Atherosclerotic Peripheral Vascular Disease Symposium II: Controversies in Carotid Artery Revascularization

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Atherosclerotic Peripheral Vascular Disease Symposium II

Controversies in Carotid Artery Revascularization

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Carotid artery disease is a major cause of ischemic stroke, the risk of which is directly related to the severity of stenosis and presence of symptoms.[1,2] Stroke is the third leading cause of death in the United States, with approximately three quarters of a million strokes per year. Stroke is the leading cause of functional impairment, with more than 20% of survivors requiring institutional care and up to one third having a permanent disability.[3] More worrisome, however, is the fact that as the population ages, the number of patients having strokes appears to be increasing.[4]

The pathophysiology of stroke may be broadly classified as hemorrhagic, embolic, or ischemic. The majority of strokes are caused by embolic events due to atheroemboli from the carotid artery, the ascending aorta, and arch vessels or cardiac thromboembolism from the left atrium or ventricle. It is estimated that carotid artery stenosis is responsible for 15% to 20% of all strokes.[5] As percutaneous treatment options expand, there is uncertainty about appropriate therapy for carotid disease. This document will focus on 3 current controversies: (1) carotid artery revascularization in asymptomatic patients, (2) carotid artery stenting (CAS) in patients who are considered to be at increased surgical risk for carotid endarterectomy (CEA), and (3) the current role for CAS in patients at average surgical risk.

Carotid Artery Revascularization in Asymptomatic Patients

Prevalence and Natural History

The prevalence of asymptomatic extracranial carotid stenosis (≥50%) in persons >65 years of age is estimated to be between 5% and 10%, whereas ≤1% of patients are estimated to have a severe narrowing (>80%).[6] In asymptomatic patients with ≥50% carotid artery stenoses, the annual risk of stroke is between 1% and 4.3%.[2,7] Long-term (10- to 15-year) cohort studies in asymptomatic patients with moderate to severe carotid stenosis demonstrate an ipsilateral stroke rate between 0.9% and 1.1% per year.[8] The asymptomatic patients at highest risk of stroke are those with more severe stenosis and those with progressive carotid artery stenosis.[2,6] With an asymptomatic carotid stenosis of >75%, the natural history risk of having a stroke may be as high as 5.5% per year.[9]

Clinical Trials

Surgery Versus Medical Therapy

CEA is the current standard of care to prevent stroke in asymptomatic patients with moderate to severe carotid artery stenosis.[10] Three large randomized, controlled trials have compared CEA with best medical therapy (aspirin) to aspirin therapy alone in asymptomatic patients with moderate to severe carotid artery stenosis (Table 1). The Veterans Affairs Cooperative Study demonstrated a 30-day perioperative risk of stroke and death of 4.7%, with 0.4% of strokes resulting from angiography. The combined end point of all ipsilateral neurological events (transient ischemic attack, transient monocular blindness, and stroke) by 4 years was reduced from 20.6% in the medical therapy group to 8% in the CEA arm of the study ($P<0.001$). Although ipsilateral stroke was reduced, CEA did not reduce the rate of all stroke or of all stroke plus death compared with medical therapy alone. The cardiovascular death rate in both treatment arms was so high that no survival benefit was realized with CEA.[11]

†Deceased.

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Table 1. Clinical Trials of Carotid Revascularization in Asymptomatic Patients

Clinical Trial	No. of Patients	30-Day D/S/M, %	30-Day D/S, %	30-Day D/MS, %	1-Year D/S/M, %	1-Year D/S, %	5-Year D/S, %
VACS (CEA)[11]	211	6.5	4.7	4.7	...	10.3	...
ACAS (CEA)[12]	825	...	2.7	...	...	6.5	31.9
ACST (CEA)[13]	1560	...	3.1	...	...	...	28.9
BEACH (CAS)[71]	557	5	4.3	2.7	8	13.6	...
CASES-PMS (CAS)[72]	1158	4.7	...	...	...	...	...
CREST (CAS)[40]	1246	...	3.4	...	...	...	...
CAPTURE (CAS)[23]	3017	5.4	...	...	...	...	...
Marine et al (CAS)[29]	93	...	2.2	2.2	...	...	...
CaRESS (CAS)[28]	99	2.1	2.1	2.1	10.9	10	...
Brooks et al (CAS)[33]	43	0	0	0	...	...	...
SAPPHIRE (registry) (CAS)[41]	281	...	5	4.9	15.7	12.4	...
SAPPHIRE (Rand) (CAS)[34]	117	5.8	4.5	2.6	10.3	6.8	...

D/S/M indicates all death, all stroke, and all myocardial infarction; D/S, all death and all stroke; D/MS, all death and all major stroke; VACS, Veterans Affairs Cooperative Study; CASES-PMS, Carotid Artery Stenting With Emboli Protection Surveillance–Post-Marketing Study; and Rand, randomized.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) screened >42 000 patients to randomize 1662 asymptomatic patients with ≥60% stenosis to CEA plus medical therapy (n=825) or medical therapy alone (n=834).[12] The 30-day perioperative stroke or death rate was 2.3%, with an additional 1.2% stroke incidence due to carotid angiography. CEA significantly cut the 5-year risk of ipsilateral stroke, perioperative stroke, or death in half (from 11% to 5.1%). One stroke was prevented over 5 years for every 19 patients undergoing surgery. CEA yielded a 66% risk reduction for ipsilateral stroke over a 5-year period in men, compared with 17% for women. Similar to the Veterans Affairs trial, the 5-year risk of all stroke and death was not reduced by CEA.

The Asymptomatic Carotid Surgery Trial (ACST) randomized 3120 asymptomatic patients with ≥60% carotid artery stenosis by ultrasound.[13] There was a 2.8% risk of stroke or death within 30 days for those randomized to CEA. The 5-year risk of stroke was reduced significantly for CEA (6.4%) compared with medical therapy (11.8%). In contrast to symptomatic patients, the severity of carotid stenosis in asymptomatic patients did not correlate with benefit from CEA, which was also observed in ACAS. At 5 years, there was no difference in the rates of all stroke and/or death between medical therapy and CEA.

These randomized trials comparing CEA took place before the routine or targeted use of atherosclerotic risk–modifying medications (hydroxymethylglutaryl coenzyme A reductase inhibitors [statins], angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers). Statins have been shown to reduce stroke, myocardial infarction (MI), and death.[14] Similarly, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reduce the rate of stroke in patients with atherosclerosis and hypertension.[15,16] Nevertheless, the benefit of these pharmacological therapies in the reduction of stroke and death in patients with severe carotid stenosis remains unknown.[17]

Carotid Stents

CAS placement is an emerging alternative revascularization strategy to prevent stroke. CAS placement is a technique in evolution that includes the recent adoption of emboli protection devices (EPDs) and low-profile self-expanding stents (Figure 1). There are specific patient- and lesion-related features that increase the risk of stent complications (Table 2).[18] The American Heart Association expert consensus committee recommended that in order for an asymptomatic patient to achieve clinical benefit from a revascularization procedure, the periprocedural threshold for stroke and death should be ≤3% in patients expected to live ≥5 years.[19,20]

CAS in asymptomatic patients has been investigated in single-center[21] and multicenter[22–27] registries, nonrandomized comparative trials,[28,29] completed randomized trials,[30–36] and several ongoing randomized trials (Table 1).[37,38] The Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH) was a multicenter registry that enrolled 747 patients at high surgical risk to evaluate the Carotid WALLSTENT and FilterWire EX/EZ EPD. Three

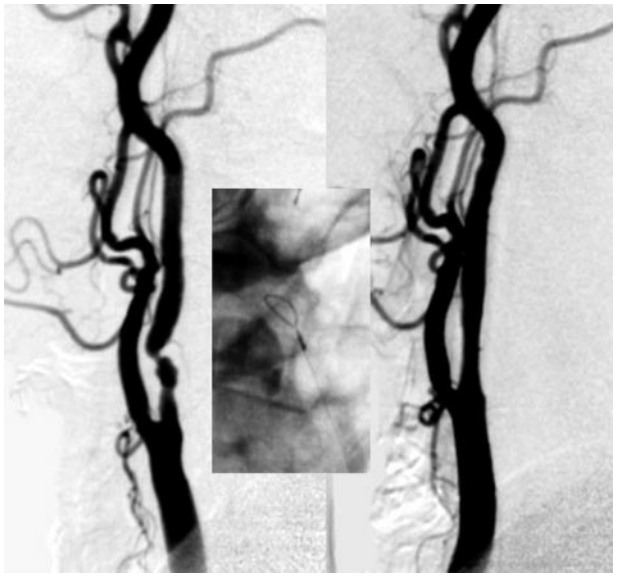

Figure 1. Angiogram showing baseline carotid stenosis (left) and final angiogram after carotid stent placement (right). Middle inset shows the EPD, with a visible nitinol ring.

Table 2. High-Risk Features for Carotid Stent Placement[18]

Clinical features
Age ≥75/80 y
Dementia
Prior (remote) stroke
Multiple lacunar strokes
Renal failure
Angiographic features
Two or more 90° bends within 5 cm of lesion
Circumferential calcification ≥3 mm in width
Intracranial microangiopathy
Intravascular filling defect (thrombus)
No vascular access

fourths (557/747) of the BEACH registry patients were asymptomatic with ≥80% carotid stenosis. The 30-day major stroke and death rate was 2.7%, below the 3% rule recommended by the expert American Heart Association panel.[39]

The largest registry trial completed to date, the Carotid Acculink/Accunet Post-approval Trial to Uncover unanticipated or Rare Events (CAPTURE), is a postmarket surveillance trial that enrolled 3500 patients, of whom 3017 were asymptomatic.[23] The 30-day rate of major (disabling) stroke and death was 2.9%. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) reported on 1246 patients in the lead-in registry, with a 30-day stroke and death rate of 3.4% for asymptomatic patients.[40]

A nonrandomized, retrospective, single-center series found no difference in periprocedural outcomes in 248 asymptomatic patients undergoing CEA or CAS.[29] The Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) trial, a multicenter, prospective cohort controlled trial, enrolled 397 patients, two thirds of whom were asymptomatic, and found no significant difference between CAS and CEA for stroke and death at 30 days (<3%).[28] A single-center randomized, controlled trial in 85 normal-surgical-risk asymptomatic patients reported no perioperative stroke, MI, or death for CAS (without embolic protection) or CEA.[33] Carotid artery patency assessed by ultrasound as much as 48 months later was equivalent for CEA and CAS.

The largest randomized, controlled trial was the Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy (SAPPHIRE) trial, which was the pivotal trial that led to US Food and Drug Administration device approval and Centers for Medicare and Medicaid Services funding for a subset of these patients. SAPPHIRE was a multicenter, prospective, randomized trial that enrolled symptomatic (30%) and asymptomatic (70%) patients considered to be at increased risk for surgery.[34] The 30-day ipsilateral major stroke and death rate was 2.6% for CAS and 2.5% for CEA, which compares favorably with both ACAS[12] and ACST[13] results. The primary end point of the trial was the 1-year incidence of major adverse events, defined as stroke, death, or MI within 30 days plus death and ipsilateral stroke between 31 days and 1 year. For the asymptomatic randomized patients (CEA=119 and CAS=117), there was a significantly lower incidence of major adverse events for CAS (10.5%) than for CEA (20.3%) at 1 year, which was primarily due to a lower incidence of MI (Figure 2).[41]

Summary

Careful patient selection and attention to atherosclerotic risk factor management are important in maximizing stroke prevention with any revascularization strategy. CEA in asymptomatic patients with hemodynamically significant stenoses (60% to 99%), if performed with an acceptable (≤3%) perioperative risk of stroke and death, reduces ipsilateral stroke but does not increase the 5-year survival rate. The benefit of CEA in asymptomatic women is not as great as for men. The periprocedural complications of disabling stroke and death with CAS when performed in asymptomatic patients appear to be within or very near the "3% rule" established as a surgical benchmark (Table 1).

CEA remains the procedure of choice for asymptomatic patients considered for carotid artery revascularization who are deemed to be at average surgical risk, pending data from ongoing randomized clinical trials comparing CEA and CAS. CAS is an option to be considered in asymptomatic patients with severe (≥80%) carotid artery stenosis who are at increased risk of surgical complications.[42]

Carotid Stents for Patients at Increased Surgical Risk for CEA

Background

The majority of carotid stent trials have been conducted in patients identified as being at increased risk of surgical

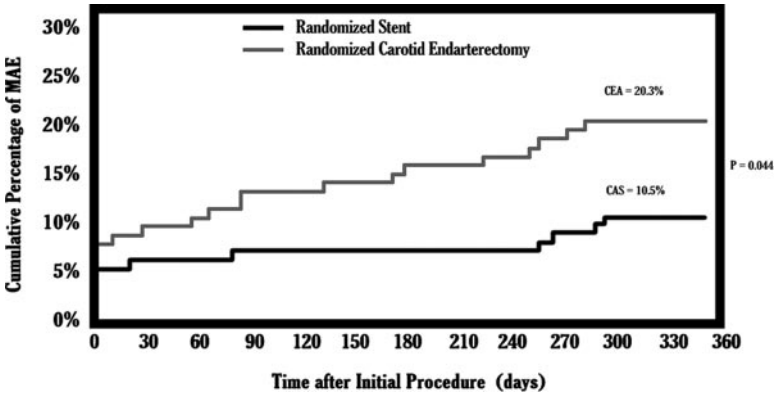

Figure 2. Cumulative percentage of major adverse events (MAE) in asymptomatic patients enrolled in the randomized SAPPHIRE trial at 1 year.[41]

Table 3. Criteria for Increased Surgical Risk

Anatomic features
Surgically inaccessible lesions at or above C2 or below the clavicle
Previous neck or head radiation therapy or surgery that included the area of stenosis/repair or ipsilateral radical neck dissection
Spinal immobility of the neck due to cervical arthritis or other cervical disorders
Restenosis after a previous or unsuccessful attempt of CEA
Contralateral laryngeal palsy
Presence of a tracheal stoma
Contralateral carotid occlusion
Comorbid conditions
Age ≥75/80 y
Congestive heart failure (New York Heart Association class III/IV)
Unstable angina (Canadian Cardiovascular Society class III/IV)
Left main disease/≥2-vessel coronary disease
Recent MI (<30 d)
Left ventricular ejection fraction ≤30%
Requirement for heart surgery within 30 d
Severe lung disease
Severe renal disease

complications because of unfavorable anatomic characteristics or medical comorbidities (Table 3). A key concept when interpreting carotid stent data is to realize that patients at increased risk for surgical complications of CEA are not necessarily at increased risk for stent complications and vice versa. As has been demonstrated in multiple randomized clinical trials, CEA reduces the incidence of cerebral infarction in symptomatic and asymptomatic patients.[12,13,43–45] Nevertheless, the benefit of CEA must be balanced against the perioperative risk associated with the procedure. Not all patients can safely undergo CEA because of a variety of unfavorable anatomic features (Figure 3) or comorbidities. High-surgical-risk criteria are listed in Table 3.[20,46–55] Patients enrolled in randomized clinical trials such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and ACAS were carefully selected and had lower rates of procedural death than did unselected patients undergoing CEA.[56] Older age has been reported as a predictor of poor outcome after CEA, with patients ≥75 years of age experiencing higher rates of stroke and death at 30 days, late neurological death, and composite morbidity and mortality at 1 year.[56,57] Elderly patients such as octogenarians have greater procedure-related risk and, of course, will have shorter postprocedural life expectancy than younger patients.[58] To date, the efficacy of carotid revascularization in asymptomatic patients ≥75 years of age is not established.[13] Increased CEA and CAS procedural risk may be attributable in part to a number of factors commonly associated with advanced age, such as decreased cerebral reserve, excessive arterial tortuosity, and heavily calcified arteries.[18,59–61] Because atherosclerosis is a systemic disease, it is expected that older patients with carotid atherosclerosis will have more extensive coronary and renal atherosclerotic vascular disease than younger patients. A considerable body of literature has documented that complication rates in the high-risk group of patients may rise above the 10% maximum recommended by the American Heart Association. The pivotal carotid stent registries in high-surgical-risk patients, with the oversight and approval of the US Food and Drug Administration, have developed objective performance criteria that have estimated 1-year end points in the 10% to 15% range, based on the published literature for CEA risk (Table 4).[47,49,50,62–65] A higher complication rate for CAS has been reported in patients >80 years of age than in those <80 years of age undergoing CAS without the use of an EPD (Table 5).[21,23,24,37]

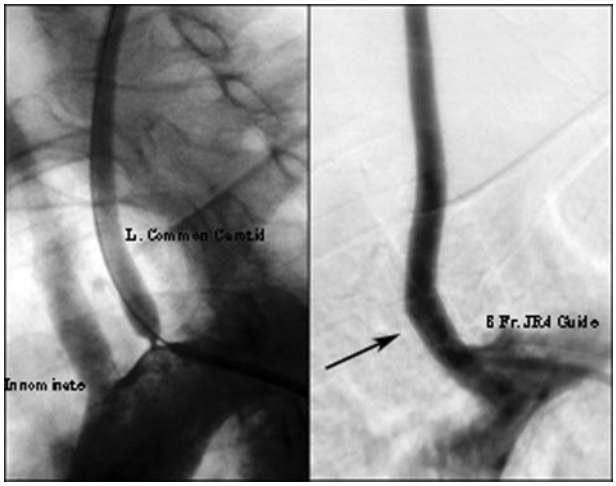

Figure 3. Angiography of a patient at high surgical risk for anatomic reasons, namely, the intrathoracic location of the ostial left (L.) common carotid artery. Baseline angiogram (left) and final angiography after deployment of a balloon-expandable stent (right).

Table 4. Nonrandomized Trials Reporting Carotid Stent Results

Trial	No. of Patients	30-Day D/S/M	30-Day D/S	1-Year D/S	1-Year D/S
ARCHeR (HSR)[22]	581	8.3	6.9	9.6	...
BEACH (HSR)[24]	480	5.8	...	9.1	...
CABERNET (HSR)[27]	454	3.8	...	4.5	...
CAPTURE (HSR)[23]	3500	6.3	5.7	...	...
CaRESS[28]	143	2.1	2.1	10.9	10
CREATE (HSR)[73]	419	6.2	5.2	...	...
CREST[40]	1246	...	3.9	...	...
MAVERIC (HSR)[26]	399	...	5.3	...	...
MOMA[74]	157	...	5.7	...	...
PRIAMUS[75]	416	...	4.6	...	...
SECURITY (HSR)[76]	305	8.5	...	...	...

D/S/M indicates death, stroke, and myocardial infarction; D/S, death and stroke; HSR, high surgical risk; CABERNET, Carotid Artery Revascularization Using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent study; PRIAMUS, Proximal Flow Blockage Cerebral Protection During Carotid Stenting; and SECURITY, Registry Study to Evaluate the Neuroshield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy.

Clinical Trials

The SAPPHIRE trial was a multicenter, prospective, randomized, controlled trial that enrolled a majority (70%) of

Table 5. Age and Perioperative Complications (30-Day Stroke and Death)

Age	Roubin et al[21]	CREST[37]	CAPTURE[23]	BEACH[24]
<80 y	6	2.8	5.6	3.4*
≥80 y	16	12.1	8.1	9.1†
P	<0.01	<0.01	<0.05	<0.002

*Age <75 years; †age ≥75 years.

asymptomatic patients who were determined by a surgeon, a neurologist, and an interventionalist to be at increased risk for CEA (Table 1).[34] The primary end point of the trial was the 1-year incidence of major adverse events, including any stroke, death, or MI within 30 days plus death and ipsilateral stroke between 31 days and 1 year. A total of 747 patients were enrolled in the study, with 334 (45%) undergoing randomization (167 to CEA and 167 to CAS). Of the 413 patients not randomized, 406 (98%) were refused CEA because of excessive risk and were entered into a stent registry, and 7 patients (2%) were refused CAS and were entered into a CEA registry. The 30-day rate of ipsilateral major stroke or death was virtually identical for CAS (2.6%) and CEA (2.5%), and the 1-year primary composite end point demonstrated statistically significant noninferiority for CAS (12.2%) compared with CEA (20.1%).

In the asymptomatic high-surgical-risk patients, there were significantly fewer major adverse events at 1 year for CAS (10.5%) than for CEA (20.3%), a difference that was largely driven by perioperative non–Q-wave MI (Figure 2).[41] In symptomatic high-surgical-risk patients, there was no significant difference for either the 30-day stroke, death, and MI rate (CEA=9.3% versus CAS=2.1%) or the primary end point at 1 year (CEA=16.5% versus CAS=16.8%).

In a systematic analysis of all published reports since 1980, Rothwell and coworkers[66] determined that there was significant heterogeneity in the reporting of results of CEA, which makes comparison of published data very difficult. The risks of perioperative stroke and death were highest in studies that relied on a neurologist to assess the patients and lowest in studies written by a single surgeon. These factors serve to emphasize the importance of direct comparative trials of CEA and CAS to determine noninferiority of CAS to CEA.

Summary

Most investigators believe a subgroup of CEA patients at increased risk for carotid surgery can be identified. Clearly, patients with high-risk anatomic features present challenges for CEA, whereas the increased procedural risk of CEA conferred by medical comorbidities continues to be debated among experts. The preponderance of the evidence, however, supports the conclusion that CAS with embolic protection is not inferior to CEA in either symptomatic or asymptomatic patients at increased risk for surgical complications of CEA.[42]

Role for Carotid Stents in Patients at Average Surgical Risk

Clinical Trials

Results from the lead-in phase of CREST reported low periprocedural complication rates with CAS that suggested clinical equipoise with CEA in usual-risk surgery patients (Table 6).[37,40] Clinical trials continue to investigate the efficacy of CEA compared with CAS for the prevention of stroke in patients with severe extracranial carotid occlusive disease who are at average risk for surgical complications.

Randomized studies comparing the efficacy of CEA versus CAS in patients at average surgical risk have demonstrated a trend toward a higher mortality risk for CEA and a higher stroke risk for CAS.[67] The WALLSTENT trial has been criticized for an inadequate sample size, inexperienced interventionalists, uneven use of antiplatelet medications, and the absence of an EPD, which resulted in premature study termination by the manufacturer (Table 6).[31] The results of a larger multicenter European trial, the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS), are not pertinent today because only one fourth of the patients in the endovascular group were treated with a stent, and an EPD was not used (Table 6).[68] A community hospital–based randomized clinical trial in average-surgical-risk patients demonstrated equivalence for CEA and CAS, but the sample size was small (n=104; Table 6).[32]

Table 6. Trials of Symptomatic Patients at Average Surgical Risk

Trial Name	No. of Patients	30-Day D/S/M, %	30-Day D/S, %	30-Day D/MS, %	1-Year D/S, %
VACS (CEA)[77]	91	...	7.7	4.7	...
NASCET (CEA)[43]	1415	...	6.5		15.8 (2 y)
ECST (CEA)[44]	1742	...	7.5	3.6	...
CAVATAS (CEA)[68]	253	...	9.9	5.9	
EVA-3S (CEA)[35]	259	...	3.9	1.5	6.1 (6 mo)
SPACE (CEA)[36]	584	...	6.5	3.8	
WALLSTENT (CAS)[31]	107	...	12.1	...	12.1
CAVATAS (CAS)[68]	251	...	10	6.4	...
CREST (CAS)[40]	1246	...	5.6	...	...
Brooks et al (CAS)[32]	53	0	0	0	...
EVA-3S (CAS)[35]	261	...	9.6	3.4	11.7 (6 mo)
SPACE (CAS)[36]	605	...	6.8	4.7	...

D/S/M indicates all death, all stroke, and all myocardial infarction; D/S, all death and all stroke; D/MS, all death and all major stroke.

The EVA-3S (Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis) trial randomized 527 symptomatic (≥60%) average-surgical-risk patients to CAS or CEA (Table 6).[35] The trial was stopped prematurely for both safety issues and recruitment futility. The 30-day incidence of stroke or death was almost 3-fold greater for CAS (9.6%) than for CEA (3.9%, $P=0.01$). Early in the trial, when use of EPDs was not required, stroke occurred in 25% (5 of 20) of the CAS patients, which caused the trial to be stopped and restarted with EPD use required. The major limitations of this trial were the inexperience of the operators who were placing carotid stents (required a minimum experience of 5 stent procedures) and the nonstandardized wide variety of equipment that was used.

The Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy (SPACE) trial was a European noninferiority trial comparing CEA to CAS in 1183 average-surgical-risk symptomatic patients with the optional use of EPDs.[36] The trial was terminated because of lack of funding after enrolling approximately half of the planned patients. The 30-day stroke and death rates were similar for CAS (6.8%) and CEA (6.3%; Table 6) and not statistically different; however, because of the premature termination of the study, not enough patients were enrolled to provide the power necessary to confirm noninferiority of CAS to CEA.

Three meta-analyses comparing CAS to CEA have been performed to date.[67,69,70] These trials demonstrate a trend toward a higher rate of periprocedural death for CEA and a higher rate of periprocedural stroke with CAS. None of the 3 meta-analyses found any difference for 30-day stroke and death between CAS and CEA.

Summary

The current clinical trial evidence conflicts with regard to clinical equipoise for symptomatic average-surgical-risk patients undergoing CAS and CEA, and very little information exists in asymptomatic patients at average surgical risk. At the present time, there is expert consensus that more data are required, particularly from the randomized trials such as ACT-1 (Asymptomatic Carotid Trial) and CREST, to accept the hypothesis that CAS is noninferior to CEA in the average-surgical-risk population.

Conclusions

Important questions about carotid artery revascularization strategies to prevent stroke remain unanswered. Assessment of the stroke-reduction benefit of "modern medical therapy" (eg, atherosclerotic risk factor modification and lifestyle modification) compared with any revascularization strategy for stroke prevention is critical to selecting any treatment strategy. It is reasonable to posit that modern medical therapy will reduce the incidence of stroke better than aspirin therapy alone did in the 1990s, but we must acknowledge that the benefits of carotid revascularization will be amplified as patients live longer because of modern medical therapy.

Knowledge gaps remain with regard to optimal stroke-prevention strategies in the elderly, in women, and in asymptomatic patients. As the risk of any revascularization strategy increases (elderly) or the margin of benefit narrows (women versus men and asymptomatic versus symptomatic patients), the periprocedural complication rate and the patient's life expectancy must be factored into the treatment recommendation.

The comparison of CEA and CAS is difficult and complicated on many levels. Nonrandomized studies are encumbered by the variability in patient subsets, differences in end point definitions, changing standards of medical therapy, and differences in reporting standards. Even randomized trials are fraught with variability in antiplatelet therapy, equipment use (including EPD and stent use), and operator qualifications. Although intuitive and broadly accepted, it remains to be proven that EPDs reduce the risk of CAS periprocedural complications. Clearly, despite retrieval of embolic material, EPDs do not completely prevent strokes. There may be better strategies or more effective methods for reducing the periprocedural stroke rate with CAS, including the use of covered stents and flow reversal with proximal occlusion devices as an emboli protection strategy. While acknowledging that much more evidence needs to be gathered, physicians must make decisions and recommendations on the basis of the current available evidence and assessment of the risks and benefits faced by individual patients.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary, which is available online at http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.108.191170.

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