15 Current Status of Carotid Endarterectomy and Carotid Stenting

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Introduction

Atherosclerotic disease of the carotid artery is a major contributor to morbidity and mortality, accounting for 10–15% of patients diagnosed with stroke [1]. Surgical intervention of carotid artery disease with carotid endarterectomy (CEA) has been well studied and shown to reduce the risk of future ischemic stroke in patients with severe symptomatic carotid artery disease or in patients where maximal medical therapy has failed [2–4]. However, the role of carotid artery stenting (CAS) has not been as clear despite being a proposed treatment option for carotid artery disease since the 1990s [5, 6]. A significant contribution to the lack of clarity is partly due to the large number of clinical trials that have either confirmed or refuted the use of CAS to treat patients with carotid artery stenosis. The goal of this chapter is to provide the reader an overview of the clinical trials that have led to our current conclusions about stenting or endarterectomy in patients with carotid artery stenosis.

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Overview of Clinical Trials

The following chapter will cover a significant majority of the landmark peer-reviewed publications and prospective research that has been published over the last 20 years regarding stenting or endarterectomy for carotid stenosis. A significant emphasis will be placed on identifying literature with randomized controlled trials (RCTs) or prospective studies, as this provided the highest quality evidence for treatment recommendations. Studies that had long-term follow-up data were also favored. An overview of these trials will be presented in a way to offer the reader a concise comprehensive summary of the literature that has led to our current practices today. However, it should be noted that there is a convoluted history surrounding many of the recommendations that have come from the literature on stenting versus endarterectomy; therefore, to help the reader better comprehend the time-relationship of the history behind carotid stenting versus endarterectomy (and avoid confusion that often stems from reading the literature), we will present each study in chronological order starting with the year of the initial patient randomization. This will help illustrate the extensive timeline for studying this disease while aiding the reader to consider the advances we have made since many of these clinical trials were published. Long-term data (when available) will also be discussed in each section. A summary of the trials can be seen in Table 15.1.

S. S. Hans (ed.), *Extracranial Carotid and Vertebral Artery Disease*,
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Table 15.1 Summary of randomized controlled trials for carotid artery stenting versus endarterectomy in patients with extracranial carotid artery stenosis

Name	Trial name	Publication	Year of original publication or long-term follow-up study	Study design	Recruitment	Number of patients	Patient type	Follow-up	Distal embolization protection rate
CAVATAS	Carotid and vertebral artery transluminal angioplasty study	Endovascular versus surgical treatment in patients with carotid stenosis in the carotid and vertebral artery transluminal angioplasty study (CAVATAS): a randomized trial	2001	RCT	1992–1997	504	Stenosis of the common carotid artery, carotid bifurcation, or internal carotid artery that investigators believed needed treatment and was suitable for both carotid endarterectomy and endovascular treatment	1 year	0.0%
		Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the carotid and vertebral artery transluminal angioplasty study: long-term follow-up of a randomized trial	2009	Follow-up	–	413		4–5 years	–
EVA-3S	Endarterectomy versus angioplasty with symptomatic severe carotid stenosis	Endarterectomy versus stenting with symptomatic severe carotid stenosis trial	2006	RCT	2000–2005 trial was stopped early	527	Symptomatic hemispheric or retinal TIA *or* non-disabling stroke or retinal infarct within 120 days prior to enrollment *and* stenosis of 60–99% with NASCET criteria. Stenosis had to be confirmed with either catheter angiography *or* both U/S and MRA	6 months	92.0%
		Endarterectomy versus angioplasty with symptomatic severe carotid stenosis trial: results up to 4 years from a randomized, multicenter trial	2008	Follow-up	2005–2007	524		4 years	–
		Long-term follow-up study for endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis trial	2014	Retrospective, follow-up	2008–2012	493		7 years	--

SAPPHIRE	Stenting and angioplasty with protection in patients at high risk for endarterectomy	Protected carotid artery stenting versus endarterectomy in high-risk patients	2004	RCT	2000–2002	334	Symptomatic with >50% stenosis or asymptomatic with >80% and at least one high-risk criteria	3 years	95.6%
		Long-term results of carotid stenting versus endarterectomy in high-risk patients	2008	Follow-up	–	–	–	–	–
SPACE	Stent-protected angioplasty versus carotid endarterectomy	30-day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomized non-inferiority trial	2006	RCT	2001–2006	1183	Symptomatic carotid artery stenosis with radiographic evidence of stenosis on imaging: at least 70% on duplex ultrasound or angiography according to ECST or 50% according to NASCET	30-days	27.0%
		Results of the stent-protected angioplasty versus carotid endarterectomy study to treat symptomatic stenosis at 2 years: a multinational, prospective, randomized trial	2008	Follow-up	–	1214	–	2 years	–

(continued)

Table 15.1 (continued)

Name	Trial name	Publication	Year of original publication or long-term follow-up study	Study design	Recruitment	Number of patients	Patient type	Follow-up	Distal embolization protection rate
ACST-2	Asymptomatic carotid surgery trial-2	Asymptomatic carotid surgery trial-2: rationale for a randomized clinical trial comparing carotid endarterectomy with carotid artery stenting in patients with asymptomatic carotid artery stenosis	2009	RCT	2008–2012	986	Asymptomatic carotid artery stenosis with low surgical risk and appropriately medical therapy	5 years	Not reported
		Status updated and interim results from the asymptomatic carotid surgery trial-2	2013	Follow-up	–	–	–	–	–
CREST	Carotid revascularization endarterectomy versus stenting trial	Stenting versus endarterectomy for treatment of carotid artery stenosis	2010	RCT	2005–2008	2502	Please see below table on "Radiographic Criteria Used for Randomization in CREST"	4 years	96.1%
		Long-term results of stenting versus endarterectomy for carotid artery stenosis	2016	Follow-up	–	1607	–	10 years	–

ICSS	International carotid stenting study	Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis: an interim analysis of a randomized controlled trial	2010	RCT	2004 to not reported	1713	Symptomatic carotid artery stenosis (within 365 days of TIA or non-disabling stroke) and stenosis of at least 50% diagnosed with NASCET criteria. Patients had to be deemed suitable for surgery and low surgical risk prior to intervention	120 days	72%
		Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the international carotid stenting study randomized trial	2015	Follow-up	–	–		Up to 10 years	–
ACT-1	Asymptomatic carotid trial-1	Randomized trial of stent versus surgery for asymptomatic carotid stenosis	2016	RCT	2005–2013	1453 (with 3:1 randomization)	<80 years old, asymptomatic with 70–99% stenosis, and not high surgical risk	5 years	97.6%

General Considerations

There are many different end points and definitions used by the authors of the following papers. For clarity, we will define the following generalizations and make note of any differences made by investigators as they present:

Stroke is generally defined as an ischemic neurological deficit that persisted for more than 24 h. *A non-disabling stroke* is generally considered patients with a modified Rankin Scale (mRS) score of 0–2, with disabling strokes being scores of 3–5 (higher the score indicates a worse stroke). *Myocardial infarction* was not always clearly defined in each study but for our generalization is defined as an elevation of creatinine kinase higher than two times the upper limit of normal with positive serum MB fractions. *Composite cardiovascular events* are defined as stroke, myocardial infarction, or death.

Criteria for measuring stenosis were performed either by using techniques from the NASCET trial [2] or ECST trial [3]. Degrees of stenosis with ultrasound measurements were assigned with standard ultrasound criteria: mild (<50%), moderate (50–69%), severe (70–99%), and occluded (100%) [7].

1992: Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)

This study [8], along with the long-term follow-up [1], was a multicenter RCT that compared a rather generalized patient population with carotid artery stenosis to endovascular treatment (with either angioplasty and/or stenting) to endarterectomy. A total of 504 patients from 1992 to 1997 were randomized. Prior to 1994, patients randomized in the study to receive endovascular treatment underwent percutaneous transluminal angioplasty with balloon catheters. Carotid stents were being developed prior to this time and when they became available they were used from 1994 onward when the radiologists believed there was a treatment benefit. Stents were allowed as either a secondary procedure after unsatisfactory balloon dilation *or* stenting alone without attempting balloon dilation first. Among other exclusion criteria, patients were specifically excluded from the study if they had "unsuitable" surgical risk factors defined as recent myocardial infarction, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis. Contralateral carotid artery occlusion was not an exclusion criterion. Patients also did not have pretreatment-defined criteria for randomization based on their degree of stenosis and investigators "used their own protocol to establish the presence of clinically important carotid stenosis before treatment." Only 3% of patients were asymptomatic from their carotid artery stenosis.

Based on these criteria, 251 patients were randomized to endovascular treatment and 253 to CEA. The degree of ipsilateral carotid artery stenosis was 86.4% in the endovascular group and 85.1% in the surgical group. In addition to their stenosis, 24 patients (10%) in the endovascular arm and 20 patients (8%) in the surgical arm were diagnosed with a contralateral carotid occlusion prior to ipsilateral carotid artery intervention.

The rates of major outcomes within the first 30 days did not differ significantly between endovascular and surgical intervention: 6.4% versus 5.9% for 30-day disabling stroke or death and 10.0% and 9.9% for any stroke lasting for more than 7 days or death. The rate of periprocedural cranial neuropathy was higher in the surgical group (8.7%) compared to none in the endovascular group. Major groin or neck hematomas also occurred less frequently in the endovascular group than after surgery (1.2% versus 6.7%).

At 1 year of follow-up, severe ipsilateral carotid stenosis was seen more often after endovascular treatment (14% versus 4%). At long-term follow-up of endovascular treatment (mean 5 years) and surgical treatment (mean 4 years), severe carotid restenosis of at least 70% occurred more often in the endovascular group than the surgical group. The adjusted 5-year incidence of restenosis was 30.7% in the endovascular treatment compared to 10.5% in the surgical group. The long-term general conclusion was that restenosis was more likely, approximately three

times, after endovascular treatment than endarterectomy and that endovascular treatment was associated with recurrent ipsilateral cerebrovascular symptoms.

The CAVATAS study and its long-term follow-up reported some interesting findings but drew criticism. First, there was no clear indication for treatment: patients were left at the operator's discretion of their own protocol if an individual, regardless of symptoms, had carotid artery disease that warranted intervention. There was no specific mention about what protocols, if any, were used for operators to decide on whether a patient required therapy. Second, there was a lack of protection against distal emboli, which the lack of doing so has largely been abandoned as it has been shown to significantly increase the risk of stroke [9]. Third, endovascular treatment consisted of balloon angioplasty in almost three quarters of patients with only 55 of the 213 patients (26%) receiving a stent. Finally, this population is rather limited when compared to the generalized population with carotid stenosis, as most patients have significant comorbidities that were excluded from this study or are asymptomatic and CAVATAS included only 3% of patients with asymptomatic disease. Therefore, the conclusions do not necessarily apply to many, if not most, patients with carotid artery disease and follow-up studies from CAVATAS would illustrate many of these points.

2000: Endarterectomy Versus Angioplasty with Symptomatic Severe Carotid Stenosis (EVA-3S)

The EVA-3S clinical trial and its two long-term follow-up publications [10–12] reported an extensive series on patients with severe symptomatic carotid stenosis treated with carotid endarterectomy or stenting. In the first study, a total of 527 symptomatic patients were randomized to stenting (with distal emboli protection used in 92% of patients) or endarterectomy. Patients with symptomatic hemispheric or retinal TIA *or* non-disabling stroke or retinal infarct within 120 days prior to enrollment were enrolled if they had carotid stenosis of 60–99% confirmed with either catheter angiography or both duplex ultrasound and magnetic resonance angiography of the carotid vessels. Initially patients were only treated if they had 70% carotid stenosis, but the study protocol was modified to include patients up to 60% after there was a potential benefit to surgically treat patients with 50–69% stenosis [4]. Patients in the initial study were followed for the perioperative 30-day period along with follow-up at 3 and 6 months post-intervention.

The first study was stopped early because of "safety and futility" at the recommendations of the trials safety committee. Patients with stenting had higher rates of 30- and 60-day stroke or death. Patients with stenting also had higher relative risks of nonfatal stroke or death within this period. There were also more local complications with stenting, mainly from injuries related to the puncture site (femoral pseudoaneurysm, arteriovenous fistula formation, lower limb arterial occlusion, or thrombosis), but these results were not statistically significant. Patients with endarterectomy had more systemic complications, mainly from pulmonary issues, but again were not statistically significant. There were significantly more cranial nerve injuries with surgery (7.7% versus 1.1%, $P < 0.001$), and shorter hospital stays with stenting (3 versus 4 days, $P = 0.01$); however, there was no statistically significant difference in myocardial infarction ($P = 0.62$). The overall conclusion at the early termination of this trial was that patients with symptomatic carotid stenosis of at least 60% had lower rates of stroke or death at 30 days and 6 months with endarterectomy when compared to stenting.

However, there were some limitations to the first publication. The most significant limitation of the first study (identified by both the primary investigators and investigators of other clinical trials) was that the stents could be placed by physicians with various degrees of experience. Interventionalists could be included if they had performed as few as five previous carotid stent procedures *or* while working under the supervision of a qualified tutor if they had no previous experience. Another limitation was that high surgical risk patients were excluded, limiting the

generalizing conclusions that were made. Finally, the consideration of patients with contralateral carotid disease was not considered during the inclusion or exclusion of criterial in this trial.

Two follow-up studies at both 4- and 7-year follow-up were published after the initial trial was completed [10, 12]. The first publication had an overall retention rate of 99% with only three patients lost to follow-up, the second having a 94% retention with only 88 patients lost. Long-term conclusions were largely influenced by the initial study with high perioperative rate of 30-day stroke or death within the stenting group. The composite incidence of periprocedural stroke or death *or* any non-procedural ipsilateral stroke was significantly higher for stented patients at 4 years (11.1% versus 6.2%, $P = 0.03$) and 7 years (11.0% versus 6.0%, $P = 0.04$). However, after the periprocedural period was over both follow-up studies concluded the long-term risk of stroke or death was low and not significant in either both treatment groups, with both treatment arms having similar hazard ratios. Furthermore, the 2014 data suggested there was no difference in restenosis, occlusion, myocardial infarction, or need for revascularization at long-term in both intention-to-treat and per-protocol analyses.

Overall it was concluded that the perioperative safety of carotid stenting had to improve before more patients were subjected to this treatment modality, and operator experience interestingly was not a determining factor in the 30-day risk of stroke or death in this study.

2000: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)

The SAPPHIRE trial included data published from *Protected Carotid-Artery Stenting versus Endarterectomy in High-Risk Patients* [13], and its subsequent long-term follow-up publication [14] was an RCT that compared stenting *with* distal embolic protection to endarterectomy alone in patients specifically with identified "high-risk" surgical features that increased the risk of both short- and long-term complications. A total number of 334 patients were randomized in a 1:1 ratio from 2000 to 2002 and followed for a mean of 3 years post-procedure. Patients were included if they had at least one high-risk criteria and *either* symptomatic carotid stenosis >50% *or* asymptomatic stenosis >80%. Distal embolization protection was used in 96% of the stented patients.

Criteria for High Risk in SAPPHIRE

At least one factor was required for treatment in this study [14].

- Clinically significant cardiac disease
  - Congestive heart failure, abnormal stress test, or need for open-heart surgery
- Severe pulmonary disease
- Contralateral carotid occlusion
- Contralateral laryngeal nerve palsy
- Previous radical neck surgery or radiation therapy to the neck
- Recurrent stenosis after endarterectomy
- Age >80 years of age

Composite cardiovascular events at one year did not show a significant difference in outcome between stenting and endarterectomy in patients with both severe carotid artery stenosis *and* classified as an increased surgical risk. Stenting patients experienced a 12.2% composite cardiovascular event rate, whereas surgical patients had a 20.1% event rate ($P = 0.004$ for non-inferiority). Carotid revascularization rates were also lower at one year post-procedure in patients who had received a stent (0.6%) compared to the surgical group (4.3%, $P = 0.04$). Patients in the stenting group had a lower rate of cranial nerve palsies (0% versus 4.9%, $P = 0.004$) and shorter inpatient length of stay (1.84 ± 1.75 days versus 2.85 ± 3.67 days, $P = 0.002$).

Long-term data published four years later further supported the primary outcomes of the initial

study, albeit with only a 77.8% overall follow-up rate. Kaplan-Meier for estimating cumulative incidence of the primary outcome was the method used to partially correct for the loss of follow-up. Composite cardiovascular events at one year plus death or ipsilateral stroke between 1 and 3 years were 24.6% for the stenting group and 26.9% for the endarterectomy group ($P = 0.71$) and 26.2% and 26.9%, respectively, with the Kaplan-Meier method. There was an overall high incidence of death in the 1–3-year period follow-up study, with 18.6% of stented patients and 21.0% of surgical patients experiencing mortality (20.0% and 24.2%, respectively, with the Kaplan-Meier method). However, the majority of deaths were contributed to non-neurological causes of death. Cardiac-related death was a contributor in both treatment groups, with 15 cardiac deaths occurring in both the stenting and surgical groups; however, there was no statistical difference when comparing the two groups ($P = 0.99$). Furthermore, it was noted the cumulative incidence of death in this study was likely related to "high-risk" patients themselves, with every patient having at least one identified high-risk factor and approximately 20% of the patients being over 80 years of age.

This study highlights that stenting is non-inferior to endarterectomy in patients with severe carotid stenosis *and* with a high surgical risk. Furthermore, there are fewer perioperative cranial nerve injury associated with stenting these patients along with a shorter length of stay. However, it should be noted that this study illustrates only a specific patient population (severe stenosis, high surgical risk) and does not provide any insight into patients with low or moderate surgical risk. This study differed from SPACE and EVA-3S (where they reported worse outcomes with stenting compared to endarterectomy) and that they did not include high surgical risk patients or asymptomatic patients. Furthermore, distal emboli protection devices, which by now were expected to be used when feasible in carotid stenting procedures, were only used in 92% of patients in the EVA-3S trial and 27% of patients in the SPACE trial.

2001: Stent-Protected Angioplasty Versus Carotid Endarterectomy (SPACE)

The SPACE trial [15] and its 2-year follow-up [16] compared carotid stenting to endarterectomy in patients with severe symptomatic carotid artery stenosis. In an RCT from 2001 to 2006, a total of 1183 patients with symptomatic carotid artery stenosis and radiographic evidence of stenosis on imaging (at least 70% on duplex ultrasound or angiography according to ECST or 50% according to NASCET) were randomized to treatment and followed for 30 days and then two years.

Patients had similar rates of death or ipsilateral ischemic stroke from either carotid artery stenting or endarterectomy at both short- (6.8% versus 6.3%, respectively, $P = 0.09$ for non-inferiority) and long-term intervals (9.5% versus 8.8%, respectively, $P = 0.62$). At long term, patients appeared to have a statistically significantly higher rate of recurrent stenosis of at least 70% in the stenting group in both intention-to-treat and per-protocol analyses (10.7% versus 4.6%, $P < 0.01$, and 11.1% versus 4.6%, $P < 0.01$, respectively). However, the overall mortality rate along with the rate of disabling stroke at both short- and long-term intervals was not inferior with stenting compared to endarterectomy.

In a subgroup analysis on the patients from SPACE [17], potential risk factors were examined including age, sex, type of qualifying event, side of intervention, degree of stenosis, and presence of high-grade contralateral stenosis or occlusion. Overall age was determined to give the greatest separation between high- and low-risk patients, particularly in the stenting population. There was an overall statistical significance of ipsilateral stroke or death within the first 30 days with increased age in the stenting population ($P = 0.001$) but not in the surgical group ($P = 0.534$). In patients under the age of 68 years old, there was a lower periprocedural risk of stroke or death with CAS than CEA ($P = 0.001$); however, the opposite trend was seen in patients over the age of 68, with patients having a lower

risk of stroke or death at 30 days with surgery compared to stenting ($P = 0.026$). All the other aforementioned risk factors examined in the subgroup analysis did not have a statistically different prediction of ipsilateral stroke or death at 30 days, including sex, degree of stenosis, or degree of pathology in the contralateral carotid artery.

An important limitation of the SPACE study was the low use of distal embolic protection in the stenting population. The SPACE collaborators suggested there was a "tendency towards better results in the carotid endarterectomy group within 30 days, apart from death and hemorrhagic stroke"; however, only 27% of patients received some form of distal embolic protection during the stenting procedure, which may have influenced the outcome. The results may have favored stenting if the use of distal embolic protection been more universal in this study. High surgical risk patients also were not included, and the SPACE conclusions cannot necessarily be generalized toward this patient population.

2004: International Carotid Stenting Study (ICSS)

The ICSS was an RCT enrolling 1713 patients starting in 2004 with the primary goal to establish safety and efficacy. The ICSS addressed some of the concerns and limitations in previous trials, namely, by expanding some of the safety parameters and requirements needed for physicians to enroll in the study. Centers had to have providers that had performed at least 50 carotid operations (10 or more cases per year), and a physician had to have done a minimum of 50 stenting procedures, 10 of which had to be in the carotid artery. This requirement was more rigorous than other previous studies, namely, the EVA-3S trial. Patients enrolled in the study had to have symptomatic carotid stenosis of >50% measured by NASCET criteria (or another noninvasive equivalent), and symptoms had to occur within 12 months prior to the patient's enrollment. Distal embolic protection was used in only 72% of patients.

The primary outcome measured in the first ICSS publication was a 3-year rate of fatal or disabling stroke in any vascular territory [18]. Between the time of randomization and 120-day post-intervention, the event rate for disabling stroke or death was 4.0% in the stenting group and 3.2% in the surgical group. The composite cardiovascular risk (stroke, myocardial infarction, or death) was 8.5% in patients who received a stent compared to 5.2% in the endarterectomy group ($P = 0.006$). Risks of stroke and overall all-cause death within the stenting group were also higher compared to the endarterectomy group. Cranial nerve palsies were significantly higher in the surgical group, and there were fewer hematomas in the stented patients. Overall, the initial data from ICSS suggested that carotid endarterectomy is a safer treatment option for patients with symptomatic carotid stenosis. At the time of their initial publications, the data from SPACE, EVA-3S, and ICSS all appeared to favor carotid endarterectomy over stenting, specifically because of the high perioperative risk associated with stenting. At the time of the ICSS publication, it was also recommended that endarterectomy remain treatment of choice given the more inferior outcomes linked to stenting.

The long-term data from ICSS [19] was consistent with most other long-term studies: in this study the number of fatal or disabling strokes and the overall 5-year cumulative risk of adverse outcome did not differ between stenting and endarterectomy. However, the ICSS did suggest that *any* stroke (including non-disabling strokes) was more frequent in the stenting population. Restenosis of at least 70% was not significantly different between the two groups. Subgroup analysis was performed in ICSS but not discussed at length because the study lacked the statistical power to draw appropriate conclusions.

2005: Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

The CREST trial is one of the most widely cited and discussed trials on intervention for carotid artery stenosis in recent years. This RCT, which began randomization in 2005 and completed enrollment in 2008, included 2502 patients with

either symptomatic or asymptomatic stenosis of varying degrees depending on the modality used to detect. Distal embolic protection was used in 96.1% of patients who underwent stenting. Initial results were published in 2010 [20], and a 10-year follow-up was reported in 2016 [21].

The initial study reported no significant difference in primary composite cardiovascular end point (stroke, myocardial infarction, or death) within the immediate periprocedural period or during the first 4-year postoperative period. There was a higher rate of stroke or death within 4 years of randomization among combined symptomatic and asymptomatic patients with carotid stenosis treated with stenting compared to endarterectomy (6.4% versus 4.7%, $P = 0.03$) with a difference only observed in the asymptomatic population but *not* when patients with symptomatic disease were separately examined (8.0% versus 6.4%, $P = 0.14$). Rates of myocardial infarction were higher in patients treated with endarterectomy (2.3% versus 1.1%, $P = 0.03$). While there was also no significant difference when comparing all symptomatic statuses ($P = 0.84$) or sex ($P = 0.34$) collectively, there were differences in subgroup analysis. A crossover age of 70 years was noted for patients undergoing stenting or endarterectomy, with patients younger than 70 years of age doing better with stenting and older patients doing better with endarterectomy. Patients with stenting also had far fewer rates of cranial nerve palsies compared to endarterectomy (0.3% versus 4.7%).

Radiographic Criteria Used for Randomization in CREST

At least one was required for enrollment [20].

- Symptomatic stenosis of at least 50% on angiography
- Symptomatic stenosis of 70% or more on ultrasonography
- Symptomatic stenosis of 70% or more on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasound was 50–69%
- Asymptomatic stenosis of at least 60% on angiography
- Asymptomatic stenosis of at least 70% on ultrasonography
- Asymptomatic stenosis of at least 80% on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasound was 50–69%

In the CREST long-term follow-up study, where the median follow-up was 7.4 years but up to 10 years, there was no significant difference in primary composite end points (stroke, myocardial infarction, or death) between the stenting and endarterectomy groups. When symptomatic patients were separately analyzed from asymptomatic patients, there was no statistical difference at outcomes up to 10 years. Other end points that were of importance were the lack of statistical significance in restenosis, as there was no difference observed in restenosis between the two patient populations. One of the major limitations, however, was the high number of patients lost to follow-up and was not included in this study (36% of patients initially randomized from the 2010 publication). The high loss was mainly from patients who did not consent to long-term follow-up, withdrew from the study, or expired.

The CREST trial and its long-term follow-up, however, illustrated some key findings. The study suggested that "symptomatic status is of relevance in the context of periprocedural risk but ceases to be of useful characterization of patients at 5 and 10 years after revascularization" highlighting the importance of correctly identifying the perioperative risk factors that may contribute to a poor outcome after treatment [21]. The CREST trial also illustrated the importance in applying appropriate patient selection to individual treatments.

2005: Asymptomatic Carotid Trial-1 (ACT-1)

The ACT-1 trial [22] was an RCT comparing CAS *with* distal embolic protection to CEA in patients <80 years of age with severe carotid artery stenosis. A total number of 1453 patients

were randomized in a 3:1 stent to surgery ratio from 2005 to 2013 and followed for a mean of 5 years post-procedure. Patients were included if they were <80 years of age with asymptomatic carotid stenosis and specifically *not* a high-risk patient. Patients were considered asymptomatic if they never had a stroke, TIA, or amaurosis fugax within the 180 days prior to enrollment.

All the patients had stenosis of the carotid bifurcation of 70–99% based on ultrasound or angiography *without* contralateral carotid stenosis (>60%). Distal embolization protection was used during the CAS in 97.6% of the patients. The primary outcome was assessed by either (1) a composite cardiovascular event of death, a major or minor stroke (either ipsilateral or contralateral), or a myocardial infarction during the first 30 days after the procedure *or* (2) an ipsilateral stroke during the first 365 days after the procedure.

Comparing the two treatment groups of asymptomatic patients with (1) significant carotid stenosis, (2) <80 years of age, and (3) not at high surgical risk, there was no difference in primary outcome at both 30 days and 1 year when comparing CAS with CEA (3.8% and 3.4%, respectively, $P = 0.01$ for non-inferiority). However, there was a greater number of cranial nerve injury during the periprocedural period in patients treated with endarterectomy (1.1% versus 0.1%, $P = 0.02$).

In a long-term follow-up, there was also no difference in rates of ipsilateral stroke from 30 days to 5 years between the two treatment groups. Five-year overall survival rates were also non-inferior in CAS (93.1%) compared to CEA (94.7%, $P = 0.44$); however, there was a higher rate of restenosis in patients treated with endarterectomy after 1 year post-procedure.

A few of the significant limitations identified by the authors of this chapter were a slightly high rate of patients lost to follow-up (over 10%) and a long period of study enrollment to complete the study (8 years); however, overall, this study highlighted some key points: in the younger and asymptomatic patient population, stenting was non-inferior to endarterectomy, as previously suggested by some of the findings from the trials above. This is likely due to the rather selective patient population that underwent stenting versus endarterectomy, a reflection of good practice in a randomized trial. Furthermore, there was a higher perioperative risk of cranial nerve injury in the surgical arm compared to the endovascular arm. There was also a higher rate of revascularization in the stenting group at 1 year (99.4%) compared to the surgical group (97.4%, $P = 0.005$).

2008: Asymptomatic Carotid Surgery Trial-2 (ACST-2)

The ACST-2 clinical trial is currently an ongoing study to assess asymptomatic patients with high-grade carotid artery stenosis randomized to either carotid artery stenting or endarterectomy. Randomization for the study began in 2008 [23] and has recently had interim results published for patients enrolled up to 2012. A total of 986 patients with asymptomatic stenosis (no ipsilateral carotid territory neurological symptoms for at least 6 months and no previous ipsilateral carotid procedure) with low surgical risk (appropriately medically managed up to the point of randomization with adequate time for recovery from any recent procedures or events and with an expected life-span of at least 5 years) were enrolled. Baseline characteristics and 30-day results were recently reported [24].

The study had a majority of patients with baseline ipsilateral carotid stenosis >70% (96% of patients) and no significant contralateral carotid disease in 63% (a carotid occlusion was present in 8% of patients). Initial 30-day results revealed that both patients who undergo stenting and endarterectomy have a 1.0% risk of major disabling stroke, fatal myocardial infarction, or death with a 2.9% risk for a non-disabling stroke.

The trial plans to report long-term results of this study after all patients randomized undergo a follow-up of 5 years.

Authors' Recommendations

When a physician considers treating carotid artery stenosis, a decision to intervene with either stenting or endarterectomy should be based on the current clinical evidence along with provider experience. However, as seen above, the timeline and extensive history of these clinical trials can make decisions quite difficult and confusing, given the convoluted and extensive literature that currently exists. This summary is intended to weave together the past 20+ years of clinical evidence with modern medical practice.

Some general considerations need to be addressed about the abovementioned trials. None of the randomized trials published to date have examined the role of intense medical therapy compared to revascularization *with* intense medical therapy. However, the CREST-2 trial is currently underway to examine the role of intense medical therapy versus revascularization with modern techniques (i.e., endarterectomy or stenting with distal embolic protection). This study is currently ongoing and its protocol was recently published [25].

All of the trials illustrated the importance of identifying perioperative risk to individual patients. The CREST trial highlighted the importance of age as a consideration for intervention: older patients (above 70 years of age) did better with endarterectomy, whereas younger patients did better with stenting [20]. However, this information should be weighed with a patient's perioperative risk factors, as patients undergoing endarterectomy had a higher risk of myocardial infarction, whereas patients undergoing stenting had a higher risk of stroke. These potential perioperative complications should also be delicately weighed in patients with an extensive cardiac history or vasculopathy. The rates of stroke or death among patients after stenting and endarterectomy were lower when compared to the SPACE, EVA-3S, and ICSS trials. However, it is important to note the advancements that were being made in patient safety, selection, and physician training for the procedure during the time of these trials. "High surgical risk" itself should not preclude a patient from stenting. Yadav et al., in the SAPPHIRE trial, noted some of the highest-risk candidates for stenting "resulted in rates of complications for all major adverse events (death, stroke or myocardial infarction) that were statistically equivalent to or lower than those among patients who underwent endarterectomy both in the overall study population and in the subgroups" [13]. Patients with stenting also had lower cranial nerve palsy rates and higher target vessel revascularization compared to endarterectomy. Finally, both SPACE and ICSS had a rather low use of distal embolic protection during stenting, thereby certainly potentially increasing the risk of ischemic stroke following vessel manipulation during endovascular treatment.

Given the information from clinical trials (particularly later investigatons) combined with clinical experience, it is the suggestion of the authors for the following:

Appropriate choices for CEA:

1. Anatomically difficult to access, i.e., C2 vertebral body level or higher
2. Contralateral carotid occlusion
3. Isolated hemispheres, i.e., an absence of collateral circulation from the contralateral or posterior cerebral circulation
4. Contralateral cranial nerve palsy
5. Ipsilateral restenosis, previous irradiation, or major surgery
6. Age <70

Appropriate choices for CAS:

1. Anatomically accessible lesions
2. Type III arch, severe atherosclerotic disease aortic arch
3. Age 70–80

Consideration About Clinical Equipoise

Consideration of the patient, their age, medical comorbidity, and the natural history of atherosclerotic disease and stroke is important. Patients over the age of 80 with incidental asymptomatic carotid

artery disease may not benefit from intervention whether it is CEA or CAS. The 5-year nontarget vessel rate versus the risk of CEA or CAS in this cohort is essentially the same and approaches 20%. Thus, a strong argument can be made to only treat *symptomatic* target vessels which have failed best medical therapy. We are sworn to "do no harm," and subjecting patients with asymptomatic disease to significant periprocedural morbidity in the absence of compelling data to suggest significant benefit should be avoided.

Review Questions

1. Which of the following are false: the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial:
   A. Was a multicenter randomized control trial with a generalized patient population
   B. Was initiated at a time when carotid stents were commercially available
   C. Included both symptomatic and asymptomatic patients with carotid artery stenosis
   D. Used stenting as second-line treatment for patients randomized to endovascular therapy, only after they failed attempted treatment with balloon angioplasty
   E. Did not exclude patients with contralateral carotid artery occlusions

   Answer: B: Experimental carotid stents were only in development in 1992 when the trial initiated. The first FDA-approved carotid stent was not released for commercial use until 1994.

2. The International Carotid Stenting Study (ICSS) addressed limitations and safety concerns by:
   A. Certifying that centers enrolled in the study had surgeons who performed at least 50 carotid operations (10 or more cases per year).
   B. Requiring that interventionalists had performed a minimum or 50 stenting procedures, 10 of which had to be in the carotid artery.
   C. Patients had to have symptomatic carotid stenosis >50% measured by NASCET criteria or another noninvasive equivalent.
   D. All of the above are true.

   Answer: D

3. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST):
   A. Included both symptomatic and asymptomatic patients with distal embolic protection in over 95% of patients randomized to endovascular treatment.
   B. Demonstrated a higher rate of myocardial infarction in patients treated with endarterectomy during the periprocedural period.
   C. Revealed patients had fewer cranial nerve palsies with endovascular treatment compared to endarterectomy.
   D. Demonstrated there was no significant difference in stroke, myocardial infarction, or death between stenting and endarterectomy at a 10-year follow-up.
   E. All of the above are true.

   Answer: D

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