Chapter 5

# Update on Carotid Revascularization: Evidence from Large Clinical Trials

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Additional information is available at the end of the chapter

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## 1. Introduction

In the era of evidence-based medicine, doctors rely on clinical trials to guide their decisions. The best method of treating carotid stenosis is still debatable after six decades from the first carotid surgical revascularization performed. Despite the conduct and publication of dozens of trials on carotid revascularization, the truth remains shaggy. The interpretation of these trials is influenced by the design, inclusion criteria, credentialing of the operators and even their specialties. We will try to discuss the trials of carotid endarterectomy and carotid artery stenting trying to reach a conclusion of where is the truth regarding carotid revascularization. We will discuss the trials of CEA versus medical therapy, then the initials registries of CAS, then the trials that compared CEA against CAS, we will elaborate on the two techniques in peculiar situations and finally we will give a short notice about ongoing trials and future directions.

## 2. Carotid endarterectomy

Carotid endarterectomy (CEA) started in the early 1950s and is now the most commonly performed peripheral arterial surgery in the USA. The aim of CEA is to remove the entire atherosclerotic plaque from the carotid bifurcation en bloc leaving a rough surface to be endothelialized over the following weeks. Most procedures are performed under general anesthesia. However, local anesthesia and mild intravenous sedation are sometimes successful and can allow monitoring of neurologic functions during surgery. Local anesthesia also should

be considered in the hemodynamically unstable patient or in situations where general anesthesia may be too risky.

## 3. The early years of carotid endarterectomy

Early attempts at reconstruction of the carotid artery at the bifurcation were carried out by Carrea, Molins, and Murphy in 1951 and subsequently by Eastcott, Pickering, and Robb in 1954. In 1965 DeBakey reported that he performed the first CEA in 1953. Although not published, there is controversy about this claim.[1] Subsequently, a group of neurologists, vascular surgeons, and neurological surgeons performed a study on the "new technique" comparing it with medical therapy. Interestingly, the surgical mortality was surgical mortality of 4.5% in 2400 operations. This early study the study delineated careful methods of measuring common carotid and internal carotid and vertebral artery stenosis. The study also determined the upper level of ready surgical accessibility as well as the contraindications to the operation. [2] Additionally, myocardial infarction was identified as the principal cause of late mortality in those patients undergoing successful surgical treatment. Providing the patients survived the surgical therapy, the occurrence of new stroke was 4% in the surgical group. However, the superiority of surgery over medical therapy was not definitive. Despite criticism, CEA became extremely popular. It became the most commonly performed peripheral arterial procedure in the United States, reaching a peak of 107,000 operations in nonveteran hospitals in the United States in 1985.[1] At that time, however, neurologists were skeptical. Their fears were supported by reports that the rates of death or stroke from CEA were 10%. Endarterectomy turned from a great procedure to an operation "that has escaped critical analysis to be let loose on an unsuspecting public"![3] These concerns stressed the need to perform well-designed randomized trials under independent neurological audit. Those trials established the role of CEA versus medical treatment for stroke prevention.

## 4. The landmark trials of CEA versus medical therapy; NASCET, ACAS and ECST

The role of CEA in prevention of stroke was established based on large randomized trials performed mostly in the early 1990s.

This meta-analysis of ECST and NASCET trials showed that surgery increased the 5-year risk of ipsilateral ischemic stroke in patients with <30% stenosis (absolute risk reduction of –2.2%, P = 0.05), had no effect in patients with 30-49% stenosis (absolute risk reduction of 3.2%, P = 0.6), was of marginal benefit in those with 50% to 69% stenosis (absolute risk reduction of 4.6%, P =0.04), and was highly beneficial in those with ≥70% stenosis without near-occlusion (absolute risk reduction of 16.0%, P < 0.001). There was a trend toward benefit from surgery in patients with near occlusion at 2 years' follow up (absolute risk

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| | No of patients in specified trial | Medical risk (%) at 2 years | Surgical risk (%) at 2 years | Risk difference (%) | Relative risk reduction (%) | No need to treat* | Perioperative stroke and death rate (%) |
|---|---|---|---|---|---|---|---|
| **Symptomatic patients** | | | | | | | |
| 70-99% NASCET | 659 | 21.4 | 8.6 | 12.8 | 60 | 8 | 5.8 |
| 70-99%ECST** | 501 | 19.9 | 7.0 | 12.9 | 65 | 8 | 5.6 |
| 50-69% NASCET | 858 | 14.2 | 9.2 | 5.0 | 35 | 20 | 7.1 |
| 50-69% ECST** | 684 | 9.7 | 11.1 | -1.4 | -14 | - | 9.8 |
| <50%NASCET | 1368 | 11.6 | 10.1 | 1.5 | 13 | 67 | 6.5 |
| <50% ECST** | 1882 | 4.3 | 9.5 | -5.2 | -109 | - | 6.1 |
| **Asymptomatic patients** | | | | | | | |
| ≥50%, VA, men only | 444 | 7.7† | 5.6† | 2.1 | 27 | 48 | 4.4 |
| ACAS | 1662 | 5.0 | 3.8‡ (actual) | 1.2 | 24 | 83 | 2.6 |
| ACE | 2848 | 5.0§ **(assumed)** | 5.8 | -0.8 | - | - | 4.6 |

ACE=aspirin and carotid endarterectomy trial.

*NNT = Number needed to treat by CEA to prevent one stroke in 2 years after the procedure, compared with medical treatment alone.

**By NASCET measurement.

†Extrapolated from results.

‡Assigning a perioperative risk of 2.6% based on 724 of 825 patients who actually received endarterectomy in the surgical arm of ACAS, and utilizing the 0.6% risk of stroke in each of the two years after endarterectomy. The same

1.2% risk is assumed for the ACE patients and VA patients.

§No medical arm—assumed from ACAS data.

**Table 1.** Number needed to treat by endarterectomy to prevent one stroke in 2 years in patients with carotid stenosis

reduction of 5.6%, P = 0.19), but no benefit at 5 years (absolute risk reduction of –1.7%, P =0.9). Both ACST and ACAS studies showed benefit from CEA in >60% asymptomatic stenosis. However, neither showed increasing benefit from surgery with increasing degree

of stenosis. This observation was assumed to be attributable to a lack of statistical power of the trials. The benefit from CEA relates to the complication rates. Reported benefits were predicated on operative risks of stroke or death of 7.5% in the ECST and 6.5% in the NASCET. If the disabling stroke and death rates exceed this by as little as 2%, the benefit from CEA disappears.[4]

## 5. The spread of CEA among vascular surgeons worldwide

There have been a dramatic fall and a rise in the rates of carotid endarterectomy in both the United States and Canada, which correlate with the publication of first unfavorable and then favorable clinical studies. The absence of selective referral of patients to centers with the lowest mortality rates raises questions about whether the benefits of carotid endarterectomy in the general population are similar to those demonstrated in the clinical trials. Rates of carotid endarterectomy fell in all three regions from 1984 to 1989 (from 126 to 66 per 100,000 adults 40 years of age or older in California, from 65 to 40 per 100,000 in New York, and from 40 to 15 per 100,000 in Ontario), after the publication of studies demonstrating that the rates of complications of carotid endarterectomy were unacceptably high. However, the clinical trials of the 1990s, which showed benefit from carotid endarterectomy, were associated with a dramatic resurgence in the rates of the procedure from 1989 to 1995 (from 66 to 99 per 100,000 in California, from 40 to 96 per 100,000 in New York, and from 15 to 38 per 100,000 in Ontario). These increased rates were not associated with proportionally greater numbers of referrals of patients to hospitals with low mortality rates.[5]

## 6. The limitations of carotid endarterectomy

This NASCE, ACAS and ESCT trial as well as the spread of carotid endarterectomy worldwide unveiled the problems and limitations inherent to the procedure. It became clear that the coexistence of cardiac co-morbidity is a powerful predictor of mortality and that myocardial infarction can be the most dreaded complication, even more than stroke. This was evident, despite the fact that patients with myocardial infarction in the prior six months, congestive heart failure and patients scheduled for coronary revascularization were excluded from the large CEA trials.[6] Other limitations of the procedure were more located to the local environment in the neck as prior endarterectomy, prior neck dissection or radiation, cranial nerve palsies and inaccessible high/low carotid bifurcations. The presence of contra-lateral carotid occlusion also posed a problem during cross clamping that increased the risk of CEA.

## 7. Carotid angioplasty

While carotid endarterectomy was growing to maturity, anther contender was born. After the fundamental work in endovascular therapy by Charles Dotter and Andreas Grüntzig, it was

inconceivable at the end of the 1970s to apply their work to arteries supplying the brain. Klaus Mathias chose to ignore this strict limit and was able to successfully perform angioplasty of atherosclerotic stenoses at the carotid bifurcation in 1980.[7] The technique evolved slowly from simple balloon dilatation to involve stenting, used first by Théron in 1990 and then widespread use of cerebral protection devices.

## 8. The initial case-series and registries of carotid stenting

| Author | No of Patients | No of stents | Asymptomatic stenosis (%) | Technical success rates (%) | 30-day Morbidity or Mortality (%) | No of Deaths/ Mortality Rate | Major Stroke Rate (%) | Minor Stroke Rate (%) | Restenosis rate |
|---|---|---|---|---|---|---|---|---|---|
| Roubin | 146 | 210 | 37 | 99 | NS | 1 / 0.65 | 1.3 | 4.6 | 6 mo, ,5%; 12 mo, ID |
| Theron | 69 | 69 | NS | 100 | NS | … | … | … | 4% (time not specified) |
| Diethrich | 110 | 129 | 72 | 99.1 | 7.3 | 2 / 1.8% | 2 | 4.5 | 6 mo, NS; 12 mo, NS |
| Yadav | 107 | 189 | 36 | 100 | 7.9 | 1 / 0.9% | 1.9 | 6.5 | 6 mo, 4.9%; 12 mo, NS |
| Vozzi | 22 | 19 | 55 | 96 | NS | 1 / 4.5% | 4.5 | 4.5 | 6 mo, NS; 12 mo, ID |
| Criado | 33 | NS | 27 | 100 | NS | 0 | 0 | 0 | 3% (mean 8-mo follow-up) |
| Wholey | 108 | NS | 44 | 95 | NS | 2/ 1.9% | 1.8 | 1.8 | 1% (mean 6-mo follow-up) |
| Henry | 163 | 178 | 35 | 99.4 | NS | 0/ .. | 1.8 | 1.2 | 6 mo, 2.3%; 12 mo, ID |
| Teitelbaum | 22 | 31 | 32 | 96.2 | 27.3 | 1 / 4.5% | 13.6 | 9.0 | 6 mo, 14.3%; 12 mo, NS |
| Waigand | 50 | 56 | 72 | 100 | 2 | 1 / 2% | 2 | 2 | 8.7% (mean 8-mo follow-up |
| Bergeron | 99 | 99 | 42 | 97 | 2.0 | 0/… | 0 | 1 | 4.2% (mean 13-mo follow-up) |

**Table 2.** Carotid Stent Series [8]

## 9. Results of multicenter registries

The Global Carotid Artery Stent Registry: In 1998, Wholey et al collected data from major interventional centers worldwide as well as from peer-reviewed journals. The total number of

procedures that have been performed till that date included 2,048 cases, with a technical success of 98.6%. The stroke rate was 3.08%. The 30-day post-procedure mortality rate was 1.37%. The registry was updated in 2003. The total number of stent procedures performed then became 12392 with a technical success rate of 98.9%. Overall, there was TIA rate of 3.07%, minor strokes of 2.14%, major strokes of 1.20%, and procedure-related deaths of 0.64%. There were 6753 cases done without protection and which incurred a 5.29% rate of strokes and procedure-related deaths. In the 4221 cases with cerebral protection, there was a 2.23% rate of strokes and procedure-related deaths. The rate of neurologic events was 1.2%, 1.3%, and 1.7% at 1, 2, and 3 years, respectively.[9]

In the following years, several registries that were supported by the device industry were reported. These registries included patients who are considered high risk for CEA because one or more of the following features:

1. Class-III/IV congestive heart failure
2. Left ventricular ejection fraction<30%
3. Open heart surgery within 6 weeks
4. Recent myocardial infarction (>24 h <30 d)
5. Unstable angina: class III/IV
6. Concurrent requirement for coronary revascularization
7. Severe pulmonary disease
8. Contralateral carotid occlusion
9. Previous radiation to head/neck
10. Previous CEA
11. Age >80 y
12. Surgically inaccessible lesions

| Acronym | Sponsor | Stent | Protection device | Result; 30-day death/ stroke/MI rate |
|---|---|---|---|---|
| BEACH | Boston Scientific | WallStent | Ex filter | 5.4% |
| CABERNET | Boston Scientific/ Endotex | Nex Stent | EPI Filter | 3.9% |
| ARCHER | Guidant | AccuLink | AccuNet | 7.8% |
| MAVErIC | Medtronic | Exponent | PercuSurge | 4% |
| PASCAL | Medtronic | Exponent | Any approved | 8% |
| SECuRITY | Abott | Xact | Emboshield | 7.2% |

**Table 3.** Carotid stent industry-supported high-risk registries

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## 10. Comparisons of stenting versus endarterectomy

Markus et al studied the effect of carotid PTA compared to CEA on cerebral hemodynamics of symptomatic stenoses as reflected by $CO_2$ reactivity. After PTA there was a significant improvement in ipsilateral hypercapnic reactivity. There was a similar improvement in ipsilateral hypercapnic reactivity after CEA.[10]

Golledge et al performed a systematic comparison of the 30-day outcome of angioplasty with or without stenting and CEA for symptomatic carotid disease reported in single-center studies, published between 1990 and 1999. All the results were in favor of CEA. Mortality within 30 days of angioplasty was 0.8% compared with 1.2% after CEA (P=0.6). The stroke rate was 7.1% for angioplasty and 3.3% for CEA (P<0.001).[11]

## 11. The UK Leicester halted trial

The most outstanding negative trial of carotid angioplasty was form Leicester Royal Infirmary. The study consisted of 23 patients with focal carotid territory symptoms and severe ICA stenosis (>70%) who were randomized to either CEA or CAS. However, only 17 had received their allocated treatment before trial suspension. All 10 CEA operations proceeded without complication, but 5 of the 7 (71.4%) patients who underwent CAS had a stroke, 3 of which were disabling at 30 days. The Data Monitoring Committee invoked the stopping rule and the trial was suspended. The investigators and the Ethics Committee subsequently decided that the trial should not be restarted even in an amended format because of problems with informed consent.[12, 13]

The CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study), was the first randomized trial of CEA versus CAS. 504 patients were randomized from 22 centers in between 1992 and 1997. The majority of patients had recently symptomatic lesions. Only 26% of the angioplasty patients received a stent. The rates of major outcome events within 30 days of first treatment did not differ significantly between endovascular treatment and surgery (6.4% vs. 5.9%, respectively, for disabling stroke or death; 10.0% vs. 9.9% for any stroke lasting more than 7 days, or death). (Figure 21) At 1 year after treatment, restenosis was more usual after endovascular treatment (14%vs. 4%, p<0.001). Complications of cranial nerve injury and myocardial ischemia were only reported in the surgical group. The trial described rates of death and disabling stroke after 3 years of 14.3% in the endovascular group and 14.2% in the surgical group.[14]

Crawley et al compared cerebral hemodynamics and microembolization during CAS versus CEA using TCD. The period during which the ICA was occluded by PTA balloon or by clamp during CEA was timed. Ischemic time was defined as the period during which mean MCA velocity fell to a third or less of baseline. CEA resulted in significantly longer occlusion time and ischemic time than PTA. There were significantly more microembolic signals during PTA than during CEA. There was no correlation between any of the parameters measured and periprocedural stroke.[15]

The SAPPHIRE trial (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) randomized patients with co-morbid conditions that represented exclusion criteria from the previous major randomized trials of CEA. The rationale was that patients with these co-morbid conditions appear to represent the majority of patients undergoing CEA, and concerns have been raised about the generalizability of the CEA trial results in view of the exclusion of those patients in major CEA trials. SAPPHIRE was designed to test "non-inferiority" of CAS versus CEA in the high-risk population with >50% symptomatic or >80% asymptomatic stenosis.[16, 17]

All carotid stenting procedures were done with the Angioguard protection device. The trial was conducted at 29 US centers which all had mean complication rate less than 3% for CEA and 4% for CAS. All patients were seen by a team made up of a neurologist, a surgeon, and an interventionist. If the surgeon felt that he or she could not operate, and the interventionist felt that intervention was possible, the patient was entered into a stent registry. Conversely, if the interventionist did not feel that he or she could perform the intervention, and the surgeon felt that surgery was possible, the patient was entered into a surgical registry. 723 patients were enrolled initially. Consensus was achieved in 307 patients who were randomized to either stenting (n = 156) or CEA (n = 151). The stent registry consisted of 409 patients, and the surgical registry included seven. Individual endpoints of death, stroke, and MI at 30 days were lower in patients randomized to stenting. The combined endpoint of death/stroke/MI was statistically significantly lower in patients randomized to stenting vs. CEA. The death, stroke or myocardial infarction rate was 11.9% in the CAS group and 19.9 % in the CEA group after 1-year. The SAPPHIRE results indicated that CAS has become a promising alternative to CEA, at least "not inferior".

## 12. SAPPHIRE long-term results

At 3 years, data were available for 260 patients (77.8%), including 85.6% of patients in the stenting group and 70.1% of those in the endarterectomy group. There was no significant difference could be shown in long-term outcomes between patients who underwent carotid artery stenting with an emboli-protection device and those who underwent endarterectomy The prespecified major secondary end point occurred in 41 patients in the stenting group (cumulative incidence, 24.6%; Kaplan–Meier estimate, 26.2%) and 45 patients in the endarterectomy group (cumulative incidence, 26.9%; Kaplan–Meier estimate, 30.3%) (absolute difference in cumulative incidence for the stenting group, −2.3%; 95% confidence interval, −11.8 to 7.0). There were 15 strokes in each of the two groups, of which 11 in the stenting group and 9 in the endarterectomy group were ipsilateral.[18]

The SAPPHIRE data are specific to patients who are at high surgical risk, and they provide no insight into outcomes of treatment of a carotid artery stenosis in patients at low-to-moderate risk. On the basis of the similar long-term outcomes among high-risk patients in the two treatment groups, it may be tempting to infer that endarterectomy is preferable for lower-risk patients.

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## 13. The CARESS trial

Carotid REvascularization with Stenting Systems was a prospective, multicenter non-randomized industry-sponsored trial compared standard CEA to carotid stenting in patients with symptomatic (≥50%) and asymptomatic (≥75%) carotid stenosis. There was no significant difference in the 30-day combined all-cause mortality and stroke rate between CEA (2%) and CAS (2%). There was no significant difference in the secondary endpoint of combined 30-day all-cause mortality, stroke, and myocardial infarction between CEA and CAS.[19]

Following the publication of the SAPPHIRE and the CARESS trials, carotid artery stenting rocketed. There was a general felling that carotid artery stenting will prevail and become the preferred choice for carotid revascularization. However, the following randomized trials did not come in favor of carotid stenting.

## 14. SPACE

Stent-protected angioplasty versus carotid endarterectomy in symptomatic patients included 1183 patients with symptomatic carotid-artery stenosis. Patients were randomly assigned within 180 days of transient ischemic attack or moderate stroke (modified Rankin scale score of < or =3) to carotid-artery stenting (n=605) or carotid endarterectomy (n=595). The primary endpoint of this hospital-based study was ipsilateral ischemic stroke or death from time of randomization to 30 days after the procedure. The non-inferiority margin was defined as less than 2.5% on the basis of an expected event rate of 5%. Analyses were on an intention-to-treat basis. The rate of death or ipsilateral ischemic stroke from randomization to 30 days after the procedure was 6.84% with carotid-artery stenting and 6.34% with carotid endarterectomy (absolute difference 0.51%, 90% CI -1.89% to 2.91%). The one-sided p value for non-inferiority is 0.09. SPACE failed to prove non-inferiority of carotid-artery stenting compared with carotid endarterectomy for the periprocedural complication rate.[20]

Lon term data showed that in both the intention-to-treat and per-protocol analyses the Kaplan-Meier estimates of ipsilateral ischemic strokes up to 2 years after the procedure and any periprocedural stroke or death do not differ between the carotid artery stenting and the carotid endarterectomy groups (intention to treat 9 5% vs. 8 8%; hazard ratio (HR) 1 10, 95%CI 0 75 to 1 61; log-rank p=0 62; per protocol 9 4% vs. 7 8%; HR 1 23, 95%CI 0 82 to 1 83; log-rank p=0 31). In both the intention-to-treat and per-protocol populations, recurrent stenosis of 70% or more is significantly more frequent in the carotid artery stenting group compared with the carotid endarterectomy group, with a life-table estimate of 10 7% versus 4 6% (p=0 0009) and 11 1% versus 4 6% (p=0 0007), respectively.[21]

## 15. EVA-3S

262 patients were randomly assigned to endarterectomy and 265 to stenting. The cumulative probability of periprocedural stroke or death and non-procedural ipsilateral stroke after 4

years of follow-up was higher with stenting than with endarterectomy (11 1% vs. 6 2%, hazard ratio [HR] 1 97, 95% CI 1 06–3 67; p=0 03). The HR for periprocedural disabling stroke or death and non-procedural fatal or disabling ipsilateral stroke was 2 00 (0 75–5 33; p=0 17). A hazard function analysis showed the 4-year differences in the cumulative probabilities of outcomes between stenting and endarterectomy were largely accounted for by the higher periprocedural (within 30 days of the procedure) risk of stenting compared with endarterectomy. After the periprocedural period, the risk of ipsilateral stroke was low and similar in both treatment groups. For any stroke or periprocedural death, the HR was 1 77 (1 03–3 02; p=0 04). For any stroke or death, the HR was 1 39 (0 96–2 00; p=0 08). The results of this study suggest that carotid stenting is as effective as carotid endarterectomy for middle-term prevention of ipsilateral stroke, but the safety of carotid stenting needs to be improved before it can be used as an alternative to carotid endarterectomy in patients with symptomatic carotid stenosis.[22]

In the same study, the rate of carotid restenosis of ≥50% or occlusion was significantly higher after CAS (12.5%) than after CEA (5.0%; time ratio, 0.16; 95% CI, 0.03–0.76; *P*=0.02). The rates of severe restenosis of ≥70% or occlusion were low and did not differ significantly between the 2 groups (3-year rates are 3.3% in the CAS group and 2.8% in the CEA group). Age at baseline was the only vascular risk factor significantly associated with carotid restenosis. Our study could not detect any effect of carotid restenosis on ipsilateral stroke.[23]

It was notable that the risk of ipsilateral stroke or death increased significantly with age in the CAS group (p=0 001) but not in the CEA group (p=0 534). Classification and regression tree analysis showed that the age that gave the greatest separation between high-risk and low-risk populations who had CAS was 68 years: the rate of primary outcome events was 2 7% (8/293) in patients who were 68 years old or younger and 10 8% (34/314) in older patients.[24]

In the first 120 days after randomization (ITT analysis), the primary outcome event occurred in 153/1725 patients in the CAS group (8.9%) compared with 99/1708 patients in the CEA group (5.8%, risk ratio [RR] 1.53, 95% confidence interval [CI] 1.20–1.95, p = 0.0006; absolute risk difference 3.2, 95% CI 1.4–4.9). Age was the only subgroup variable which significantly modified the treatment effect: in patients <70 years old (the median age), the 120-day stroke or death risk was 5.8% in CAS and 5.7% in CEA (RR 1.00, 0.68–1.47); in patients 70 years or older, there was an estimated two-fold increase in risk with CAS over CEA (12.0% vs. 5.9%, RR 2.04, 1.48–2.82, interaction p = 0.0053).[25]

Endarterectomy was safer in the short-term than stenting, because of an increased risk of stroke associated with stenting in patients over the age of 70 years. Stenting should be avoided in older patients, but may be as safe as endarterectomy in younger patients. Determination of the efficacy and ultimate balance between the two procedures requires further data on long-term stroke recurrence.[25]

## 16. ICSS study

The incidence of stroke, death, or procedural myocardial infarction was 8.5% in the stenting group compared with 5.2% in the endarterectomy group (72 vs. 44 events; HR 1.69, 1.16-2.45,

p=0.006), Risks of any stroke (65 vs. 35 events; HR 1.92, 1.27-2.89) and all-cause death (19 vs. seven events; HR 2.76, 1.16-6.56) were higher in the stenting group than in the endarterectomy group. Three procedural myocardial infarctions were recorded in the stenting group, all of which were fatal, compared with four, all non-fatal, in the endarterectomy group.[26]

At 1 month, there were changes on fluid-attenuated inversion recovery sequences in 28 (33%) of 86 patients in the stenting group and six (8%) of 75 in the endarterectomy group (adjusted OR 5 93, 95% CI 2 25–15 62; p=0 0003). In patients treated at a center with a policy of using cerebral protection devices, 37 (73%) of 51 in the stenting group and eight (17%) of 46 in the endarterectomy group had at least one new DWI lesion on post-treatment scans (adjusted OR 12 20, 95% CI 4 53–32 84), whereas in those treated at a center with a policy of unprotected stenting, 25 (34%) of 73 patients in the stenting group and ten (16%) of 61 in the endarterectomy group had new lesions on DWI (adjusted OR 2 70, 1 16–6 24; interaction p=0 019).[27]

These discordant results may be explained by the fact that the EVA-3S and SPACE studies differ from ours in numerous ways, including in the selection criteria (e.g., the EVA-3S and SPACE trials included neither patients with a high surgical risk nor asymptomatic patients), the rate of use of specific emboli-protection devices (in 92% of cases in the EVA-3S trial and 27% in the SPACE trial), and the experience level of the physician who placed the stent (in the EVA-3S trial, stents could be placed by physicians who had performed as few as five previous carotid-stent procedures or, if working under the direction of a tutor, no previous procedures).[18]

The results of the previous studies were a major setback for stenting. They created a general belief among practicing physicians and neurologists that carotid artery stenting has only a limited role in the prevention of stroke. This set the stage ready for a more comprehensive larger trial trying to reach the truth.

## 17. CREST trial

The CREST (Carotid Revascularization Endarterectomy vs. Stent Trial) was a multicenter trial supported by the National institute of health. The study includes symptomatic (>50% stenosis) and asymptomatic (>70% stenosis) patients. The CREST was probably the largest study on carotid revascularization and had the best design. Centers were required to have a team consisting of a neurologist, an interventionist, a surgeon, and a research coordinator. Patients could not be randomly assigned to a treatment group until the operators performing carotid artery stenting and carotid endarterectomy had been certified. Certification was achieved by 477 surgeons, whose clinical results were audited by means of a validated selection process documenting that they performed more than 12 procedures per year and that the rates of complications and death were less than 3% among asymptomatic patients and less than 5% among symptomatic patients. The 224 interventionists were certified after satisfactory evaluation of their endovascular experience, carotid-stenting results, participation in hands-on training, and participation in a lead-in phase of training.[28]

There was no differential treatment effect with regard to the primary end point according to symptomatic status (P = 0.84) or sex (P = 0.34). The 4-year rate of stroke or death was 6.4% with stenting and 4.7% with endarterectomy (hazard ratio, 1.50; P = 0.03); the rates among symptomatic patients were 8.0% and 6.4% (hazard ratio, 1.37; P = 0.14), and the rates among asymptomatic patients were 4.5% and 2.7% (hazard ratio, 1.86; P = 0.07), respectively. Periprocedural rates of individual components of the end points differed between the stenting group and the endarterectomy group: for death (0.7% vs. 0.3%, P = 0.18), for stroke (4.1% vs. 2.3%, P = 0.01), and for myocardial infarction (1.1% vs. 2.3%, P = 0.03). After this period, the incidences of ipsilateral stroke with stenting and with endarterectomy were similarly low (2.0% and 2.4%, respectively; P = 0.85).[28]

The results of the CREST were "satisfying" for both surgeons and interventionists. Surgeons were glad to prove that CEA resulted in lower stroke rates in the short term and the long term. Interventionists were reassured that the primary end-point was similar in the two methods.

Restenosis and occlusion were infrequent and rates were similar up to 2 years after carotid endarterectomy and carotid artery stenting. Subsets of patients could benefit from early and frequent monitoring after revascularization.[29]

CAS was associated with better health-related quality of life HRQOL during the early recovery period as compared with CEA-particularly with regard to physical limitations and pain-but these differences diminish over time and are not evident after 1 year. Although CAS and CEA are associated with similar overall quality of life at 1 year, event-specific analyses confirm that stroke has a greater and more sustained impact on HRQOL than MI.[30]

The MI rates were slightly lower after CAS (1.3% vs. 2.6%; P =.24). In performing CAS, vascular surgeons had outcomes for the periprocedural primary end point comparable to the outcomes of all interventionists (HR, 0.99; 95% CI, 0.50-2.00) after adjusting for age, sex, and symptomatic status. Vascular surgeons also had similar results after CEA for the periprocedural primary end point compared with other surgeons (HR, 0.73; 95% CI, 0.42-1.27).[31]

## 18. Carotid endarterectomy and stenting in specific situations

### 18.1. Restenosis after carotid stenting

The restenosis rate after carotid stenting is remarkably low at 2.3-10% compared to other endovascular interventions. Although self-expanding carotid stents generate considerable neointimal hyperplasia, the process is balanced by marked late stent enlargement. Small stent dimensions immediately post-procedure were associated with a higher risk of restenosis.[32] In the 2003 global carotid stent registry, restenosis rates have been 2.7%, 2.6%, and 2.4% at 1, 2, and 3 years, respectively.[9] A retrospective, single-center review was conducted of 399 carotid stent procedures in 363 patients over 9 years, with a mean follow-up of 24 months (range 6-99 months). Overall, restenosis occurred in 15 patients (3.8%). However, the restenosis occurred in 7 of 35 (20%) patients who had previous neck radiation, 6 of 57 (10.5%) patients who had previous CEA, and 2 of 9 (22%) patients who previously had both CEA and neck

radiation. The only analyzed variables that were significantly associated with an increased risk of restenosis were previous CEA (OR 4.28, P = 0.008) or XRT (OR 11.3, P <or=<or= 0.0001).[33] In another study, among 215 CAS procedures that had clinical and serial carotid duplex ultrasound investigations, restenosis was detected in 6.1% of patients. Contralateral carotid occlusion (OR 10.11, 95% CI 2.06-49.63, p = 0.004), carotid endarterectomy (CEA) restenosis (OR 8.87, 95% CI 1.68-46.84, p = 0.010) and postprocedural carotid duplex ultrasound with a PSV >/=120 cm/s (OR 6.33, 95% CI 1.27-31.44, p = 0.024) were independent predictors of stent restenosis.[34] Most restenoses occur within 6 to 12 months after the intervention. Usually they are located either in the mid or at the distal end of the stent. Restenoses are often overestimated by ultrasound compared to angiography. Most of restenoses can be treated by balloon angioplasty. Drug-eluting balloons can be a promising modality[35] and only rarely, stent removal and eversion endarterectomy will be required.[36]

### 18.2. Restenosis after carotid endarterectomy

The incidence ranges from 1.2% to 23.9% depending on the operative technique. The highest rates of restenosis, 21.4%, after CEA came with direct suture and the lowest rate 3.9% were after patch angioplasty only Long-term risk of recurrence is about 1% per year. The risk is highest in the first few years after CEA and is very low later.[37]. Most of restenoses are asymptomatic and only 1.2-3.6% require re-intervention.[38]

The type of operative technique for reoperations depends on the cause of the recurrent disease. Myointimal hyperplasia has a smooth luminal surface and appears to be associated with a low potential for embolization therefore simple patching may be all that is necessary. By contrast, the soft nature of the plaque in recurrent atherosclerosis, which appears later, has a greater potential for embolization therefore repeat CEA with carotid patch angioplasty is preferable. AbuRahma et al showed the 30-day perioperative stroke and transient ischemic attack rates for reoperation and primary CEA were 4.8% versus 0.8% (P=0.015) and 4% versus 1.1%, respectively. There was an increase in the number of transient cranial nerve injuries in the reoperation group compared with the primary CEA group (15.3% versus 4.9%).[39]

CAS for restenosis after CEA has a complication rate lower than primary CAS. The time interval between CEA and CAS did not influence micro embolic load.[40] Statistical analysis demonstrated that post-CEA restenosis was the most important predictive factor for the development of in-stent restenosis after CAS. This review of our 10-year experience confirms that patients who develop restenosis after CEA are also prone to developing in-stent restenosis after CAS.[41]

### 18.3. Carotid stenosis in patients requiring bypass cardiac surgery

Patients who have concomitant severe carotid and coronary artery disease pose a serious dilemma. Stroke remains a major non-cardiac complication after CABG and myocardial infarction is the major non-neurological cause of early and late morbidity after CEA. The risk of stroke after CABG ranges from 0.7-5.2%[42]

Hemodynamically significant carotid stenoses are associated with 30% of early post-CABG strokes. The perioperative stroke risk is <2% when carotid stenoses are <50%, 10% when stenoses are 50% to 80%, 11% to 18.8% in patients with stenoses >80%. The risk shoots to 20% with untreated, bilateral, high-grade stenoses or an occluded carotid artery and contralateral high-grade stenosis.[43]

The majority of strokes happen after the first 24 hours post CABG. This suggests that majority of strokes cannot be simply be ascribed to an adverse intra-operative event (low flow, hypotension and carotid embolism). The overall case fatality following post-CABG stroke as 23.1%.[43]In real life, it is not possible to state how often carotid stenosis of any degree of severity contributes to the incidence of ischemic stroke after CABG. Naylor et al concluded that primary carotid thromboembolic disease alone was not responsible for up to 59% of post CABG strokes. A significant proportion of post-operative strokes was in the vertebro-basilar territory or located contralateral to the severely stenosed carotid or ipsilateral to an insignificant stenosis. Aortic arch atherosclerosis embolization may be an important cause of stroke in the majority of cases.[43]

## 19. Approaches to treatment

1. Staged approach: Advocates of a staged procedure perform CEA several days prior to CABG or several weeks following cardiac surgery. The rationale of the staged procedure is to decrease the risk of stroke in the cardiac procedure and eliminate the need for longer and more stressful combined procedure. Increased cardiac morbidity and mortality resulting from CEA may offset potential benefits of this approach.[42]

In those with a history of TIA or stroke who have a significant carotid artery stenosis (50% to 99% in men or 70% to 99% in women), the likelihood of a post-CABG stroke is high; as a result, they are likely to benefit from carotid revascularization. Conversely, CABG alone can be performed safely in patients with asymptomatic unilateral carotid stenoses, because a carotid revascularization procedure offers no discernible reduction in the incidence of stroke or death in these individuals. Men with asymptomatic bilateral severe carotid stenoses (50% to 99%) or a unilateral severe stenosis in conjunction with a contralateral carotid artery occlusion may be considered for carotid revascularization in conjunction with CABG. Little evidence exists to suggest that women with asymptomatic carotid artery disease benefit from carotid revascularization in conjunction with CABG. Whether the carotid and coronary revascularization procedures are performed simultaneously or in a staged, sequential fashion is usually dictated by the presence or absence of certain clinical variables. In general, synchronous combined procedures are performed only in those with both cerebrovascular symptoms and ACS.[44]

2. Combined approach: performing CEA and CABG in the same setting: If the combined approach can be done safely, a second surgical procedure and hospital stay may be eliminated, with significant cost reduction. Long-term stroke free survival may also be significantly improved.[42] The problem with this approach is that the stroke rate is exceedingly high.

3. Ignoring the carotid disease initially and addressing it weeks to months later after the CABG procedure may be another approach. This idea is supported by a retrospective review of 94 patients with asymptomatic high-grade carotid stenosis undergoing CABG. There was one perioperative stroke and no deaths in this group of patients. These data combined with findings of Naylor et al that prophylactic CEA could barely prevent < 40% of post-CABG strokes [43] would support this approach in asymptomatic carotid stenoses. In the absence of clear guidelines, the decision is better individualized dealing with the more symptomatic vascular bed first. The simultaneous performance of CABG and CEA carries a high risk but is warranted in patients with recent symptoms of both severe coronary disease (unstable angina) and severe carotid stenosis.

Carotid stenting can be an alternative in endarterectomy in this subset of patients.[45, 46] A recent Comparison of Early and Late Outcomes with Three Approaches to Carotid Revascularization and Open Heart Surgery showed that Staged CAS-OHS and combined CEA-OHS are associated with similar risk of death, stroke or MI in the short term, with both being better than staged CEA-OHS. However, the outcomes are significantly in favor of staged CAS-OHS after the first year.[47]

## 20. CEA in the presence of contralateral occlusion

Patients with contralateral carotid occlusion have higher surgical risk for CEA due to multiple reasons; reduced collateral circulation during carotid clamping, cerebral hemorrhage secondary to hyperperfusion syndrome, and the overall advanced status of the vascular disease. Surgical mortality was extremely high in patients with a contralateral carotid occlusion and only 34% of the surgically treated patients were alive at 66 months in contrast to 63% of medically treated patients.(88) Results from the NASCET study demonstrated that medically treated patients with a contralateral occluded carotid were more than twice as likely to have a stroke compared to patients with a patent contralateral artery. However, when compared with medically treated patients, the overall risk of stroke contralateral to an occluded carotid artery was significantly reduced in the surgical patients. The risk of stroke in medically treated patients was 69% at 2 years versus 22% in patients treated surgically. (2) Thus, CEA with contralateral occlusion is a risky procedure but its risk may be justified considering the natural history of the disease.

## 21. CEA vs. CAS in the real world

### 21.1. The limitations of published trials comparing CEA and CAS

The influence of the industry is strong, where all the industry-sponsored registries had lower rates of complications compared to randomized trials. The levels of expertise of operators vary significantly among trials as well as the obligatory use of protection devices. The percentage of symptomatic and asymptomatic patients also varies rendering interpretation of results and

generalizing them to the general practice an intriguing issue. There also seems a publication bias in reporting the trial results. Vascular surgery periodicals tend to note better results with CEA while cardiology journals tend to report superiority or non-inferiority of CAS.

## 22. Ongoing trials and future directions

The modern medical treatment and optimized medical therapy (OMT) were not available at the time of some landmark trials like NASCET and ECST. There is a growing enthusiasm to test if OMT renders intervention unnecessary or only restricted to high risk patients. A new set of trials called "Trials 2" are now developing and ongoing:

- **European Carotid Surgery Trial-2 (ECST-2):** The trial will include patients with symptomatic or asymptomatic moderate or severe carotid stenosis at low or intermediate risk of future stroke. The trial compares the risks and benefits of treatment by modern optimized medical management alone versus the addition of immediate carotid surgery (or stenting) to optimize medical management.
- **Asymptomatic Carotid Surgery Trial-2 (ACST-2):** To compare carotid endarterectomy with carotid artery stenting in the prevention of stroke in patients with asymptomatic carotid stenosis.
- **Stent-protected angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy Trial-2 (SPACE-2):** A three-arm randomized-controlled clinical trial. The trial based on German speaking countries. The trial initially randomized patients with asymptomatic stenosis between carotid artery stenting vs. Carotid endarterectomy and recently the trial modified to include third arm with optimized medical therapy (OMT) only.
- **Carotid Revascularization Endarterectomy versus Stenting Trial-2(CREST-2):** North American trial testing revascularization vs. contemporary medical management alone.

## 23. Conclusion

What we can infer from these trials that CEA has a lower stroke rate than CAS but CAS has a lower MI rate than CEA. If mortality, stroke and MI are mingled together as a single end-point, then both strategies are equivalent on the long-term. Advancing age is strongly against selecting CAS as the initial choice of revascularization. The results of either technique are critically dependent on the skills of the performing physician. Restenosis after CAS may be slightly more than restenosis after CEA but the severe, clinically significant restenosis is uncommon. In patients with concomitant coronary and carotid disease, stenting may have an advantage over CEA.

There remains a need for more trials assessing the future roles of medical management, carotid stenting, and carotid endarterectomy. Future trials should be designed with the assumption

that some patients will be best managed medically, some with medical therapy plus stenting, and some with medical therapy plus endarterectomy. These treatments are complementary and not competing. Varying treatment algorithms including more or less liberal use of each modality can be designed, patients randomly assigned to one of the algorithms, and their results compared.[48]

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