abstract

Atherosclerotic carotid artery stenosis is relatively frequent in older patients and is a major cause of disabling stroke or death. Carotid endarterectomy is currently considered the standard of care for all patients with severe symptomatic and asymptomatic carotid stenosis. However, data regarding the efficacy of this treatment in the older patient are limited. In the past few years, carotid angioplasty and stenting have increasingly been used as an alternative to surgery. Although these endovascular techniques have the advantage of avoiding general anesthesia and surgical incisions, preliminary trial data do not support their widespread use in older patients.

Key words: *carotid stenosis, carotid endarterectomy, angioplasty, stent, old age*

Treatment of Symptomatic and Asymptomatic Internal Carotid Artery Stenosis in Older Adults

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Introduction

Atherosclerotic stenosis of the extracranial carotid artery is a major cause of disabling stroke or death, and it therefore constitutes a huge medical, social, and economic problem. In the United States, for instance, carotid artery disease causes a significant portion (approximately 10–20%) of the 500,000-plus strokes that occur each year. Carotid stenoses may result in brain ischemia either through direct hemodynamic impairment of the cerebral blood circulation or, more commonly, as a source of thromboembolic material (Figure 1). The risk of first or recurrent stroke has been found to increase with the degree of severity of the carotid artery stenosis, although a linear relationship between the degree of stenosis and risk of stroke has not been demonstrated. Carotid artery stenosis is relatively frequent in older patients. In fact, findings of large population-based studies indicate that the prevalence of carotid artery stenosis is approximately 0.5% in the sixth decade and increases to 10% in persons over 80 years of age.[1] The vast majority of these cases are asymptomatic.

Against the background of a rapid rise in the aging population it is likely that the burden of brain ischemia due to carotid stenosis will increase over the coming decades.

Carotid endarterectomy (CEA) (Figure 2) was first performed in 1954 to prevent imminent stroke, and its effectiveness in preventing stroke has been proven in prospective randomized clinical trials comparing CEA to best medical treatment in patients with both symptomatic and asymptomatic carotid stenosis.[2–5] Therefore, it is currently considered to be the standard of care for patients with severe symptomatic and asymptomatic carotid stenosis.[6] In the past few years, however, carotid angioplasty and stenting (CAS) (Figure 3) has increasingly been used as an alternative to CEA for the primary and secondary prevention of stroke related to carotid stenosis. Since CAS has the advantage of avoiding general anesthesia and surgical incisions, the risk to benefit ratio may be greatest in high-risk and older patients.

In this article we will briefly review evidence demonstrating the proven efficacy of CEA and possible efficacy of CAS in the management of carotid stenosis, and then discuss the role of these techniques in the older patient. We will only discuss the management of patients with high-grade (70–99%) carotid stenosis.

Randomized Trials of Carotid Endarterectomy for Carotid Artery Stenosis

The superiority of CEA over medical treatment in the management of symptomatic and asymptomatic high-grade carotid artery stenosis has been established in four large randomized trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET);[3] the European Carotid Surgery Trial (ECST);[2] the Asymptomatic Carotid Atherosclero-

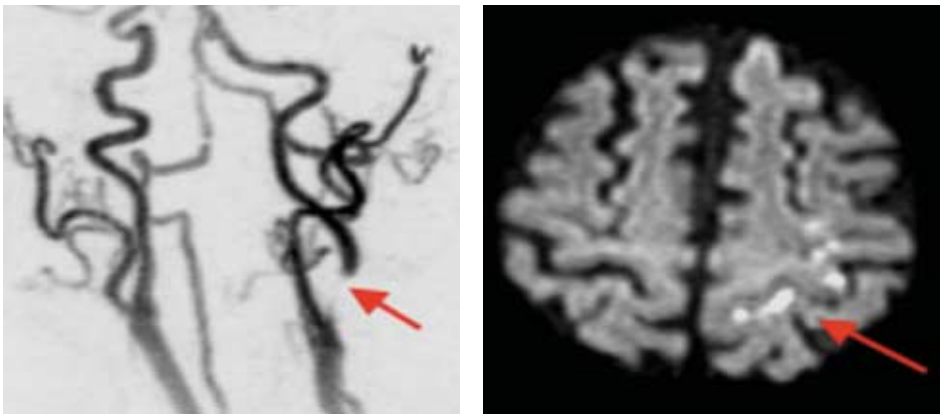


Figure 1: A 69-year-old Patient with Acute Right-Sided Paresis and Language Disturbance. Magnetic resonance angiography reveals a high-grade symptomatic carotid stenosis on the left (arrow) and diffusion weighted magnetic resonance imaging shows multiple embolic lesions.

sis Study (ACAS);[4] and the Asymptomatic Carotid Surgery Trial.[5]

The NASCET and the ECST both demonstrated the superiority of CEA combined with medical therapy over medical management alone for symptomatic patients with carotid artery stenosis of >70% (NASCET)[3] or >80% (ECST)[2] (Table 1). Because the extent of stenoses was measured differently in the ECST and NASCET, the different stenosis thresholds are likely artifacts. While the degree of carotid stenosis was determined angiographically in both studies, NASCET calculated the percentage of stenosis by dividing the residual luminal diameter by the luminal diameter of a distal portion of the same vessel where the walls of the vessel became parallel, whereas ECST divided the residual luminal diameter by the estimated normal diameter of the artery at that level. Stenoses were reported to be 70–99% in the NASCET and were thus equivalent to 82–99% by the ECST method; conversely, stenoses reported to be 70–99% by the ECST were 55–99% by the NASCET method.[7]

In NASCET, CEA reduced the two-year risk of ipsilateral stroke from 26% in the medical group to 9% in the surgical group, yielding an absolute risk reduction of 17%. A 5.8% incidence of perioperative stroke or death was reported for patients in the surgical arm. The ECST reported a similar efficacy of CEA in the secondary prevention of stroke. In this trial the frequency of a major stroke or death at three years was 26.5% in the control group vs. 14.9% in the surgical group, so that surgery was associated with an absolute benefit of 11.6%. The 30-day incidence in stroke and death in the surgical group was higher in women (10.6%), in patients with 180mmHg or greater systolic blood pressure (12.3%), and in patients with peripheral vascular disease.[8] It is also noteworthy that endarterectomy was of no benefit in patients with "near occlusion." In both trials, these patients had a paradoxically low risk of stroke on medical treatment that was most likely due to the presence of a good collateral circulation.[9,10] There have been numerous secondary publications based on post hoc subgroup analyses of these two trials that are beyond the focus of this review article.

There have been two major randomized trials of endarterectomy for patients with asymptomatic extracranial carotid artery stenosis[4,5] (Table 2). The Asymptomatic Carotid Atherosclerosis Study (ACAS) evaluated the efficacy of endarterectomy in patients with a >60% diameter reduction in asymptomatic carotid stenosis.[4] Patients were aged 40–79 years and had a life expectancy of at least five years. Approximately 30% of patients had other cerebrovascular symptoms. The event rate in surgically treated patients for the primary endpoint (ipsilateral stroke, perioperative stroke, or death) was 5.1% over five years. This included a 1.2% risk of angiography-related complications among the 424 patients undergoing postrandomization angiograms and a 1.1% surgical risk (2.3% aggregate perioperative stroke risk). The corresponding rate in medically treated patients was 11% (5.9% absolute risk reduction; number needed to treat=17; P=0.004).

The recently published ACST confirmed the benefit of CEA in patients with asymptomatic severe stenoses.[5] In this study, 3,120 asymptomatic patients with >60% carotid stenosis identified during ultrasonography were assigned to immediate CEA or deferral of surgery and were followed for a mean period of 3.4 years. The risk of stroke or death within 30 days of CEA was 3.1% in the CEA group and 0.8% in the deferral group, whereas five-year risks of nonpreoperative stroke were 3.1% and 11% (P<0.0001). When the preoperative and nonperioperative stroke risk were combined, a highly significant

Table 1: Efficacy of Carotid Endarterectomy for High-Grade (70–99% according to NASCET criteria) Symptomatic Carotid Stenosis in Major Randomized Trials

	ARR (%)	RRR (95%)	NNT
Outcome: Any stroke or operative death at five years			
NASCET	12.7	0.63 (0.45–0.82)	8
ECST	21.2	0.36 (0.22–0.51)	5
Outcome: Disabling or fatal ipsilateral stroke or operative stroke/death at five years			
NASCET	8.9	0.31 (0.10–0.52)	11
ECST	7.3	0.39 (0.12–0.67)	14

ARR: absolute risk reduction; RRR: relative risk reduction; NNT: to prevent one event over five years

Table 2: Efficacy of Carotid Endarterectomy for Asymptomatic Carotid Stenosis in Major Randomized Trials

Five-year risk (%) of any ipsilateral stroke or perioperative stroke/death				
	CEA	Control	ARR (%)	NNT
ACAS	5.1	11.0	5.9	17
ACST	6.4	11.7	5.3	19

ARR: absolute risk reduction; NNT: to prevent one event over five years

5.4% absolute risk reduction occurred, very similar to the ACAS results. The benefits were similar in males and females and were not substantially different with varying degrees of carotid stenosis. In both the ACAS and ACST, an extremely low perioperative stroke rate was achieved, without which there would be no benefit from surgical management of asymptomatic carotid artery stenoses. A combined analysis of ACAS and ACST suggests that CEA in asymptomatic patients with >60% carotid stenosis leads to a small but significant overall benefit if the surgery can be performed with low preoperative morbidity and mortality rates.[5]

CEA for Carotid Artery Stenosis in Older Patients

Data from randomized controlled studies regarding the efficacy of carotid endarterectomy in older patients are limited. NASCET, for instance, was limited to patients aged <80 years and only 14% of all randomized patients were ≥75 years. Similarly, only 6% of all randomized patients were ≥75 years in the ECST.

In a subgroup analysis of NASCET, the benefit of CEA for patients aged ≥75 years with symptomatic carotid stenosis was compared with that of those aged 65–74 years and <65 years (Table 3).[11] Among medically treated patients with 70–99% carotid stenosis, the risk of ipsilateral ischemic stroke at two years was highest (36.5%) in patients aged ≥75 years. The rates of perioperative stroke and death were 7.9%, 5.5%, and 5.2% in patients younger than 65 years, 65–74 years, and ≥75 years, respectively. Because patients aged ≥75 years had the highest risk with medical treatment, the absolute risk reduction by CEA was greatest in this subgroup (28.9%). Only three patients had to undergo surgery to prevent one ipsilateral ischemic stroke at two years. In contrast, the number needed to treat was seven for patients aged 65–74 years and ten for those younger than 65 years. Thus, older patients profited more from CEA than younger patients in this trial. Likewise, the ECST data has indicated that increasing age is associated with a greater benefit from CEA for symptomatic carotid stenosis.[8]

In contrast to these data, a meta-analysis of 36 published studies found an increased perioperative risk of stroke or death in patients aged over 75 years compared with younger patients.[12] However, interpretation of these results was confounded by major differences among the studies with respect to eligibility criteria and outcome events. Moreover, the differences in absolute risk were small (only 1–2%), so that even if the operative risk of stroke or death for older patients were higher, CEA would still be beneficial because of the high risk of stroke without surgery.

In general, patients with an asymptomatic carotid stenosis have a lower annual risk of stroke without surgery than patients with symptomatic carotid disease. Therefore, a reduced life expectancy will limit the benefits of surgery in older asymptomatic patients. In support of this notion, patients aged 75 years and older did not profit from CEA in a subgroup analysis of the ACST.[5]

Taken together, these data indicate that CEA is an efficient therapy in carefully selected older patients with symptomatic carotid disease, whereas a widespread treatment of asymptomatic older patients is currently not supported by trial data.

Carotid Angioplasty and Stenting

Endovascular treatment of extracranial carotid artery stenosis has been performed for over a decade. To date, however, CAS has only been compared with CEA in a few small randomized controlled trials and single-centre studies.[13–16] Potential advantages over carotid

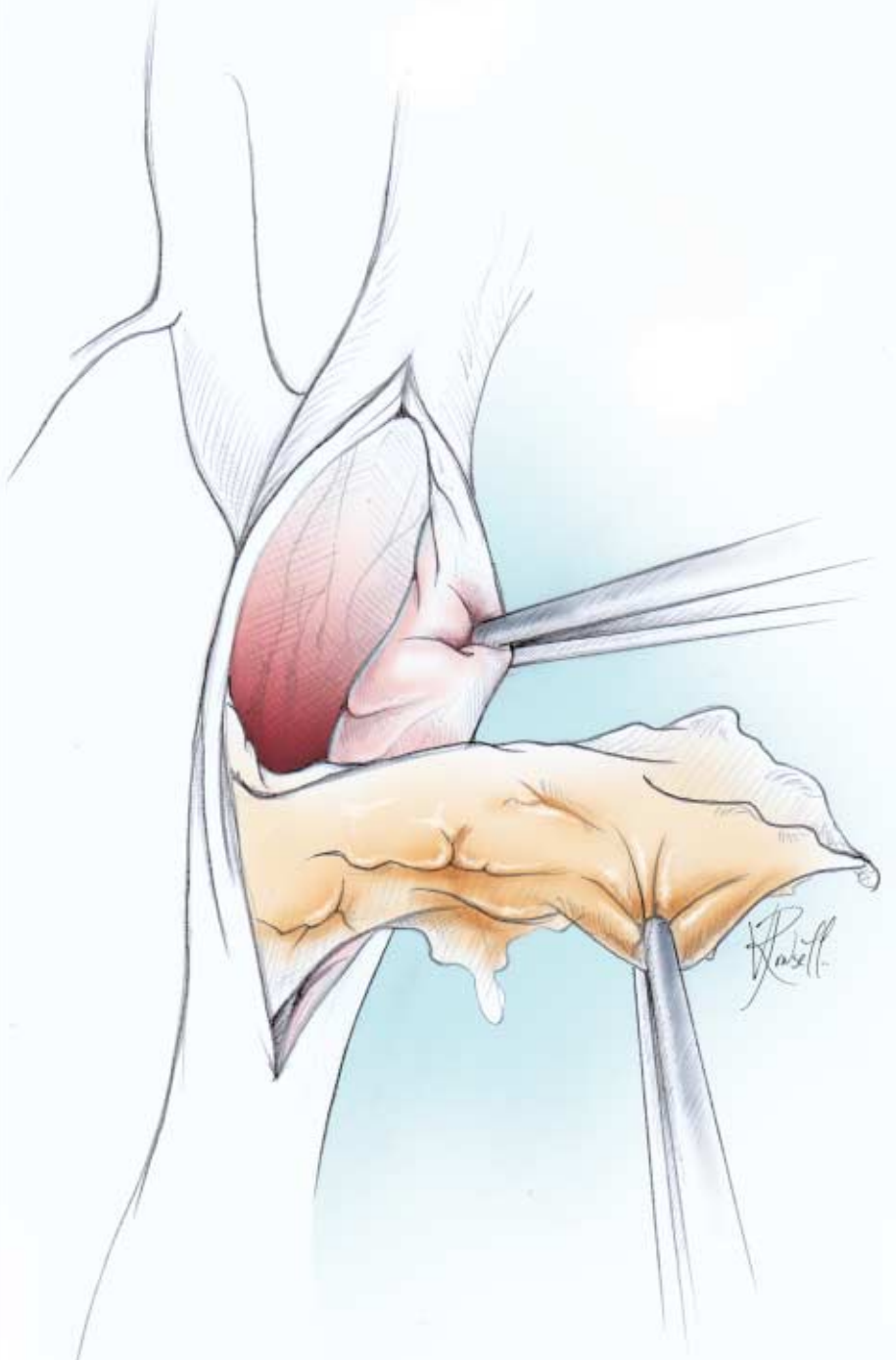
Table 3: The Effect of Carotid Endarterectomy in Patients with Symptomatic Carotid Stenosis According to Age

NASCET (Patients with 70–99% stenosis)		
Outcome: Ipsilateral stroke at two years		
	ARR (95% CI)	NNT
< 65 years	9.7 (1.5–17.9)	10
65–74 years	15.1 (7.2–23.0)	7
≥ 75 years	28.9 (12.9–44.9)	3
ECST (Patients with 50–99% stenosis according to NASCET method)		
Outcome: Ipsilateral stroke and surgical stroke/death at five years		
< 65 years	6.6 (1.1–12.0)	17
65–74 years	4.8 (-1.8–11.5)	21
≥ 75 years	19.1 (0.1–38.1)	5

ARR: absolute risk reduction; NNT to prevent one event over five years

endarterectomy include avoiding a surgical incision and its complications, including cranial nerve palsies and wound hematoma. It has also been argued that CAS does not require general anesthesia and may be associated with shorter hospitalization. On the other hand, CAS has the major disadvantage of producing more emboli to the brain than CEA.

Figure 2: Carotid Endarterectomy

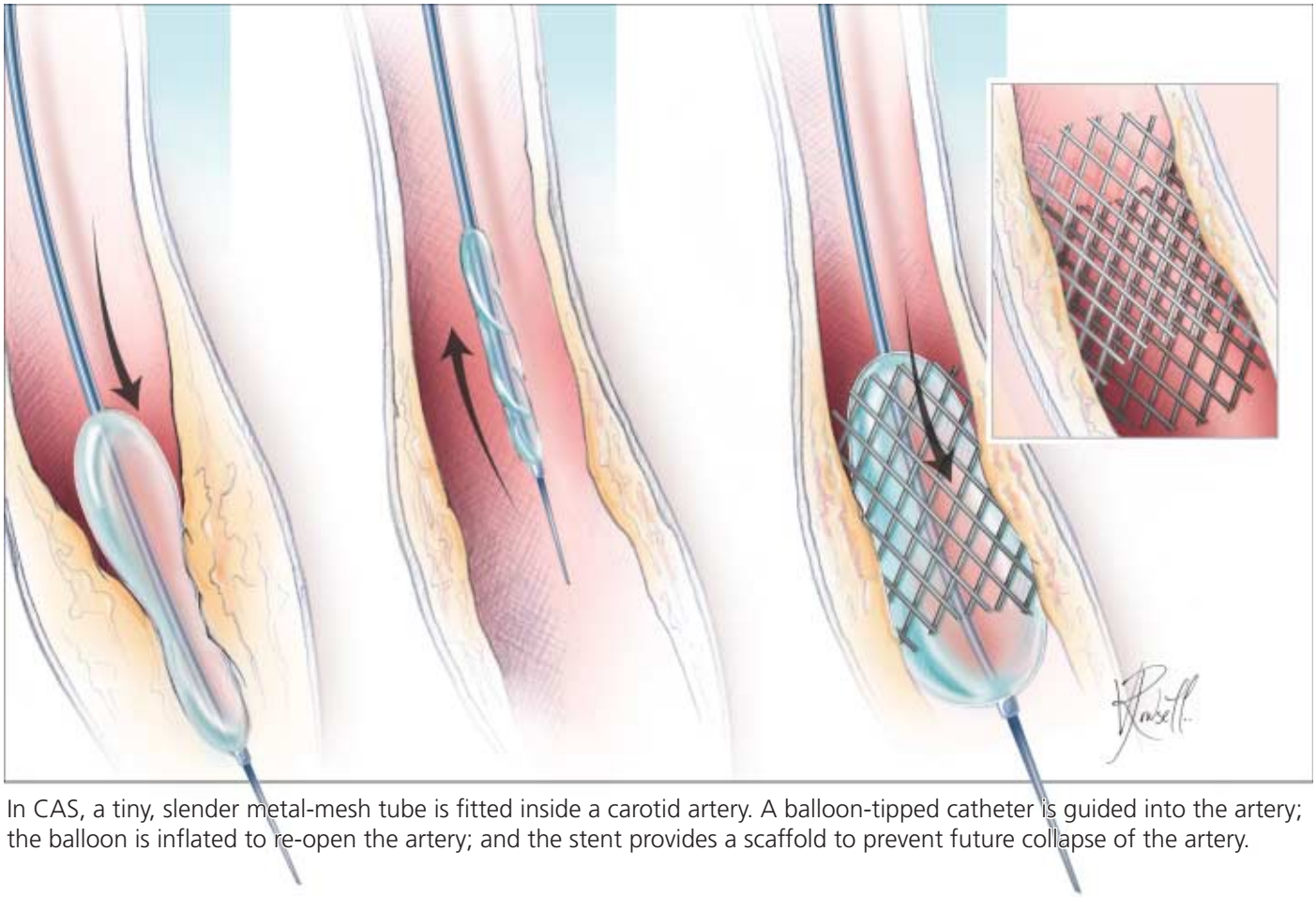


An incision is made on the side of the neck to expose the blocked carotid artery. The sections of the carotid artery affected by plaque buildup are separated from surrounding tissue and clamped to temporarily stop blood flow. The inner carotid lining containing the plaque is removed and the arteriotomy is closed.

The multicentre Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first completed, prospective, multicentre trial comparing endovascular vs. surgical treatment of patients with symptomatic (96.4%) and asymptomatic carotid stenosis. CEA was performed in 253 patients, whereas 251 patients received endovascular treatment (mainly angioplasty alone). Suitable stents became available during the course of the study but were used in only 26% (n=55) of the procedures. Periprocedural stroke and death rates were higher than in above cited trials of endarterectomy but were similar for endovascular treatment and surgery (10.0% vs. 9.9%). The endovascular approach was less frequently associated with cranial neuropathy (0% vs. 8.7%) and less frequently associated with major neck or groin hematoma (1.2% vs. 6.7%). The relatively high perioperative complication rates in both groups were a cause of concern in this study. Moreover, CAVATAS makes clear that the field of endovascular therapy is subject to rapid technological advances. In this trial, only 55 of 240 patients underwent carotid angioplasty in combination with stenting, and no procedure was performed with cerebral protection devices. In fact, fear of distal embolization of plaque fragments to the brain has generated great concern regarding the safety of CAS, so that recent technical refinements have led to the widespread use of CAS with cerebral protection devices.[17]

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study compared endarterectomy with stenting, including the use of a distal embolic protection device, for the treatment of patients with moderate-to-severe carotid stenosis who also had comorbid conditions that might increase the risk of surgery (e.g., severe cardiac or pulmonary disease).[16] The trial was terminated early because of an abrupt slowing in the pace of patient enrollment. A total of 334 patients who had either a symptomatic carotid stenosis of at least 50% of the luminal diameter or an asymptomatic

Figure 3: Carotid Angioplasty and Stenting (CAS)



In CAS, a tiny, slender metal-mesh tube is fitted inside a carotid artery. A balloon-tipped catheter is guided into the artery; the balloon is inflated to re-open the artery; and the stent provides a scaffold to prevent future collapse of the artery.

stenosis of at least 80% were randomized to undergo CAS or CEA. The primary endpoint (composite of stroke, myocardial infarction, or death within 30 days or ipsilateral stroke between 31 days and one year) occurred in 20 CAS patients vs. 32 CEA patients (12.2% vs. 20.1%, P=0.004 for noninferiority and P=0.053 for superiority). Although CAS was not demonstrated to be superior to CEA, neither was it found to be inferior in terms of its one-year cumulative association with stroke, myocardial infarction or death. It should be stressed that the main difference between the treatment groups in the composite endpoint at one year was related to the greater association of CEA with perioperative myocardial infarction, mainly non-Q-wave events. Nevertheless, the SAPPHIRE trial has provided some evidence that protected CAS can be performed with acceptable complication rates in symptomatic and asymptomatic patients who have risk factors for high rates of surgery-related morbidity or mortality.

The Carotid Revascularization using Endarterectomy or Stenting Systems (CARESS) trial was a small industry-funded phase I clinical trial which compared CEA (n=254) with protected CAS (n=143) in a low-risk patient population with symptomatic and asymptomatic carotid stenosis.[14] In this trial there was no significant difference in the 30-day all-cause mortality and stroke rate between CEA (2%) and CAS (2%). Moreover, there was no significant difference in the secondary endpoint of combined 30-day all cause mortality, stroke, and myocardial infarction between CEA (3%) and CAS (2%).

Most of the current data regarding the performance of endovascular carotid procedures are based on case series, surveys, and enrollment of patients in voluntary registries. In the largest multicentre survey, which is based on self-reported data, a total of 12,254 vessels were stented.[18] The overall rate of stroke and death within 30 days was 4.75% and the major stroke rate was 1.2%. The combined stroke and death rates in asymptomatic and symptomatic patients were 2.95% and 4.94%, respectively. Several other large single-centre studies (with several hundreds of patients) have also indicated that CAS can be performed with acceptable complication rates.[17]

It is beyond doubt that the results reported for CAS thus far are very promising. However, many previous studies have been subject to reporting and other types of biases so that the definitive role of these techniques for the treatment of asymptomatic and symptomatic carotid stenosis remains to be clarified in large, randomized controlled trials. Therefore, all efforts should concentrate on finishing

the pending trials such as SPACE (Stent Protected Angioplasty versus Carotid Endarterectomy, Germany), CAVATAS-2 (Carotid and Vertebal Artery Transluminal Angioplasty Study, UK), EVA-3S (Endarterectomy Versus Angioplasty in patients with symptomatic severe carotid stenosis trial, France), and CREST (Carotid Revascularization Endarterectomy versus Stent Trial, US) that are comparing CEA with CAS.

Carotid Angioplasty and Stenting in Older Patients

As outlined above, preliminary data indicate that CAS can be performed with acceptable complication rates. Since CAS has the main advantage of avoiding general anesthesia and surgical incisions, one might intuitively consider that the risk to benefit ratio may be greatest in older patients. However, advanced age has been associated with high complication rates after CAS in several large single-centre studies.[19,20] In one of these studies, octogenarians had a 30-day stroke and death rate of 16% after unprotected CAS, whereas patients aged ≥75 years had a 30-day stroke and death rate of 11% in another study, despite the use of protection devices. In line with these findings, increasingly high complication rates at older ages have been documented recently in the lead-in phase of the ongoing Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST).[21] Therefore, current data support the notion that older patients are a high-risk subgroup for CAS and should not be treated routinely with CAS outside the setting of randomized trials.

Conclusion

Although older patients are significantly under-represented in randomized controlled trials, subgroup analyses indicate that CEA is an efficient therapy in carefully selected older patients with symptomatic carotid disease. Widespread treatment of asymptomatic older patients is currently not supported by trial data. Despite encouraging results in subgroups of high-risk patients with severe concomitant medical diseases, preliminary data indicate that older patients do not necessarily profit from the use of CAS. However, these procedures continue to evolve from a technical standpoint and several studies are in progress. Therefore, the relative roles of CAS in older patients must await the results of further randomized trials. ◆

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