of the ICCS-SPREAD Joint Committee. *Stroke* 2006;37:2400–2409.
- 37 Lindsay AC, Biasioli L, Lee JM, Kylintireas I, MacIntosh BJ, Watt H, et al: Plaque features associated with increased cerebral infarction after minor stroke and TIA: a prospective, case-control, 3-T carotid artery MR imaging study. *JACC Cardiovasc Imaging* 2012;5:388–396.
- 38 Yoshimura S, Yamada K, Kawasaki M, Asano T, Kanematsu M, Takamatsu M, et al: High-intensity signal on time-of-flight magnetic resonance angiography indicates carotid plaques at high risk for cerebral embolism during stenting. *Stroke* 2011;42:3132–3137.
- 39 Spence JD, Song H, Cheng G: Appropriate management of asymptomatic carotid stenosis. *Stroke Vasc Neurol* 2016;1:e000016.
- 40 Hadar N, Raman G, Moorthy D, O'Donnell TF, Thaler DE, Feldmann E, et al: Asymptomatic carotid artery stenosis treated with medical therapy alone: temporal trends and implications for risk assessment and the design of future studies. *Cerebrovasc Dis* 2014;38:163–173.
- 41 Bogiatzi C, Cocker MS, Beanlands R, Spence JD: Identifying high-risk asymptomatic carotid stenosis. *Expert Opin Med Diagn* 2012; 6:139–151.
- 42 Singh TD, Kramer CL, Mandrekar J, Lanzino G, Rabinstein AA: Asymptomatic carotid stenosis: risk of progression and development of symptoms. *Cerebrovasc Dis* 2015;40:236–243.