REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

Mechanisms to explain the poor results of carotid artery stenting (CAS) in symptomatic patients to date and options to improve CAS outcomes

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Background: **Carotid artery stenting (CAS) is considered by many as an alternative to carotid endarterectomy (CEA) for the management of carotid artery stenosis. However, recent trials demonstrated inferior results for CAS in symptomatic patients compared with CEA. We reviewed the literature to evaluate the appropriateness of CAS for symptomatic carotid artery stenosis and to determine the pathogenetic mechanism(s) associated with stroke following the treatment of such lesions. Based on this, we propose steps to improve the results of CAS for the treatment of symptomatic carotid stenosis.**

Methods: **PubMed/Medline was searched up to March 25, 2010 for studies investigating the efficacy of CAS for the management of symptomatic carotid stenosis. Search terms used were "carotid artery stenting," "symptomatic carotid artery stenosis," "carotid endarterectomy," "stroke," "recurrent carotid stenosis," and "long-term results" in various combinations.**

Results: **Current data suggest that CAS is not equivalent to CEA for the treatment of symptomatic carotid stenosis. Differences in carotid plaque morphology and a higher incidence of microemboli and cerebrovascular events during and after CAS compared with CEA may account for these inferior results.**

Conclusions: **Currently, most symptomatic patients are inappropriate candidates for CAS. Improved CAS technology referable to stent design and embolic protection strategies may alter this conclusion in the future. (J Vasc Surg 2010;52: 1367-75.)**

Carotid artery stenting (CAS) has emerged as an alternative to carotid endarterectomy (CEA) for the management of carotid artery stenosis.[1-4] Large, multicenter studies have shown that CAS is not inferior to CEA for the management of carotid artery stenosis in some largely asymptomatic patient groups.[3,4] This led the supporters of CAS to dispute CEA as the "gold standard" treatment for carotid artery stenosis.[1,4]

Although CAS may provide similar results to CEA for asymptomatic carotid artery stenosis,[3,4] this may not be true for symptomatic patients. The mechanisms associated with strokes from the treatment of symptomatic carotid stenosis may involve an entirely different process in terms of lesion behavior and natural history compared with those of asymptomatic carotid artery disease. Because of these differences, several possible options to improve CAS outcomes may exist in symptomatic patients. The purpose of this article is to review the relevant literature and discuss these options.

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MATERIALS AND METHODS

PubMed/Medline was searched up to March 25, 2010 for studies evaluating the efficacy of CAS compared with CEA in symptomatic carotid artery stenosis. Search terms were "carotid artery stenting," "symptomatic carotid artery stenosis," "carotid endarterectomy," "stroke," "recurrent carotid stenosis," and "long-term results" in various combinations. The reference lists of the gathered reports were also manually searched.

RESULTS

Several studies comparing the efficacy of CAS with CEA were identified (Table).[3,5-20] The majority of these trials showed that the presence of neurological symptoms prior to CAS was independently associated with

Table. Neurological complications after CAS and CEA for symptomatic carotid artery stenosis

Study (year)	*Study design*	*Study outcome*
Leicester study[5] (1998)	Randomization of symptomatic pts with >70% carotid stenosis to CEA (n = 10) or CAS (n = 13)	- Incidence of stroke: 0 of 10 CEAs vs 5 of 7 CAS procedures; $P = .0034$ - The Data Monitoring Committee stopped this trial prematurely due to the unacceptable high stroke rate following CAS.
Qureshi et al[6] (2000)	Comparison of the angiograms of 111 pts undergoing CAS for asymptomatic (n = 54) or symptomatic (n = 57) carotid artery stenosis	- The presence of neurological symptoms prior to CAS was independently associated with a >8-fold risk of the development of periprocedural neurological deficits (OR, 8.3; 95% CI, 1.6-42.6; $P = .01$).
Golledge et al[7] (2000)	Systematic comparison of the 30-day outcome of 13 studies of angioplasty with/without stenting and 20 CEA studies for the management of symptomatic carotid artery disease.	- Any stroke: 51 of 714 vs 233 of 6970, for angioplasty vs CEA, respectively; OR, 2.22; 95% CI, 1.62-3.04; $\chi^2=26.5$; $P < .0001$. - Disabling or fatal stroke: 23 of 714 vs 78 of 4973 for angioplasty vs CEA, respectively; OR, 2.09; 95% CI, 1.3-3.33; $\chi^2=8.8$; $P < .01$. - Incidence of combined stroke and death: 56 of 714 vs 201 of 4973, or 7.8% vs 4%, after angioplasty vs CEA, respectively; OR, 2.02; 95% CI, 1.49-2.75; $\chi^2 = 20.6$; $P < .001$).
Kentucky study[8] (2001)	Randomization of symptomatic pts with a >70% carotid stenosis to CAS (n = 53) or CEA (n = 51).	- No strokes in pts undergoing either CAS or CEA. - One individual died of an MI immediately after CEA.
WALLSTENT[9] (2001)	Randomization of 219 symptomatic pts with ≥60% carotid stenosis to CAS (n = 107) or CEA (n = 112).	- 30-day periprocedural complication (any stroke or death) rate: 12.1% vs 4.5%, for CAS vs CEA, respectively; $P = .049$.
ICAROS[10] (2004)	Correlation of a highly reproducible index of carotid plaque echogenicity, the GSM, with the risk of stroke after CAS.	- Incidence of stroke after CAS: 7.1 ± 2.1% vs 1.5 ± 0.8%, for GSM ≤25 vs GSM >25, respectively; $P = .005$. - Independent predictors of stroke after CAS: i) GSM ≤25 (OR, 7.11; 95% CI, 2.06-24.57; $P = .002$) and, ii) ≥85% stenosis (OR, 5.76; 95% CI, 1.51-21.91; $P = .010$).
Kastrup et al[11] (2005)	Comparison of complication rates in 129 asymptomatic with 170 symptomatic pts with carotid artery stenosis (≥70% for symptomatic; ≥90% for asymptomatic pts) undergoing CAS.	- Incidence of TIA, stroke, and death: 15.3% vs 3.1%, for symptomatic vs asymptomatic pts, respectively; $P < .01$). - A previous hemispherical TIA prior to CAS was associated with an almost 5-fold higher risk (OR, 4.7; 95% CI, 1.6-13.3; $P = .004$) for the development of postprocedural TIA, minor/major stroke and death. - A history of stroke prior to CAS was associated with an 8-fold higher risk (OR, 8.0; 95% CI, 2.6-24.4; $P < .001$) for the development of postprocedural TIA, minor/major stroke, and death.
CAVATAS[12] (2005)	Randomization of 504 pts with carotid artery stenosis to endovascular treatment[a] or CEA (251 vs 253 pts, respectively).	- Rate of death/disabling stroke in any vascular territory/ipsilateral stroke rate: 14.3% vs 14.2% for endovascular treatment vs CEA, respectively. - Severe (70%-99%) recurrent carotid stenosis on ultrasound at 1 year: 25 vs 7 pts, or 14% vs 4%, for endovascular treatment vs CEA, respectively, $P < .001$. - Severe stenosis or occlusion at 1 year in the subgroup of pts treated by stenting:[a] 9 of 41 pts (22%).
SPACE[13] (2006)	Randomization of pts with ≥70% symptomatic carotid stenosis to CAS (n = 613) or CEA (n = 601).	- 30-day death or ipsilateral ischemic stroke rates: 6.84% vs 6.34%, for CAS vs CEA, respectively; absolute difference, 0.51%; 90% CI, −1.89% to 2.91%; $P = .09$.
EVA-3S[14] (2006)	Comparison of CAS (n = 265) vs CEA (n = 262) for symptomatic carotid artery stenosis ≥60%.	- Incidence of nonfatal stroke: 8.8% vs 2.7%, for CAS vs CEA, respectively; RR, 3.3; 95% CI, 1.4-7.5; $P = .004$. - Incidence of 30-day stroke or death: 9.6% vs 3.9%, for CAS vs CEA, respectively; RR, 2.5; 95% CI, 1.2-5.1; $P = .01$. - Incidence of any stroke or death at 6 months: 11.7% vs 6.1%, for CAS vs CEA, respectively; $P = .02$.
Pro-CAS[15] (2008)	Multicenter (n = 25) prospective analysis of possible predictors of death and stroke after CAS procedures (n = 5341)	- Periprocedural stroke or death: 4.3% vs 2.7% for symptomatic vs asymptomatic carotid stenosis, respectively; $P = .0019$. - The presence of symptoms was associated with a >1.5-fold increased risk for the occurrence of stroke and/or death following CAS (OR, 1.54; 95% CI, 1.1-2.1; $P = .008$).
EVA-3S[16] (2008)	4-year follow-up data of the original EVA-3S study.[14]	- Incidence of 30-day stroke/death rate or nonprocedural ipsilateral stroke: 6.2% vs 11.1%, for CEA vs CAS, respectively; HR, 1.97; 95% CI, 1.06-3.67; $P = .03$ for CAS vs CEA. - Any stroke or periprocedural death: HR, 1.77; 95% CI, 1.03-3.02; $P = .04$. - Any stroke or death: HR, 1.39; 95% CI, 0.96-2.00; $P = .08$.

Table. Continued

Study (year)	*Study design*	*Study outcome*
SPACE[17](2008)	2-year follow-up data of the original SPACE study.[13]	- Incidence of ≥70% recurrent carotid stenosis (intention-to-treat): 10.7% vs 4.6%, for CAS vs CEA, respectively; $P = .0009$. - Incidence of ≥70% recurrent carotid stenosis (per protocol): 11.1% vs 4.6%, for CAS vs CEA, respectively; $P = .0007$.
Steinbauer et al[18] (2008)	Single-center randomized study comparing the long-term (mean follow-up: 66 ± 14.2 vs 64 ± 12.1 months, respectively) results of CAS (n = 43) with CEA (n = 44)	- Ipsilateral stroke rates: 4 of 42 CAS vs 0 of 42 CEA pts; $P < .05$. - >70% recurrent carotid stenosis rates: 6 of 32 CAS vs 0 of 29 CEA pts; $P < .05$. - Reintervention rates for >70% restenosis: 5 of 32 CAS vs 0 of 29 CEA pts, respectively; $P < .05$.
CAVATAS[19] (2009)	5-year results of the initial CAVATAS Study.[12]	- Incidence of ≥70% recurrent stenosis: 53 vs 20 pts, or 30.7% vs 10.5%, for pts receiving endovascular treatment vs CEA respectively; adjusted HR, 3.17; 95% CI, 1.89-5.32; $P < .0001$).[b]
ICSS[20] (2010)	Randomization of 1710 symptomatic pts to CAS (n = 853) vs CEA (n = 857)	- Risk of 120-day stroke: 7.7% vs 4.1%, for CAS vs CEA, respectively; HR, 1.92; 95% CI, 1.27-2.89; $P = .002$. - Risk of any stroke or death: 8.5% vs 4.7%, for CAS vs CEA, respectively; HR, 1.86; 95% CI, 1.26-2.74; $P = .0001$. - Risk of all-cause death: 2.3% vs 0.8%, for CAS vs CEA, respectively; HR, 2.76; 95% CI, 1.16-6.56; $P = .017$. - Risk of any stroke, death, or procedural MI: 8.5% vs 5.9%, for CAS vs CEA, respectively; HR, 1.69; 95% CI, 1.16-2.45; $P = .006$.
CREST[3] (2010)	Randomization of 2,502 pts (1321 symptomatic; 1181 asymptomatic) to CAS (n=1262) or CEA (n=1240).	- Primary endpoint of 30-day death/MI/stroke and ipsilateral stroke >30 days: 7.2% vs 6.8%, for CAS vs CEA, respectively; HR, 1.11; 95% CI, 0.81-1.51; $P = .51$. - Periprocedural stroke rate: 4.1% vs 2.3%, for CAS vs CEA, respectively; $P = .01$. - Debilitating/major stroke rate: 0.9% vs 0.7%, for CAS vs CEA, respectively; $P = .52$. - Minor stroke rate: 2.7% vs 1.5%, for CAS vs CEA, respectively; $P < .05$.

CAS, Carotid artery stenting; *CAVATAS,* Carotid and Vertebral Artery Transluminal Angioplasty Study; *CEA,* carotid endarterectomy; *CI,* confidence interval; *CREST,* Carotid Revascularization: Endarterectomy versus Stenting Trial; *EPD,* emboli-protecting device; *EVA-3S,* Endarterectomy Versus Angioplasty in Pts with Symptomatic Severe Carotid Stenosis; *GSM,* gray-scale median; *HR,* hazard ratio; *ICSS,* International Carotid Stenting Study; *ICAROS,* Imaging in Carotid Angioplasty and Risk of Stroke study; *MI,* myocardial infarction; *OR,* odds ratio; *Pro-CAS,* Prospective registry of carotid artery stenting; *TIA,* transient ischemic attack; *pts,* patients; *RR,* relative risk; *SPACE,* Stent-Protected Angioplasty versus Carotid Endarterectomy.

[a]For endovascular patients treated successfully (n = 213), stents were used in 55 (26%) and balloon angioplasty alone in 158 (74%).

[b]The risk of ≥70% recurrent stenosis at 5 years was lower in those patients treated with a stent than in those patients treated by angioplasty alone (16.6% vs 36.2%, respectively; adjusted HR, 0.43; 95% CI, 0.19-0.97; $P = .04$), but it was higher than in patients undergoing CEA (10.5%).

an increased incidence of periprocedural neurological events.[5-7,9-11,14-16,18,20] Interpretation of these results suggests that currently most symptomatic patients with a history of transient ischemic attack (TIA) or stroke should probably not be treated by CAS.

More recently, one single-center[18] and two multicenter[16,17] randomized trials comparing the late results of CAS with CEA for the management of symptomatic carotid artery stenosis indicated that CAS provides inferior long-term results compared with CEA. A higher rate of recurrent carotid stenosis[17,18] or a higher incidence of stroke/periprocedural death[16] were the main drawbacks for CAS compared with CEA. A detailed evaluation and critical overview of the results of these trials is presented elsewhere.[21] This review also concluded that CAS is inferior to CEA for symptomatic patients but noted that "the results of soon-to-be reported trials (Carotid Revascularization: Endarterectomy vs Stenting Trial [CREST], International Carotid Stenting Study [ICSS], or others) may alter the current impression that CAS is inferior to CEA for the treatment of symptomatic carotid stenosis."[21]

ICSS recently reported its 120-day results after randomization to CAS or CEA.[20] Eligible patients undergoing CAS (n = 828) had a higher 120-day risk of any stroke (65 vs 35 events, or 7.7% vs 4.1%, respectively; hazard ratio [HR], 1.92; 95% confidence interval [CI], 1.27-2.89; $P = .002$), any stroke or death (72 vs 40 events, or 8.5% vs 4.7%, respectively; HR, 1.86; 95% CI, 1.26-2.74; $P = .0001$), all-cause death (19 vs 7 events, or 2.3% vs 0.8%, respectively; HR, 2.76; 95% CI, 1.16-6.56; $P = .017$), as well as any stroke, death, or procedural myocardial infarction (MI) (72 vs 44 events, or 8.5% vs 5.9%, respectively; HR, 1.69; 95% CI, 1.16-2.45; $P = .006$) compared with individuals undergoing CEA (n = 821).[20] Furthermore, in a substudy where a magnetic resonance imaging (MRI) scan with vascular sequences was carried out before the procedure, followed by an early (1-3 days) and a late (27-33 days) postprocedural scan, new ischemic lesions on diffusion-weighted imaging were found in half of CAS vs <20% of CEA patients (50% vs 17%, respectively; adjusted odds ratio [OR], 5.21; 95% CI, 2.78-9.79; $P < .0001$).[22] The conclusion reached was that, despite the use of embolic-pro-

tection devices (EPDs), CAS is associated with several-fold more new ischemic lesions on diffusion-weighted imaging compared with CEA.[22] The final results of ICSS, which include the 3-year rates of fatal or disabling stroke in any territory after CAS and CEA, remain to be reported.

Recently, CREST also announced its results.[3] A total of 2,502 patients were randomized to CAS (n = 1,262) or CEA (n = 1,240). The primary endpoint of death, MI, or stroke at 30 days plus ipsilateral stroke occurring >30 days following the procedure was similar between patients undergoing CAS and CEA (7.2% vs 6.8%, respectively; HR, 1.11; 95% CI, 0.81-1.51; $P = .51$). Nevertheless, patients undergoing CAS suffered more periprocedural strokes (4.1% vs 2.3%, for CAS vs CEA, respectively; $P = .01$) and more minor strokes (2.7% vs 1.5%, for CAS vs CEA, respectively; $P < .05$) compared with individuals undergoing CEA.[3] In contrast with previous studies,[5-7,9-11,14-16,18,20] there was no difference in the incidence of 30-day stroke rates between the two groups based on the presence of preprocedural symptoms (TIA/stroke). The extensive and rigorous credentialing process for carotid interventionalists in CREST may explain these contradictory results.[23]

The results of two recent meta-analyses lend support to the superiority of CEA over CAS in symptomatic patients. According to the first meta-analysis (10 trials; 3,580 patients), when a subgroup analysis of trials was performed including only symptomatic patients with a ≥60% carotid stenosis, the 30-day risks for stroke (relative risk [RR], 1.62; 95% CI, 1.13-2.31 after CAS use; $P < .05$) and any stroke or death (RR, 1.63; 95% CI, 1.18-2.25 after CAS use; $P < .05$) were significantly higher in CAS patients, "making it a suboptimal choice for symptomatic patients with moderate to severe stenosis."[1] In the second meta-analysis,[2] when considering only previously symptomatic patients, CAS was associated with a higher incidence of stroke and death within 30 days (54 of 1011 vs 90 of 1032 events for CEA vs CAS, respectively; RR, 0.53; 95% CI, 0.30-0.95; $P = .003$).

A retrospective study including 3,179 CAS procedures performed at four European high-volume carotid centers validated CAS as a durable procedure for stroke prevention.[24] At 5 years, freedom from mortality, stroke-related death, ipsilateral fatal/major stroke, and any stroke rate were 82%, 93.5%, 93.3%, and 91.9%, respectively.[24] Freedom from restenosis at 1, 3, and 5 years was 98.4%, 96.1%, and 94%, respectively. Nevertheless, the presence of neurological symptoms before CAS was the only predictor for neurological complications postprocedurally (HR, 1.38; 95% CI 1.05-1.82; $P = .02$).[24] Similarly, in the report of the Vascular Registry of the Society for Vascular Surgery (6,403 procedures; 3,259 CEA patients; 2,763 CAS patients), a higher 30-day incidence of death/stroke/MI was demonstrated for symptomatic patients undergoing CAS compared with CEA (7.13% vs 3.75%, respectively).[25] Although patients undergoing CAS had a higher incidence of preprocedural TIA or stroke episodes (49.2% vs 42.4%, for CAS vs CEA, respectively; $P < .001$), better outcomes were still demonstrated for CEA compared with CAS after risk adjustment for factors found to be significant confounders in outcomes (ie, age, history of stroke, diabetes, and American Society of Anesthesiologists grade; adjusted OR, 1.965 for CAS vs CEA; $P < .001$).[25]

A survey in the United States of all carotid revascularization procedures performed in 2005 (135,701 CEA and CAS procedures; CEAs: 91%, CAS procedures: 9%) showed that CAS was associated with both increased postoperative stroke (1.8% vs 1.1%, respectively; OR, 1.7; 95% CI, 1.2-2.3; $P < .05$), as well as overall mortality rates (1.1% vs 0.57%, respectively; OR, 1.5; 95% CI, 0.96-2.5; $P < .05$), compared with CEA.[26] More importantly, the mortality difference increased considerably in patients with symptomatic disease (4.6% vs 1.4%, for CAS vs CEA, respectively; $P < .05$).[26] The same group showed that stroke and mortality rates did not differ between vascular surgeons and nonvascular surgeons (interventional cardiologists and interventional radiologists).[27] In the report of two large CAS studies on patients at high risk for surgery, Emboshield and Xact Post Approval Carotid Stent Trial (EXACT; n = 2,145 patients; 9.9% symptomatic [TIA, amaurosis fugax, or stroke episode <180 days preprocedurally]) and Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2; n = 4,175 patients; 13.1% symptomatic), the 30-day combined endpoint of death and stroke was 6.4% (95% CI, 4.8%-8.4%) for the combined symptomatic population, while it was 50% lower for the combined asymptomatic population (3.2%; 95% CI, 2.8%-3.7%).[28] Finally, a recent systematic review (n = 206 studies; 54,713 patients) concluded that symptomatic patients undergoing CAS were about twice as likely to suffer a perioperative stroke episode/death compared with asymptomatic individuals (30-day risk [95% CI] of stroke/death: 7.6% [3.6-9.1] vs 3.3% [2.6-4.1], respectively).[29]

DISCUSSION

To determine what may influence poor CAS outcomes, it is appropriate to examine the mechanisms accounting for the inferior results reported to date for CAS compared with CEA in symptomatic patients so that measures to offset these mechanisms can be used maximally in the future.

Differences in carotid plaque morphology: the "unstable" plaque

The carotid plaques of equally stenotic symptomatic and asymptomatic carotid artery lesions vary considerably in morphology and structure.[30,31] Downstream of a high-grade internal carotid artery stenosis, cerebral microemboli occur, which are detectable with transcranial Doppler ultrasonography.[32,33] The frequency of ultrasonographically-detected (although not always clinically relevant) microembolic events is greater in patients with recent neurological symptoms compared with patients having similarly severe asymptomatic stenosis.[32,33] These observations lead to the "unstable plaque" theory.[30,31] A detailed discussion of the "unstable plaque" concept is provided elsewhere.[30,31] Briefly, there are broadly two types of carotid plaque: one is stable and unlikely to produce symp-

tomatic embolization, and the other form (while not necessarily more stenotic) is unstable and at a higher risk of producing symptomatic or asymptomatic embolization. A thinner or ulcerated fibrous cap with an increased degree of inflammation (ie, a greater number of macrophage and T lymphocytes) overlying a core of lipid and necrotic debris are prominent characteristics of the "unstable" symptomatic plaque. Such plaques are associated with an increased risk of rupture and neurological symptoms.[30-33]

Concerns about the safety and efficacy of CAS in treating unstable plaques were raised in an earlier commentary.[34] Maneuvering CAS guidewires and catheters in a stenotic carotid artery with an "unstable" plaque may dislodge atherosclerotic material and cause thromboembolism to the cerebral circulation, resulting in TIA or stroke.[34] A randomized study subsequently compared the number of microemboli detected with transcranial Doppler scan during CAS vs CEA.[35] A considerably higher number of microembolic signals were demonstrated for CAS compared with CEA (mean, 202; range, 18-426 signals vs mean, 52; range, 0-269 signals for CAS vs CEA, respectively; $P < .001$).[35] The higher incidence of microemboli after CAS compared with CEA was verified in other reports, as well.[36,37] A recent systematic review (n = 32 studies; 1,363 CAS and 754 CEA procedures) also showed that the incidence of new embolic lesions detected by diffusion-weighted MRI is considerably higher after CAS than after CEA (37% vs 10%, respectively; $P < .01$).[38] By performing a meta-analysis including those single-center studies that directly compared the incidence of new diffusion-weighted MRI embolic lesions after the two procedures, a greater-than-six-fold-higher incidence of new embolic lesions was demonstrated after CAS compared with CEA (OR, 6.1; 95% CI, 4.19-8.87; $P < .01$).[38] Therefore, unstable carotid plaques may be associated with higher embolization rates during CAS compared with CEA.[35-38]

Embolic events during CAS vs CEA: use of EPDs. As CAS is associated with a higher incidence of microemboli compared with CEA,[35-38] several EPDs were introduced in an attempt to reduce the number of embolic events during CAS. EPDs successfully reduce[39,40] (but do not eliminate)[41,42] the number of embolic particles. A systematic review evaluating the efficacy of EPDs in preventing thromboembolic complications during CAS demonstrated a considerably lower 30-day combined stroke and death rate in patients treated with EPDs compared with patients treated without cerebral protection (16 events in 896 procedures vs 140 events in 2,537 procedures, or 1.8% vs 5.5%, respectively; $P < .001$).[43] There was a three-fold increased risk of any stroke or death and a greater-than-six-fold increase of minor stroke within 30 days if CAS was performed without vs with EPDs.[43] More importantly, a greater-than-six-fold higher 30-day combined stroke and death rate was demonstrated without the use of EPDs in symptomatic compared with asymptomatic patients (6.4% vs 1%, respectively; $P < .01$).[43]

A retrospective matched case-control study (301 CAS [118 symptomatic patients] and 301 CEA procedures [120 symptomatic patients]) showed a considerably higher risk of periprocedural stroke for CAS compared with CEA (7.9% vs 2.3%; OR, 5.2; 95% CI, 1.7-18; $P = .001$), despite the use of EPDs in all CAS patients.[44] There was, however, a decreasing trend in 30-day neurological event rates for the last 201 CAS matched cases, and the difference with CEA was no longer significant (5.4% vs 1.9%, for CAS vs CEA, respectively; OR, 2.8; 95% CI, 0.8-10.2; $P = .1$).[44] Finally, EPDs cannot prevent emboli occurring after the removal of the device. This is important since many neurological events occur in the 24 hours following completion of the procedure.[14] Finally, distal filters incur the additional risk of embolization at the time of crossing of the lesion.

Whether the detection of microembolic ultrasonic signals during CAS or CEA using transcranial Doppler ultrasound correlates with the development of ipsilateral focal cerebral ischemia remains the subject of debate.[45,46] A recent study, however, provided evidence that detection of solid and gaseous microemboli during CAS and CEA correlates with the development of procedure-related ipsilateral ischemic strokes (solid: $P = .027$; gaseous: $P = .037$) or new ipsilateral diffusion-weighted cerebral MRI lesions (solid: $P = .043$; gaseous: $P = .026$).[47] Patients undergoing CAS had more solid ($P < .001$) and gaseous ($P < .001$) emboli and more new ipsilateral ischemic strokes ($P = .033$) compared with CEA patients. More importantly, echolucent plaques ($P = .02$) and the presence of preprocedural diffusion-weighted cerebral MRI ischemic lesions were associated with an increased number of solid emboli ($P = .002$).[47] Finally, the recently published results of the ICSS substudy revealing a greatly increased risk of new lesions after CAS compared with CEA support the need for improved EPDs and perhaps the use of microfilm-covered stents.[22] Since CAS is associated with the generation of more microemboli compared with CEA,[35-38] this is further evidence that symptomatic patients should not be treated by CAS unless means are introduced to render symptomatic plaques more stable.

Possible options to improve CAS outcomes

1. Modification of vascular risk factors — plaque stabilization. Several risk factors for the development of symptomatic carotid artery stenosis and, thus, an increased stroke risk, have been identified, namely hypertension, hypercholesterolemia/hyperlipidemia, diabetes mellitus, smoking, obesity, and physical inactivity.[48] Since CAS does not eliminate the actual cause of carotid stenosis (it merely displaces the carotid artery atherosclerotic plaque), it should be expected that maintenance of these risk factors may be associated with a greater risk of developing recurrent carotid stenosis. Thus, modification of the risk factor profile (eg, weight loss, use of antihypertensive, antiplatelet, and lipid-lowering medication, optimal glucose management, and adoption of exercise) may decrease the odds of developing symptomatic carotid artery disease.[48]

Since unstable carotid plaques are lipid-rich, a possible option to improve stroke rates before, during, and after CAS procedures may be aggressive pre- and post-

procedural statin use. Three meta-analyses have demonstrated that routine statin use significantly reduces the risk of stroke.[49-51] Statins also reduce the incidence of perioperative cardiovascular and cerebrovascular events in patients undergoing CEA.[52,53] Although the exact mechanism is not known, statins exert these effects independent of their lipid-lowering action via anti-inflammatory, plaque stabilization, and neuroprotective pathways.[52-54] Statins are an essential component in the management of carotid artery disease.[55] In a retrospective review of all CEAs in a large center (n = 1,566 procedures), preoperative statin use was associated with a reduction in perioperative strokes (1.2% vs 4.5%, respectively; $P < .01$), TIAs (1.5% vs 3.6%, respectively; $P < .01$), and all-cause mortality (0.3% vs 2.1%, respectively; $P < .01$) when compared with patients not receiving statins.[52] Statin use was independently associated with a greater-than-three-fold reduction in the odds of stroke (1.2% vs 4.5%, for statin users vs nonusers, respectively; OR, 0.29; 95% CI, 0.14-0.61; $P = .001$) and a 7-fold reduction in the odds of death (0.3% vs 2.1%, for statin users vs nonusers, respectively; OR, 0.14; 95% CI, 0.03-0.62; $P = .009$).[52] In another study on patients undergoing CEA, statins were associated with better outcomes (reduced in-hospital mortality and in-hospital stroke/death rates) in symptomatic but not in asymptomatic individuals.[56] Similar anti-inflammatory and plaque-stabilizing effects of statin use on symptomatic patients undergoing CAS may be suspected; these effects may improve CAS results.

Assuming that statins stabilize carotid plaques,[52-55] aggressive pre- and periprocedural statin administration could decrease emboli generated during manipulation of wires and catheters during CAS procedures. Taken together with the statin-induced decrease in the incidence of adverse events,[52,53] the use of aggressive statin treatment before, during, and after CAS in symptomatic patients may improve CAS outcomes. This is supported by findings from studies on coronary stenting that suggest that routine statin use following coronary stenting is associated with reduced recurrent coronary stenosis and improved major adverse cardiovascular and mortality rates.[57,58] Verification of these encouraging results in CAS patients will further support routine statin use in these individuals as well. So far, only a retrospective report has investigated the effect of preprocedural statin use on the incidence of cardiovascular events after CAS.[59] This study compared the effect of preprocedural statin treatment between 53 patients with vs 127 patients without preprocedural statin treatment.[59] The overall 30-day MI rate was 1% (2 of 180 patients), the minor stroke rate was 9% (16 of 180 patients), the major stroke rate was 0.5% (1 of 180 patients), and the death rate was 1% (2 of 180 patients). CAS patients receiving statin therapy preprocedurally had a lower incidence of cardiovascular events (composite of stroke, MI, and death within 30 days after CAS) compared with CAS patients not receiving statins prior to the procedure (2 of 53 vs 19 of 127, or 4% vs 15%, for statin users vs nonusers, respectively; $P < .05$).[59] Although a "magical" effect of statins should not be supported, these data suggest that routine statin treatment may be beneficial for patients undergoing CAS.

2. Better patient selection. Better patient selection is mandatory to improve CAS outcomes.[60] Certain high-risk patients, including those >75 years, those with unfavorable aortic arch or carotid anatomy, and those with unfavorable lesion characteristics (eg, free-floating thrombus, heavy circumferential calcification, long string-like lesions) should probably not undergo CAS. In contrast, patients with high carotid lesions, restenosis after prior CEA, and previous neck irradiation or infection will likely benefit more from CAS than CEA.[60]

An in-depth review on the identification of clinical and angiographic features associated with increased procedural risk after CAS indicated that age ≥80 years, decreased cerebral reserve, dementia, prior (remote) stroke, multiple lacunar infarcts, and intracranial macroangiopathy are clinical features associated with inferior outcomes after CAS.[61] Additionally, excessive vascular tortuosity (defined as ≥2 bend points $>90^0$, within 5 cm of the lesion) and heavy concentric calcification increase the difficulty of access to the lesion and are important predictors of CAS complications.[61] A higher risk for periprocedural complications for octogenarians undergoing CAS compared with younger individuals was also suggested by others.[62,63] A higher incidence of unfavorable anatomy associated with age >80 years may explain the poor results of CAS for these patients.[64] Furthermore, the type of aortic arch morphology ("simple" vs "bovine"), the presence of atherosclerotic arch lesions (<5 mm vs >5 mm or with mobile debris), and the degree of tortuosity may account for a higher number of embolic brain lesions following CAS.[65] Finally, the presence of certain angiographic carotid lesion characteristics (ie, lesion length ≥15 mm and ostial involvement) is associated with increased 30-day stroke rates after CAS.[66]

3. Improved CAS skills/techniques. A possible explanation for the inferior results reported to date for CAS may be associated with operator inexperience and lack of standardization of the technique. This certainly applies to a new treatment method such as CAS when it is compared to CEA, which has been well-established and refined for >50 years. In support of this, a report presenting an analysis of the periprocedural complications of CAS underlined the importance of appropriate and considerable experience before undertaking systematic use of CAS.[67] Similarly, in the Pro-CAS registry, the risk of stroke after CAS decreased with center experience (5.9% vs 3.0%, for the first 50 vs >150 interventions, respectively; OR, 1.77; 95% CI, 1.1-2.8; $P = .017$).[15] A similar association was demonstrated with patient volume (stroke risk: 2.9% vs 4.6%, for physicians/centers performing >50 vs ≤50 interventions/year; $P = .0014$). Finally, a decrease in periprocedural stroke risk was shown with accumulating experience and evolving CAS techniques (6.1% vs 3.0% for the periods July 1, 1999-June 30, 2000 vs July 1, 2004-June 30, 2005; $P = .0294$).[15] This may result from two factors: increased technical skill and better patient selection, both of which may come with greater experience. The recently reported

CREST results further support the importance of stringent credentialing of carotid interventionalists and appropriate experience.[3,23] In CREST,[3,23] approval of carotid interventionalists to participate in the trial was based on adequate experience (defined as >30 CAS procedures with low event rates), use of proper standard CAS technique, or an adequate number of submitted procedures (15-30 cases [median, 29] with low event rates), plus appropriate interventional skills using the correct standard technique.[23] In contrast, in ICSS, a minimum of 10 CAS procedures was required for participation in the trial,[20] whereas in the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial,[14,16] participating interventional physicians should have performed at least 12 CAS procedures. Unlike CREST,[3,23] the inclusion of inexperienced operators and lack of uniform use of EPDs in EVA-3S[14,16] and ICSS[20] may limit the values of these studies. Therefore, it may be expected that future trials comparing CAS with CEA for the management of symptomatic carotid artery stenosis will be designed better and may produce better results for CAS.[68]

4. Improved technology for CAS — better EPDs (flow reversal and proximal occlusion) and better stents (membrane-covered, ultra-closed cell, and biodegragable). Several issues may improve CAS outcomes, such as the introduction of new and better stents. An ex vivo study showed that use of a polyurethane membrane-covered stent resulted in lower cerebral embolization rates.[69] Membrane-covered stents also have the potential to reduce the incidence of late embolization, that is, after the removal of the EPD.[70] Furthermore, proximal EPDs (such as the Mo.Ma flow interruption device [Invatec, Roncadelle, Italy][71] or the Parodi flow reversal Anti-Emboli System [W.L. Gore, Flagstaff, AZ])[72] offer the advantage of cerebral protection during most of the procedure.

In the Mo.Ma trial,[71] a new technique was compared with the standard technique. The new technique included several technical tips and modifications, such as the engagement of the guidewire's floppy tip through the carotid lesion while cerebral blood follow was maintained, a slow release postdilation (1 Atm/2 sec), a quicker manual aspiration procedure following postdilation, a redirection of blood flow into the external carotid artery with the postdilation balloon inflated in the internal carotid artery, and a further manual aspiration and subsequent release of the Mo.Ma system. The application of this novel technique had less neurological complications compared with patients treated with the standard technique (1.1% vs 3.7%, respectively).[71] The multicenter Proxim**A**l P**R**otection with the **Mo**.Ma Device D**U**ring Ca**R**otid Stenting (ARMOUR) trial evaluated the 30-day safety and effectiveness of the Mo.Ma proximal cerebral protection device in high-surgical-risk patients undergoing CAS.[73] The 30-day major adverse cardiac and cerebrovascular event rate was as low as 2.7% (95% CI, 1.0%-5.8%), with a 30-day major stroke rate of only 0.9%. Importantly, no symptomatic patient suffered a stroke during this trial.[73] Finally, the GORE **EM**bolic **P**rotection w**i**th **RE**verse Flow (EMPiRE) Study demonstrated the safety and efficacy of the GORE Flow Reversal System for neuroprotection during CAS.[74] The GORE Flow Reversal System provides neuroprotection by reversing the blood flow at the carotid stenosis, thereby directing embolic particles away from the brain. The 30-day death and any stroke rate was 2.9%, which is considerably lower compared with other EPD trials. This study also showed encouraging results in symptomatic patients demonstrating combined death, stroke, and MI rates of 3.8%.[74] These results, pointing out the potential benefits of proximal occlusion/flow reversal systems in symptomatic patients, require further evaluation.

Finally, other technological advances for CAS include better filters (eg, Fibernet,[75] Emboshield,[28] etc.), lower profile, and improved ways to cannulate arch vessels with end-manipulateable tipped catheters. Some technical factors that may also improve CAS outcomes include minimizing manipulation, poststenting balloon dilatation, and filter dwell time, as well as accepting a less-than-perfect result in terms of luminal restoration. As CAS technology and these technical improvements are introduced and used in trials, CAS results are expected to improve.[68]

AUTHOR CONTRIBUTIONS

Conception and design: KP
Analysis and interpretation: KP, FV
Data collection: KP
Writing the article: KP, DM, FV
Critical revision of the article: KP, DM, FV
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