

Cerebral Protection for Carotid Artery Stenting: Safety, Efficacy and Limitations

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Although carotid endarterectomy (CEA) has been proven more effective than medical management in the prevention of stroke in patients with symptomatic or asymptomatic carotid artery stenosis, it has its disadvantages, including a neck incision and the requirement for general anesthesia in some patients. Additionally, surgical intervention also has limitations for those patients with severe bilateral carotid artery stenosis, the stenosis caused by neck irradiation for nasopharyngeal cancer, high level of carotid artery stenosis, or restenosis following CEA. Carotid artery stenting, which is a less invasive percutaneous procedure, has been widely accepted as an alternative for patients with severe carotid artery stenosis. Furthermore, a number of randomized clinical trials have demonstrated that carotid stenting with emboli-protection device for treatment of patients with symptomatic and asymptomatic stenosis is not inferior to CEA in terms of short-term and long-term outcomes. Therefore, it is foreseeable that percutaneous transluminal stenting with emboli-protection device for patients with high-grade carotid artery stenosis will gain increasing popularity in the near future. Accordingly, it is of utmost importance to understand the benefits, safety, and the limitations of carotid stenting.

Key Words: Catheter-based carotid stenting • Symptomatic carotid artery stenosis

INTRODUCTION

Stroke, a growing epidemic, is an important cause of mortality and disability worldwide.^{1,2} Atherosclerotic obstructive carotid artery disease, which frequently occurs at the level of carotid bifurcation in the neck or in the proximal portion of the internal carotid artery, causes about 20% of all ischemic stroke and transient ischemic attacks.³ High-grade stenosis of the carotid artery is a

major cause of recurrent transient ischemic attack or strokes.⁴⁻⁶ The risk of recurrent stroke is up to 20% or more within 2 years in patients with symptomatic severe carotid artery stenosis who have been treated medically.³⁻⁷

Since the reports from two large randomized clinical trials, the European Carotid Surgery Trial⁵ and the North American Symptomatic Carotid Endarterectomy Trial (NASCET),^{4,8} have demonstrated that the risks of stroke are substantially reduced by carotid surgery in patients with recent symptoms and severe carotid stenosis, the number of carotid endarterectomy (CEA) performed has been reported to have doubled in the United State and Europe.^{6,9-11} The consistent results⁴⁻⁶ of these clinical studies have convincingly established CEA as the standard therapy for patients with high-grade carotid artery stenosis.¹²

RATIONALE FOR CATHETER-BASED CAROTID ARTERY INTERVENTION

Interestingly, these clinical trials^{4,5,8} excluded pa-

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tients of advanced age, presumably because of their potentially higher risk of periprocedural complications.¹³ Further, surgery does have the disadvantage of requiring an incision in the neck and in some centers, the necessity for general anesthesia. Moreover, some unfavorable anatomical and treatment-related factors, including restenosis of previous CEA, total occlusion of contra-lateral carotid artery, previous cervical irradiation or surgery, surgically inaccessible lesions at or above C2 level or below the clavicle, neck immobility, tracheostomy, laryngeal nerve palsy or bilateral stenosis requiring treatment will increase the operative risk and limit the benefit of surgical intervention. Accordingly, patients with multiple comorbidities are frequently ineligible for surgical revascularization because of increased perioperative risks and, therefore, become candidates for medical therapy which may carry a notably higher cumulative risk of stroke.^{14,15} In view of this, an alternative treatment strategy which is at least not inferior to CEA should be established.¹⁶

Carotid angioplasty and stenting (CAS) is a less invasive percutaneous procedure that may allow avoidance of some perioperative complications of CEA and has been investigated in the United States since 1994.¹⁷ In the past decade, evidence has accumulated that catheter-based carotid CAS might become an alternative to CEA in patients with high-grade symptomatic or asymptomatic carotid artery stenosis.^{16,18-22} For the past few years, randomized clinical trials have been in progress to compare these techniques with and without emboli-protection during catheter-based carotid revascularization.^{3,23,24}

EVIDENCE SHOWING CAROTID ARTERY STENTING IS NOT INFERIOR TO ENDARTERECTOMY FOR PATIENTS WITH SYMPTOMATIC CAROTID ARTERY STENOSIS

The relationship between the volume of surgery and operative mortality has been fully discussed.²⁵⁻²⁷ It is not surprising that patients can improve their chances of survival remarkably, even at hospitals with high volume of surgery, by selecting surgeons who are experts in CEA.²⁷ Large clinical trials have reported rates of 30-day disabling stroke or death in symptomatic and asymptomatic

patients of less than 7.0% and 3.0%, respectively, and rate of permanently disabling stroke or death on long-term follow-up of less than 3.0%, in these post CEA patients.^{4-6,28-31} These clinical outcomes^{4-6,28-31} set the standard for the safety and efficacy of catheter-based CAS.

Investigation on the feasibility of CAS first started in the United States in the middle of the last decade.¹⁷ Since then, this procedure has frequently been utilized by cardiologists and radiologists as an alternative for the treatment of patients with symptomatic and asymptomatic carotid artery stenosis.^{3,13,17-24}

The Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS), an international multicenter clinical trial, randomly assigned 504 patients with carotid stenosis to CAS (n = 251) or CEA (n = 253).³ All endovascular techniques were allowed for the patients. However, use of emboli-protection device was not reported in the study. The trial³ found the rates of major outcome events within 30 days of first treatment similar between CAS and CEA (6.4% vs. 5.9%, respectively). However, cranial neuropathy was reported in 8.7% of CEA patients, but not after CAS treatment (p < 0.0001).³

The WALLSTENT study³² was another multicenter randomized clinical trial that enrolled patients with symptomatic internal carotid artery stenosis of at least $\geq 60.0\%$ undergoing either stenting (n = 107) or CEA (n = 112). The trial found that the 30-day peri-procedural complication rate (i.e. any stroke or death) was notably higher in the stenting group than in those who underwent CEA (12.1% vs. 4.5%, p = 0.049).³³ Further results from this trial have not been reported.

The Kentucky study was a single-center randomized clinical trial to compare the clinical outcomes between CAS and CEA.³⁴ This trial included 104 symptomatic patients with ipsilateral internal carotid artery stenosis greater than 70% who were then randomized into the CAS (n = 53) and CEA (n = 51) groups. Moreover, an asymptomatic arm of 85 patients with internal carotid artery stenosis of greater than 80% was randomized into two other treatment groups: CAS (n = 43) and CEA (n = 42).³⁵ With the exception of one mortality due to complication of myocardial infarction immediately after CEA in the symptomatic group of the study, there were no other deaths or stroke in symptomatic or asymptomatic patients treated with CAS or CEA.

The SAPPHERE study²³ was a recent US-based

multicenter randomized clinical trial comparing CAS with the use of emboli-protection device to CEA in patients who had > 50% symptomatic stenosis or > 80% asymptomatic stenosis plus one or more comorbidity conditions (e.g., congestive heart failure, left ventricular dysfunction, recent myocardial infarction, or severe pulmonary disease) with the enrollment of three hundred thirty-four patients who were randomized to receive either CAS (n = 167) or CEA (n = 167). The cumulative incidence of adverse events at 30 days (i.e., death, stroke or myocardial infarction) did not differ between patients having undergone CAS and patients receiving CEA (p = 0.09). The primary end point (i.e. death, stroke, or myocardial infarction at 30 days plus ipsilateral stroke or death from neurologic causes within 30 days to 1 yr) occurred in 12.2% of CAS patients and 20.1% of CEA patients (p = 0.004, log-rank test for non-inferiority; p = 0.053, log-rank test for superiority). Furthermore, cranial-nerve palsy within one year was significantly higher in CEA than in CAS (5.3% vs. 0%, p = 0.003).

Global CAS registry data on more than 12,390 patients have shown a 30-day combined adverse outcome rate (i.e. death or any stroke) of 5.36% for symptomatic patients and 2.91% for asymptomatic patients.³⁶ Therefore, the results of this study were consistent with those of CEA clinical trials.^{4-6,28-31} The registry data also identified that the CSA volume is indirectly proportional to 30-day co-morbidity and mortality. Interestingly, real world data has indicated that medicare patients' perioperative mortality following CEA is substantially higher than that reported in trials, even in those institutions that participated in the randomized studies.²⁷ Accordingly, the real-world results between CEA³⁶ and CAS²⁷ are similar during the same contemporary perspective period. Recently, data from the European Long-term Carotid Artery Stenting Registry on more than 2,170 patients have also revealed a 30-day combined adverse outcome of less than 2.0% and one-year combined endpoint of less than 5.0% after CAS procedure.³⁷ These registry data,^{36,37} review of randomized evidence,²⁴ and randomized clinical trials,²³ therefore, support that emboli-protection for CAS is not inferior to CEA in patients with carotid artery stenosis.^{4-6,28-30}

Only a few clinical trials^{29,31,35} have focused on the issue of the addition of CEA to aggressive medical management in the reduction of the incidence of stroke in pa-

tients with asymptomatic carotid artery stenosis. The Executive Committee for ACAS Study³¹ was a prospective, randomized, multicenter trial based in the US and Canada comparing CEA with aggressive medical treatment in patients who had $\geq 60\%$ asymptomatic carotid artery stenosis. A total of 1662 patients were enrolled, with follow-up data available on 1659 (CEA = 825; medical treatment = 834). The results demonstrated that the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.1% for surgical patients and 11.0% for patients treated medically (aggregate risk reduction 53%, p = 0.004).³¹ The results of these studies^{29,31,35} suggest that aggressive treatment by CEA for those patients with significantly asymptomatic carotid artery stenosis can offer an additional benefit in the prevention of future cerebral infarction. In contrast to CEA, there was no available data from large clinical trial to determine whether a combination of CAS and aggressive medical management could also reduce the incidence of cerebral infarction in patients with asymptomatic carotid-artery stenosis.

EMBOLI-PROTECTION DEVICES AND ROUTE FOR PERCUTANEOUS TRANSLUMINAL CAROTID STENTING

Recognition of embolization in microvasculature during endovascular intervention in atherosclerotic vascular disease is always an important concern.^{38,39} Emboli-protection device has been strongly recommended to be routinely used during CAS^{22,40} to reduce distal embolization which would frequently cause cerebral infarction. Among the many protective devices available in our clinical practice in Taiwan, the PercuSurge GuardWireTM system (GuardWire PlusTM, temporary occlusion system, Medtronic AVE) and the FilterWire EZTM System (Boston Scientific Co., embolic protection system) with a self-expanding stent (Carotid Wallstent, Boston Scientific Co.) have gained most popularity for endovascular intervention (Figure 1). Of these two devices, the FilterWire EZTM is more commonly used during CAS.

Although transfemoral arterial approach (TFA) is most frequently adopted for cerebral angiographic examination or carotid artery intervention, this conventional approach for CAS has its anatomical limitations, includ-

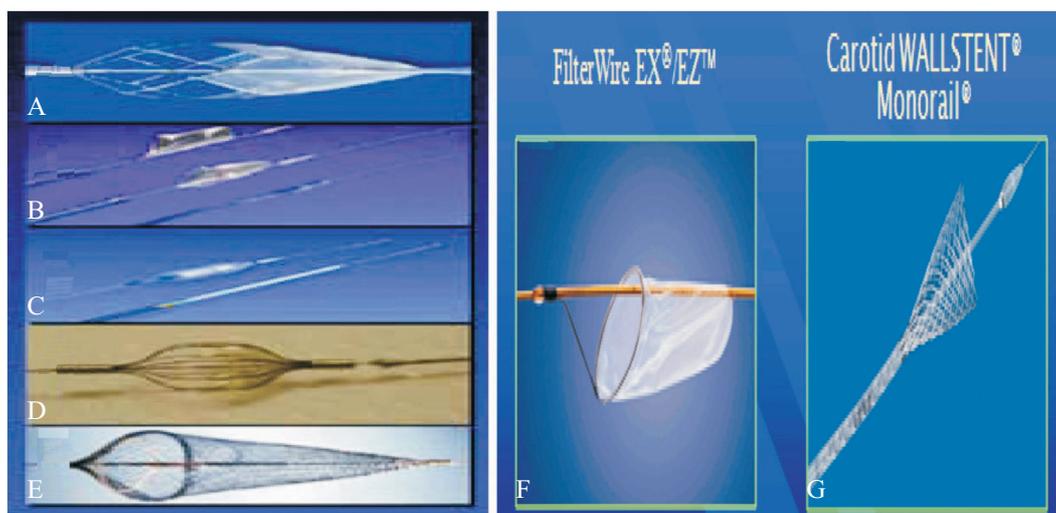


Figure 1. Left panel: different kinds of available emboli-protection devices. A = Guidant-ACCUNET; B = BSC-Filter Wire; C = ABBOTT-Emboshield; D = Cordis-Angioguard; E = EV3-Spider. Right panel: Boston Scientific filter Wire (F) and expandable carotid WALLSTENT (G).

ing difficulty in engaging the common carotid artery due to the presence of bovine arch (i.e. left and right common carotid artery stems from a main trunk), aortic arch anomaly (Kommerell's diverticulum), distal abdominal aortic disease, and morbid obesity, as well as very tortuous or occluded ilio-femoral or abdominal aorta. Additionally, patients with symptomatic degenerative spine or hip problems, and those with benign prostate hyperplasia would be unable to tolerate a long period of bed rest after TFA for carotid artery intervention. Furthermore, TFA is also occasionally associated with hemostatic and groin complications that may prolong hospitalization. As a result, the transradial artery approach (TRA) for cerebral angiographic study and CAS has been recently developed in some centers.^{41,42} The results from recent studies^{41,42} conclude that TRA is safe and feasible for CAS and can serve as a secure alternative to TFA for patients with severe carotid artery stenosis. Figure 2 shows the method and results of TRA for CAS.

CONCLUSION

To date, the available real-world data do not suggest a superiority of CAS to CEA in the treatment of patients with symptomatic or severe asymptomatic carotid artery stenosis, and vice versa. Therefore, there is still insufficient evidence to justify the widespread shift in current

clinical practice from CEA to CAS for patients with severe carotid artery stenosis. In Taiwan, there is also no large randomized clinical trial that can serve as an evi-

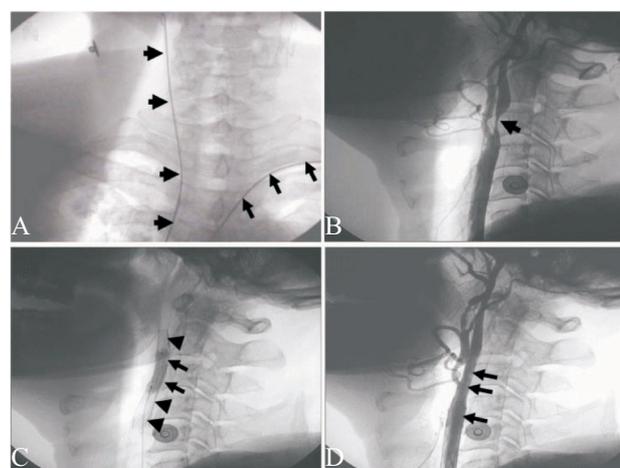


Figure 2. (A) Left transradial arterial approach (black small arrows) was utilized for right carotid angiographic study using a looping method (a retrograde looping technique). The J-tip Teflon wire was already advanced into right common carotid artery (black large arrows). (B) The carotid angiographic result showed critical stenosis of right internal carotid artery. (C) The 7 F Kimmy guiding catheter was advanced into the right common carotid artery along with J-tip Teflon wire. The carotid expandable WALLSTENT was advanced to right internal carotid artery and was then deployed into right common and internal carotid artery (black arrow heads). Balloon dilatation was performed following carotid artery stent implantation (black arrows). (D) Good carotid angiographic result was observed following carotid stenting (black arrows).

dence base to govern our daily clinical practice. The clinical practice in our country for the treatment of carotid stenosis depends on the experience of individual centers and may be not similar to that in the Western countries.

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