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Asymptomatic carotid stenosis: What we can learn from the next generation of randomized clinical trials

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Abstract

Stroke remains an exceedingly incident and prevalent public health burden across the globe, with an estimated 16 million new strokes per annum and prevalence over 60 million, and extracranial internal carotid artery atherosclerotic disease is an important risk factor for stroke. Randomized trials of surgical treatment were conducted (North American Symptomatic Carotid Endarterectomy Trial, European Carotid Surgery Trial) and demonstrated efficacy of carotid endarterectomy for secondary prevention of stroke in patients with cerebrovascular events (e.g. ipsilateral stroke, transient ischemic attack, and/or amaurosis fugax) attributable to a diseased artery with 50–99% stenosis. Therapeutic clarity, however, proved elusive with asymptomatic carotid artery disease. Asymptomatic Carotid Atherosclerosis Study (ACAS), Asymptomatic Carotid Surgery Trial, and Veterans Affairs Cooperative Study (VACS) suggested only modest benefit from surgical intervention for primary stroke prevention and the best medical therapy at the time of these trials is not comparable to modern medical therapy. ACT-1, Asymptomatic Carotid Surgery Trial-2, Stent-Protected Angioplasty in asymptomatic Carotid artery stenosis versus Endarterectomy Trial-2, European Carotid Surgery Trial-2, Carotid Revascularization Endarterectomy Versus Stenting Trial-2 are trials that are recent, ongoing, or in development that include diverse populations across Europe and North America, complementary trial designs, and a collaborative spirit that should provide clinicians with evidence that informs best clinical practice for asymptomatic carotid artery disease.

Keywords

Carotid stenosis, primary and secondary stroke prevention, cardiology, carotid endarterectomy, angioplasty and stenting

Introduction

Stroke remains an exceedingly incident and prevalent public health burden across the globe, with an estimated 16 million new strokes per annum and prevalence over 60 million.[1] Estimates in the United States alone suggest nearly 800,000 incident strokes annually, 75% of which are new, and leaving almost 7 million Americans with the stigmata of stroke.[2] Extracranial internal carotid artery atherosclerotic disease is one of the major high-risk mechanisms of stroke. Epidemiologic estimates of first-time ischemic stroke attributable to carotid artery disease vary, but range from roughly 7[3] to 18%[4] of all incident stroke (the latter number representing combined extra- and intracranial carotid stenosis in that population). Acknowledging carotid artery disease as a risk factor for stroke, randomized trials of surgical treatment (North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST)) demonstrated efficacy of internal carotid endarterectomy (CEA) for secondary prevention of stroke in patients with cerebrovascular events attributable to a diseased artery with 50–99% stenosis.[5–8] The efficacy was clear-cut in NASCET. In ECST, the benefit was debatable because the benefit was not significant in the group with 50–69% stenosis using the measurement techniques employed in NASCET and other larger randomized trials.[8] Therapeutic clarity has also proven elusive with asymptomatic carotid artery disease.

Multicenter randomized studies of CEA for asymptomatic carotid artery disease (ACAS, Asymptomatic

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Carotid Surgery Trial (ACST), VACS) demonstrated some secondary stroke risk reduction as compared to medical therapy.[9–11] However, although statistically significant, the absolute risk reduction tended to be small. For example, in ACST at a median follow-up of 9 years, the 5- and 10-year risk of any stroke was 6.4 and 13.9% for the CEA group and 10.9 and 17.9% for the deferral of any CEA group, respectively, for an absolute risk reduction of 4.1% at 5 years and 4.6% at 10 years.[12] The high number of surgeries required to prevent one ipsilateral stroke, in combination with recent advances in best medical therapy, has called into question the relevance of these data to inform current clinical practice.[13] To again use ACST as an example, the use of lipid lowering drugs rose rapidly to 80 and 82% of patients in the CEA and deferral groups, respectively, by 2007 from initial rates of 11 and 7%, respectively, in 1993. Approximately half of participants in the trial were on lipid lowering drugs in 2001.[12] The ACAS and VACS trials used aspirin alone as the ''medical therapy'' comparator. The potential for driving down event rates in patients with cerebrovascular atherosclerosis with intensive medical management became evident with the publication of the results of the prematurely halted Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial.[14,15] In that trial, the noninterventional arm was conceptually based on historical data from the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID)[16] trial, which included patients on similar ''best medical therapy'' as compared to the first generation of asymptomatic carotid surgery trials (e.g. aspirin alone), and ended up demonstrating a dramatically lower stroke-related event rate than expected (e.g. 30 day and 1 year primary event rates of 6 and 8%, respectively versus 10 and 25% expected based on WASID). Since that publication, ''best medical therapy'' has been conceptualized as the synergistic combination antiplatelet therapy (in some cases temporary dual antiplatelet therapy), intensive management of elevated blood pressure, dyslipidemia and diabetes mellitus, as well as lifestyle interventions aimed at tobacco use, obesity, and sedentariness.

Further complicating therapeutic decision making with asymptomatic carotid artery disease, randomized controlled trials of internal carotid artery stenting (CAS) as compared to CEA has been performed as well, namely Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectom (SAPPHIRE) and Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST).[17–19] These studies included mixed populations of symptomatic and asymptomatic patients, and the inclusion criteria were somewhat disparate. SAPPHIRE enrolled only severe asymptomatic carotid artery disease (≥80%) and CREST enrolled patients with moderate-to-severe carotid artery disease (≥60% by conventional angiography, >70–80% by noninvasive techniques). Both informed clinical practice in a similar and substantial way: neither technique is clearly superior to the other for secondary stroke prevention. They also are subject to some of the criticisms of ACAS and ACST: low event rates and subsequently high numbers needed to treat, particularly in the asymptomatic subset of CREST (no such parsing of data is available for SAPPHIRE), calling into question the utility of surgical intervention for asymptomatic carotid artery disease in the era of modern, multifaceted ''best medical therapy.''

The question of how intervention, either CEA or CAS, fares against best medical therapy for secondary prevention of stroke in the setting of asymptomatic carotid artery disease remains unanswered by high-quality trial data. There are ongoing large, multicenter, international trials in recruitment or development phase to address this very question. Five major trials will be discussed in chronological order of recruitment start date. See Table 1 for a comparative overview.

Asymptomatic Subjects with Significant Extracranial Carotid Occlusive Disease Trial (ACT-I)

ACT-1[20] was a large, multicenter, prospective randomized trial of CAS versus CEA for severe carotid artery disease. The stated aim[21] of the study was to demonstrate the noninferiority and safety of CAS for primary prevention of stroke as compared to CEA in the setting of asymptomatic carotid artery disease. Adult, ''nonoctogenarian'' patients with ''severe'' carotid artery disease, no symptoms suggestive of a cerebrovascular event referable to the lesion within 180 days of randomization, and perceived eligibility for either stenting or surgery were randomized in a 3:1 fashion to CAS or CEA. Information clarifying determination of procedural eligibility and/or concurrent medical management is not publicly available. The primary outcome measure was any stroke, myocardial infarction, or death within 30 days of a procedure and rate of any ipsilateral stroke within 1 year of the procedure. The study began recruiting patients in April 2005 and enrolled 1665 patients over the next 8 years across 62 centers in the United States, which neatly approximated target enrollment of 1658 patients. The planned sample size was designed to have 80% power to test the primary objective (personal communication). A unique feature of this trial as compared to its contemporaries is the focus on procedural interventions as active comparators; the other modern carotid trials employ ''best medical therapy'' in conjunction with intervention if not an active comparator. This study was halted by the sponsor, but ''not as a result of patient or product issues.''[20]

Table 1. Asymptomatic carotid trial characteristics.

	Comparators	Trial start	Inclusion	Recruitment [total], (goal)	Outcomes	Trial duration	Asymptomatic only	CEA versus CAS	Surgery + BMT	Testing BMT alone	Structured BMT	Embolic protection devices
ACT-1	CEA versus CAS	2005	Severe asymptomatic CAD, eligible for CAS or CEA	[1665], (1658)	Stroke/MI/death @ 30 days, ipsilateral stroke @ 1 year	8 years	Y	Direct	UNK	N	N	Y, Emboshield (Abbot)
ACST-2	CEA versus CAS	2008	"needs intervention" and "substantial uncertainty" CEA versus CAS	[1330], (5000)	Stroke/MI/death @ 30 days and 5–10 years	10 years	Y	Direct	Y	N	N	Y, varied
SPACE-2	CEA versus BMT/ CAS versus BMT	2008	≥70% CAD by US	[UNK], (3272)	Stroke, death @ 30 days, 5 years ipsilateral stroke	5 years	Y	Indirect	Y	Y	N	UNK
ECST-2	CEA/CAS versus BMT	2012	≥50% CAD by US, CAR score	[30], (2000)	Stroke, ICH, death @ 2 years/stroke and nonstroke death 5–10 years	10 years	N	N	Y	Y	Y	Y, varied
CREST-2	CEA versus BMT/ CAS versus BMT	a	≥70% CAD by angiography, definite US or suggestive US + noninvasive confirmatory	(2480)	Periprocedural stroke/death, ipsilateral stroke @ 4 years	6 years	Y	N	Y	Y	Y	UNK

[a]Recruitment has not yet commenced.

BMT, best medical therapy; CAD, carotid artery disease; CAR score, Carotid Artery Risk[26] score; CAS, carotid artery stenting; CEA, carotid endarterectomy; ICH, intracranial hemorrhage; MI, myocardial infarction; UNK, unknown; US, ultrasound.

The Asymptomatic Carotid Surgery Trial-2 (ACST-2)

The ACST-2 trial[22] is a phase III, randomized, open, multicenter international collaboration originating from the United Kingdom, with principal investigators that were involved in ACST, comparing the relative efficacy of CEA to CAS for primary stroke prevention in the setting of asymptomatic carotid artery disease. The design of the study is notable in that the inclusion criteria are relatively broad, with the hope of recruiting many thousands of patients and achieving generalizable results. The basic eligibility criterion is that a "patient has asymptomatic carotid artery stenosis that is thought to need some procedural intervention, angiography shows CEA and CAS are both anatomically practicable, [and] both [the] doctor and patient are substantially uncertain whether CEA or CAS is preferable." Although that entry criterion seems vague, the investigators left it as such by design in an attempt to be compatible with "real-world" practice across the globe where strict entry criteria (and the administrative burden of complex randomization) slows or inhibits recruitment. To be clear, no prespecified degree of asymptomatic carotid artery disease is required for study entry, but simply a recommendation by the treating physician to pursue an intervention of some kind provided the patient has "no ipsilateral carotid territory symptoms (or none for some months) and no previous procedure done on it… [or] [s]mall likelihood of worthwhile benefit." Once that decision is made, and there is perceived clinical and technical equipoise between CEA and CAS, the patient is randomized to one or the other procedure and followed for up to 10 years. There is no described standardization of medical therapy pre- or postintervention, but a statement that patients are eligible if they have "already started any appropriate medical treatment." The registry states a recruitment goal of 5000 randomized patients, but state the hope for and importance of many more enrolled over a 10-year period. Data analysis is to be done on an intention to treat (ITT) basis. The primary outcomes of the study include any myocardial infarct, stroke, or death in the periprocedural period at 30 days and any stroke or death in the subsequent 5–10 years. The secondary outcomes include identifying subgroups of patients for whom one procedure is "clearly preferable" to the other as well as health economic analysis of procedural and stroke-related costs. The study began recruiting in January 2008 and has enrolled 1330 patients in 98 centers across 26 countries as of 31 December 2013.[23] The estimated primary completion date is January 2019.

The Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis versus Endarterectomy Trial-2 (SPACE-2)

The SPACE-2 trial[24] is another large, phase III, multicenter, international effort that seeks to test the hypotheses of "[s]uperiority of stent-protected angioplasty or carotid endarterectomy as compared to best medical treatment," and that "[s]tent-protected angioplasty is not inferior to carotid endarterectomy" for adult patients (50–85 years) with asymptomatic (e.g. no symptoms within 180 days of screening) carotid artery disease of $\geq$70% by ultrasound criteria. The original design, which began recruitment in 2008, was randomized, open, controlled, multicenter, with a three-arm intervention: best medical therapy alone versus CAS versus CEA. It is worthwhile noting that the SPACE-2 trial is the first of the current wave of trials to include best medical therapy alone as an individual treatment arm, although all treatment groups will receive the same medical therapy. The definition of best medical therapy is based on the individual risk factor profile of each patient, but generically involves optimal medical management of hypertension, dyslipidemia, and diabetes as well as an antithrombotic agent. A fundamental revision to the design of the trial was initiated in April of 2013: the SPACE-2 trial is now two parallel superiority trials of CEA (SPACE-2a) versus medical therapy and CAS versus medical therapy (SPACE-2b). The recruitment target remained the same as the original design, however, with an even split between comparators. Over a 3-year recruitment period, the investigators target roughly 1600 patients in each of the two subsets (e.g. SPACE-2a and SPACE-2b), and patients will be followed in a structured fashion for 5 years. The primary efficacy endpoints by which superiority (or noninferiority) will be determined are 30-day combined stroke or death from any cause and 5-year ipsilateral stroke, and data analysis is by ITT. Indirect comparisons of CEA versus CAS are planned, as is data sharing with ACST-2 investigators for a composite analysis. Current enrollment data were not publicly available at the time this manuscript was written.

The European Carotid Surgery Trial-2 (ECST-2)

The ECST-2 trial,[25] also originating out of England, is a phase III, open, randomized, multicenter, prospective clinical trial of patients with symptomatic or asymptomatic carotid artery disease who will be randomized to either best medical therapy alone or best medical therapy plus urgent revascularization (CEA or CAS), defined as within 2 weeks of randomization for symptomatic patients and within 4 weeks for

asymptomatic patients. Patients are screened for inclusion based on radiographic evidence of ≥50% carotid artery disease in conjunction with a clinical risk prediction model. The aim of the study is to evaluate whether or not surgical revascularization adds appreciable stroke risk reduction in patients—with or without recent symptoms referable to their carotid stenosis—who are deemed low-to-intermediate risk by the prediction model. Patients who are considered high risk by the model or those who "convert" to high risk (e.g. because of a recurrent cerebral ischemic event) are revascularized per usual clinical practice. Best medical therapy consists of "optimal antiplatelet therapy, statin, or other cholesterol lowering treatment with target total cholesterol of <4 mmol/l and low-density lipoprotein (LDL) cholesterol of <2 mmol/L, antihypertensive treatment with target blood pressure of 135/85 mmHg." Patients enrolled in the full trial will be followed for at least 5 and up to 10 years. Recruitment started in 2012 but is limited, by design, to 320 patients as part of a trial self-assessment substudy. These 320 patients will be screened for the combined 2-year rate of cerebral ischemia, intracerebral hemorrhage, myocardial infarction, and periprocedural death. This assessment includes MRI of the brain at 2 years to screen for silent cerebral infarction, which is factored in as "cerebral ischemia" for this analysis. This interim analysis will inform the total trial sample size, but the expected target recruitment of the full trial is 2000 patients. The trial has recruited 30 patients in four centers as of December 2013. Patients will be tracked for 5–10 years to assess for any stroke at any point in time beyond randomization and periprocedural nonstroke death. This study has a number of unique features. First, the foundational element of the study is a clinical risk prediction model, developed by the Oxford Stroke Unit,[26] which considers a patient's cardiovascular comorbidity profile, chronologic proximity of the cerebrovascular event, and some imaging characteristics to stratify patients into low/intermediate/high risk tertiles based on data extrapolated from the medical therapy (e.g. antiplatelet-alone) arm of the original ECST. This is the first study to use this prediction score to triage patients with carotid artery disease, symptomatic or otherwise, as "well enough" to participate in this study. This study is also unique in combining the CEA and CAS technical approach into an intervention arm, essentially considering them equally efficacious therapeutically. The investigators "anticipate that revascularisation will be by CEA in most patients, but CAS may be used if considered more appropriate."[27] This stands in contrast to the other studies detailed earlier, which are testing CEA versus CAS directly (ACST-2) or indirectly (SPACE-2). Another notable facet of this trial is the encouraged collection of clinical data from nonrandomized patients and research-level diagnostics such as advanced transcranial Doppler studies that assist in risk stratification (e.g. vasomotor reactivity, embolic detection) to further nuance our understanding of the practice, even if not providing definitive evidence of clinical utility.

Carotid Revascularization Endarterectomy Versus Stenting Trial-2 (CREST-2)

The CREST-2 trial,[28] still in development, is designed as two parallel randomized trials. The surgical trial will test the hypothesis that CEA in addition to intensive medical therapy is superior to intensive medical therapy alone. The stenting trial will test the hypothesis that CAS in addition to intensive medical therapy is superior to intensive medical therapy alone. This design is similar to the redesign for the European SPACE-2 trial. CREST-2 will include adult patients (≥35 years old) with ≥70% carotid stenosis as measured by a number of means. Patients may be enrolled by conventional angiography (NASCET criteria) demonstrating ≥70% carotid stenosis. Patients may also be included if Doppler ultrasound (DUS) demonstrates ≥70% stenosis defined by a peak systolic velocity of at least 230 cm/s plus and an end diastolic velocity ≥100 cm/s or internal carotid/common carotid artery peak systolic velocity ratio ≥4.0, or by a peak systolic velocity on DUS ≥230 cm/s and CT angiography showing ≥70% stenosis or MRI angiography showing ≥70% stenosis. A patient with these radiographic findings must not have symptoms referable to the identified lesion within 180 days to be eligible. Patients will be randomized to the surgical or stenting trials in a 1:1 fashion. The intensive medical therapy regimen will be modeled after the clinically paradigm-shifting SAMMPRIS[14] intensive medical therapy intervention. The primary efficacy endpoint will be a composite of periprocedural stroke or death at 30 days and any ipsilateral stroke thereafter out to 4 years of follow up. The target recruitment of 2480 patients (1240 in each study) over 6 years will provide approximately 85% power to test the primary hypotheses. CREST-2 will leverage the CREST network of providers and research infrastructure developed over the last decade to recruit with similar efficiency (e.g. nearly 1200 asymptomatic patients recruited into CREST within 3 years). It is notable that, although CREST-2 is not directly comparing CEA to CAS, the investigators decided to keep the trial name to reflect the general preservation of the research team from CREST.

Embolic protection devices

Carotid artery revascularization, by CEA or CAS, is well known to cause embolization of plaque-associated atherosclerotic debris toward the brain.[29,30] There is biologic plausibility for the use of embolic protection devices, and such devices exist in current clinical practice. The predominant mechanisms of embolic protection in practice today include distal protection with a transfemorally inserted net-like device and a transcervical proximal occluder that reverses flow in the ipsilateral carotid artery. There are numerous small studies that seek to determine if one technique provides superior protection against brain ischemia[31–35]; however, there is an equally robust literature[36] that suggests that the devices do not substantially change the clinical and radiographic outcomes (e.g. silent cerebral infarcts), the latter of which have unknown clinical significance.

In this context, it is not entirely clear what role these devices might silently play in the aforementioned trials. ACST-2 and ECST-2 state their commitment to use of a range of protective devices in an attempt to mirror ''real-world'' practice. ACT-1 made use of a specific distal protection device manufactured by the study sponsor. The protocol for SPACE-2 does not clearly state a commitment to use with every case but rather mentions the use thereof during the informed consent process, acknowledging the controversy. The original CREST trial employed a one-stent-one-protection-device principle to minimize confounding variables. In CREST-2, at least several stents and several embolic protection devices will be used.

Discussion

Asymptomatic carotid artery disease remains common and poses a therapeutic dilemma for clinicians worldwide. Observational data suggest that rates of stroke referable to asymptomatic carotid artery disease are low. Heterogeneity in patient clinical and anatomical factors imparts differential stroke risk for individual patients and begs the question ''should we be doing *more*?'' In addition, we now have two surgical revascularization techniques with substantial therapeutic overlap and complementary strengths that address the weaknesses of the other; so, ''if we should do more, *how* do we do it?'' Moreover, old data suggested only modest benefit from surgical intervention for primary stroke prevention, and the best medical therapy at the time of those trials is incomparable to modern medical therapy; ''*what* exactly should we be doing?'' The aforementioned large, multicenter, randomized trials including diverse populations across Europe and North America, complementary trial designs, and a collaborative spirit that should provide clinicians with evidence that informs best clinical practice for asymptomatic carotid artery disease.

Declaration of Conflicting Interests

None

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None

Guarantor

Dr. Meschia.

Contributorship

MNR contributed to the initial and final drafting of the manuscript. The other authors provided review for the final draft.

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