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# Carotid revascularization and medical management for asymptomatic carotid stenosis: Protocol of the CREST-2 clinical trials

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## Abstract

**Rationale:** Trials conducted decades ago demonstrated that carotid endarterectomy by skilled surgeons reduced stroke risk in asymptomatic patients. Developments in carotid stenting and improvements in medical prevention of stroke caused by atherothrombotic disease challenge understanding of the benefits of revascularization.

**Aim:** Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) will test whether carotid endarterectomy or carotid stenting plus contemporary intensive medical therapy is superior to intensive medical therapy alone in the primary prevention of stroke in patients with high-grade asymptomatic carotid stenosis.

**Methods and design:** CREST-2 is two multicenter randomized trials of revascularization plus intensive medical therapy versus intensive medical therapy alone. One trial randomizes patients to carotid endarterectomy plus intensive medical therapy versus intensive medical therapy alone; the other, to carotid stenting plus intensive medical therapy versus intensive medical therapy alone. The risk factor targets of centrally directed intensive medical therapy are LDL cholesterol $<$70 mg/dl and systolic blood pressure $<$140 mmHg.

**Study outcomes:** The primary outcome is the composite of stroke and death within 44 days following randomization and stroke ipsilateral to the target vessel thereafter, up to four years. Change in cognition and differences in major and minor stroke are secondary outcomes.

**Sample size:** Enrollment of 1240 patients in each trial provides 85% power to detect a treatment difference if the event rate in the intensive medical therapy alone arm is 4.8% higher or 2.8% lower than an anticipated 3.6% rate in the revascularization arm.

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**Discussion:** Management of asymptomatic carotid stenosis requires contemporary randomized trials to address whether carotid endarterectomy or carotid stenting plus intensive medical therapy is superior in preventing stroke beyond intensive medical therapy alone. Whether carotid endarterectomy or carotid stenting has favorable effects on cognition will also be tested.

**Trial registration:** United States National Institutes of Health Clinicaltrials.gov NCT02089217

**Keywords**
Carotid endarterectomy, carotid stenting, asymptomatic carotid stenosis, medical treatment, randomized clinical trial, stroke prevention, cognitive functioning

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## Introduction

Revascularization of the carotid artery by either endarterectomy or stenting is used as a means of preventing first-time and recurrent cerebral infarction. None of the pivotal trials utilized an intensive medical management (IMM) program.[1–4] The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) is two trials assessing: (1) treatment differences between IMM alone compared to carotid endarterectomy (CEA) plus IMM, and (2) treatment differences between IMM alone compared to carotid stenting (CAS) plus IMM. Herein, we describe key elements of the two trials and unique aspects, including centralized IMM and assessment of cognitive function.

## Selection of which trial for which patient

The two parallel trials share general inclusion/exclusion criteria, and primary and secondary endpoints. Based on patient preference and characteristics, the local investigative team determines whether it would be best to revascularize by endarterectomy or stenting.

## Patient population

Eligibility includes those ≥35 years old who have high-grade asymptomatic stenosis involving the carotid bifurcation with or without involvement of the adjacent internal carotid artery. A patient is considered asymptomatic in the absence of ipsilateral symptoms <180 days prior to randomization.

Stenosis is defined as high-grade if catheter angiography documents ≥70% stenosis per criteria used in NASCET[5] or duplex ultrasonography (DU) documents peak systolic velocity (PSV) of ≥230 cm/s in combination with at least one of the following four criteria: end diastolic velocity of ≥100 cm/s, internal carotid artery-to-common carotid artery PSV ratio ≥4.0, CT angiogram showing ≥70% stenosis, or a magnetic resonance angiogram (MRA) showing ≥70% stenosis.

General eligibility criteria are listed in Table 1, general exclusion criteria in Table 2, CEA-trial-specific exclusion criteria in Table 3, and CAS-trial-specific exclusion criteria in Table 4.

## Intensive medical management

Sites implement IMM for all patients with guidance from the Medical Management Core. Patients take aspirin 325 mg/day for the entire follow-up period (CAS patients also take clopidogrel for 30-90 days after procedure). The primary risk factors, such as systolic blood pressure and LDL cholesterol are managed according to protocols targeting a systolic blood pressure <140 mm Hg and LDL <70 mg/dl.[6,7] Medications are adjusted at each visit if the patient is not in target. Management of secondary risk factors (diabetes, non-HDL cholesterol, smoking, weight, and physical activity) is coordinated with the patient's primary physician or other consultant as needed. A lifestyle modification program, INTERVENT is provided to each patient.[7]

## Carotid endarterectomy protocol

Guidelines are provided for conduct of CEA. The technique of plaque removal (regular endarterectomy or eversion endarterectomy) is not dictated. Patch angioplasty is recommended for conventional CEA but not for eversion CEA. Other techniques and methods used such as shunts, or intra-operative monitoring are variable and depend upon the individual surgeon's practice. Anticoagulation with either heparin or bivalirudin (Angiomax®) is required.

## Carotid artery stenting protocol

Guidelines for CAS include that arterial access be established by the femoral route using the Seldinger technique and that local anesthesia with sedation is preferred over general anesthesia. Embolic protection devices should be used. CREST-2 permits the use of the

**Table 1.** Primary inclusion criteria for participant selection either trial

| |
|---|
| 1. Patient age ≥35 years old (no upper age limit) |
| 2. Carotid stenosis defined as: |
| • Stenosis ≥70% by catheter angiography (NASCET criteria); |
| OR |
| • by Doppler ultrasonography with ≥70% stenosis defined by a peak systolic velocity of at least 230 cm/s *plus* at least one of the following: |
| (a) an end diastolic velocity ≥100 cm/s, or |
| (b) internal carotid/common carotid artery peak systolic velocity ratio ≥4.0, or |
| (c) computed tomography angiography with ≥ 70% stenosis, or |
| (d) magnetic resonance angiography with ≥ 70% stenosis. |
| 3. No medical history of stroke or transient ischemic attack ipsilateral to the stenosis within 180 days of randomization. |
| 4. Modified Rankin Scale score of 0 or 1 at the time of informed consent. |
| 5. Woman has no childbearing potential or, if of childbearing potential, has a negative pregnancy test prior to randomization. |
| 6. Patients must agree to comply with all protocol-specified follow-up appointments. |
| 7. Patients must sign a consent form that has been approved by the local governing Institutional Review Board (IRB)/Medical Ethics Committee (MEC) of the respective clinical site. |
| 8. Randomization to treatment group will apply to only one carotid artery for patients with bilateral carotid stenosis. |
| 9. Carotid stenosis treatable with carotid endarterectomy (CEA), or carotid artery stenting (CAS) |

**Table 2.** Primary exclusion criteria for participant selection either trial

| |
|---|
| 1. Intolerance or allergic reaction to a study medication without a suitable management alternative. |
| 2. GI hemorrhage within one month prior to enrollment that would preclude antiplatelet therapy. |
| 3. Prior major ipsilateral stroke in the past with substantial residual disability (mRS ≥2) that is likely to confound study outcomes. |
| 4. Severe dementia. |
| 5. History of major symptomatic intracranial hemorrhage within the past 12 months that was not related to anticoagulation. |
| 6. Prior intracranial hemorrhage that the investigator believes represents a contraindication to the perioperative or periprocedural antithrombotic and antiplatelet treatments necessary to complete endarterectomy or stenting per protocol. |
| 7. Current neurologic illness characterized by fleeting or fixed neurologic deficits that cannot be distinguished from TIA or stroke. |
| 8. Patient objects to future blood transfusions. |
| 9. Platelet count <100,000/μl or history of heparin-induced thrombocytopenia. |
| 10. Anticoagulation with Phenprocoumon (Marcumar®), warfarin, or a direct thrombin inhibitor, or anti-Xa agents. |
| 11. Chronic atrial fibrillation. |
| 12. Any episode of atrial fibrillation within the past six months or history of paroxysmal atrial fibrillation that is deemed to require chronic anticoagulation. |
| 13. Other high-risk cardiac sources of emboli, including left ventricular aneurysm, severe cardiomyopathy, aortic or mitral mechanical heart valve, severe calcific aortic stenosis (valve area <1.0 $cm^2$), endocarditis, moderate to severe mitral stenosis, left atrial thrombus, or any intracardiac mass, or known unrepaired PFO with prior paradoxical embolism. |

(continued)

**Table 2.** Continued

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|---|
| 14. Unstable angina defined as rest angina with ECG changes that is not amenable to revascularization (patients should undergo planned coronary revascularization at least 30 days before randomization). |
| 15. Left ventricular ejection fraction <30% or admission for heart failure in prior 6 months. |
| 16. Respiratory insufficiency with life expectancy <4 years or $FEV_1$ <30% of predicted value. |
| 17. Known malignancy other than basal cell non-melanoma skin cancer. There are two exceptions: patients with prior cancer treatment and no recurrence for >5 years are eligible, and cancer patients with life expectancy greater than five years are eligible for enrollment. |
| 18. Any major surgery, major trauma, revascularization procedure, or acute coronary syndrome within the past 1 month. |
| 19. *Either* the serum creatinine is ≥2.5 mg/dl or the estimated GFR is <30 cc/min. |
| 20. *Major* (non-carotid) surgery procedure planned within three months after enrollment. |
| 21. Currently listed or being evaluated for major organ transplantation (i.e. heart, lung, liver, kidney). |
| 22. Actively participating in another drug or aortic arch or cerebrovascular device trial for which participation in CREST-2 would be compromised with regard to follow-up assessment of outcomes or continuation in CREST-2. |
| 23. Inability to understand and cooperate with study procedures or provide informed consent. |
| 24. Non-atherosclerotic carotid stenosis (dissection, fibromuscular dysplasia, or stenosis following radiation therapy). |
| 25. Previous ipsilateral CEA or CAS. |
| 26. Ipsilateral internal or common carotid artery occlusion. |
| 27. Intra-carotid floating thrombus. |
| 28. Ipsilateral intracranial aneurysm >5 mm. |
| 29. Extreme morbid obesity that would compromise patient safety during the procedure or would compromise patient safety during the periprocedural period. |
| 30. Coronary artery disease with two or more proximal or major diseased coronary arteries with ≥ 70% stenosis that have not, or cannot, be revascularized. |

GI: gastrointestinal; mRS: modified Rankin Scale; TIA: transient ischemic attack; PFO: patent foramen ovale; ECG: electrocardiogram; FEV: forced expiratory volume; GFR: glomerular filtration rate; CEA: carotid endarterectomy; CAS: carotid stenting.

**Table 3.** Exclusion criteria specific to the carotid endarterectomy trial

| |
|---|
| 1. Serious adverse reaction to anesthesia not able to be overcome by pre-medication. |
| 2. Distal/intracranial stenosis greater than index lesion. |
| 3. Any of the following anatomical: radical neck dissection; surgically inaccessible lesions (e.g. above cervical spine level 2 (C2)); adverse neck anatomy that limits surgical exposure (e.g. spinal immobility – inability to flex neck beyond neutral or kyphotic deformity, or short obese neck); presence of tracheostomy stoma; laryngeal nerve palsy contralateral to target vessel; or previous extracranial-intracranial or subclavian bypass procedure ipsilateral to the target vessel. |

carotid stenting and embolic protection devices that have received U.S. FDA approval. The list of approved devices will evolve and CREST-2 will accommodate additional stents and/or embolic protection devices if shown to be safe and effective. Periprocedural drug recommendations for carotid stenting are summarized in Table 5.

## Baseline and follow-up data collection summary

Information collected at baseline includes: demographics, vascular risk factors, height, weight, arterial blood pressure, cigarette smoking status, stroke symptoms using the

**Table 4.** Exclusion criteria specific to the carotid artery stenting trial

| |
|---|
| 1. Allergy to intravascular contrast dye not amenable to pre-medication. |
| 2. Type III, aortic arch anatomy. |
| 3. Angulation or tortuosity (≥90 degree) of the innominate and common carotid artery that precludes safe, expeditious sheath placement or that will transmit a severe loop to the internal carotid after sheath placement. |
| 4. Severe angulation or tortuosity of the internal carotid artery (including calyceal origin from the carotid bifurcation) that precludes safe deployment of embolic protection device or stent. Severe tortuosity is defined as 2 or more ≥90 degree angles within 4 cm of the target stenosis. |
| 5. Proximal/ostial CCA, innominate stenosis or distal/intracranial stenosis greater than index lesion. Excessive circumferential calcification of the stenotic lesion defined as >3 mm thickness of calcification seen in orthogonal views on fluoroscopy. (Note: Anatomic considerations such as tortuosity, arch anatomy, and calcification must be evaluated even more carefully in elderly subjects (≥70 years).) |
| 6. Target ICA vessel reference diameter <4.0 mm or >9.0 mm. Target ICA measurements may be made from angiography of the contralateral artery. The reference diameter must be appropriate for the devices to be used. |
| 7. Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD). |
| 8. Non-contiguous lesions and long lesions (>3 cm). |
| 9. Qualitative characteristics of stenosis and stenosis-length of the carotid bifurcation (common carotid) and/or ipsilateral external carotid artery, that preclude safe sheath placement. |
| 10. Occlusive or critical ilio-femoral disease including severe tortuosity or stenosis that necessitates additional endovascular procedures to facilitate access to the aortic arch or that prevents safe and expeditious femoral access to the aortic arch. "String sign" of the ipsilateral common or internal carotid artery. |
| 11. Angiographic, CT, MR or ultrasound evidence of severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries that would preclude safe passage of sheath and other endovascular devices to the target artery as needed for carotid stenting. |

CCA: common carotid artery; ICA: internal carotid artery; FDA: Food and Drug Administration; CT: computed tomography; MR: magnetic resonance.

**Table 5.** Periprocedural drug therapy for all carotid stent patients

| Medication | Pre-procedure | Intra-procedure | Post-procedure | Post-discharge |
|---|---|---|---|---|
| Heparin[a] | PRN | Maintain ACT 250–300 s[a] | PRN[b] | None |
| Aspirin | 325 mg p.o. b.i.d. (Begin 48 hours before) | None | 325 mg p.o. daily for 30 days[c] | 325 mg[c,d] 1 tablet p.o. daily thereafter |
| Clopidogrel | 75 mg p.o. b.i.d. daily (begin 48 h before) | None | 75 mg 1 tablet p.o. daily for 30 days | – |
| Ticlopidine (instead of clopidogrel) | 250 mg p.o. b.i.d. (begin 48 h before) | None | 250 mg p.o. b.i.d. for 30 days | – |
| Ticagrelor | 180 mg p.o. once[d] | None | 90 mg p.o. b.i.d. for 4 weeks | – |
| Atorvastatin (or dose equivalent of other statin) | Total of 80 mg | None | Continue on the dose of statin started on the day of randomization | Continue on the dose of statin started on the day of randomization |

[a]Bivalirudin may be substituted for heparin. Use in accordance with manufacturer's instructions. Activated clotting time are not collected when bivalirudin is used as the procedural anticoagulant.
[b]Heparin may be given post-procedure as needed.
[c]May be substituted with 81 mg tablet if patient cannot tolerate 325 mg dosage.
[d]Dose is for those not currently taking ticagrelor.

**Table 6.** Baseline and follow-up data collection schedule in CREST-2

| Evaluation | Time | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Month | Baseline[a] | Post-procedure[b] | 44 days | 4 | 8 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
| Informed consent | X | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Interval medical history | | | X | X | X | X | X | X | X | X | X | X |
| Stroke questionnaire (QVSS) | X | | X | X | X | X | X | X | X | X | X | X |
| Modified Rankin | X | | X | X | X | X | X | X | X | X | X | X |
| National Institutes of Health Stroke Scale (NIHSS) | X | X | X | X | X | X | X | X | X | X | X | X |
| Cognitive testing | X | | X | | | X | | X | | X | | X |
| Ultrasound | X | | | | | X | | X | | X | | X |
| CTA/MRA/CBA[c] | X | | | | | | | | | | | |
| Blood pressure | X | | X | X | X | X | X | X | X | X | X | X |
| Laboratory[d] | X | | | | | X | | X | | X | | X |

Note: For patients who undergo CAS and prescribed ticlopidine, a complete blood count will be required at 2 weeks and 30 days per standard medical practice.

[a]Must be collected prior to procedure or initiation of medical management therapy.

[b]NIHSS to be collected 12–36 h post procedure.

[c]CTA indicates computed tomography angiography; MRA indicates magnetic resonance angiography; CBA indicates catheter-based angiogram.

[d]Baseline blood tests include lipids, hemoglobin A1c, creatinine, potassium, alanine and aspartate transaminases, and creatine kinase.

QVSS: questionnaire for verifying stroke-free status.

Questionnaire for Verifying Stroke-free Status (QVSS),[8] the modified Rankin Scale (mRS),[9] the National Institutes of Health Stroke Scale (NIHSS),[10] cognitive testing and selected blood tests (Table 6).

The neurocognitive battery, measuring vascular cognitive status, is administered centrally via telephone at baseline, 44 days, 12 months and annually thereafter to 48 months. This assessment includes administration of five tests comprising four domains of cognitive function: Learning (CERAD Word List Learning Test), memory (CERAD Word List Delayed Recall),[11] executive function/processing speed (animal naming and letter fluency), and attention/working memory (digit span).

The follow-up schedule is provided in Table 6. An NIHSS is performed 12 to 36 h post-CEA or CAS. For all patients, NIHSS, medical history, QVSS, mRS, and blood pressure measurements are collected at each follow-up clinic visit. For patients unable to return for a clinic visit, telephone follow-up will include an abbreviated medical history, mRS, QVSS, and cognitive assessment (if applicable.)

## Primary and secondary endpoints

In each trial, the primary outcome is any stroke or death from randomization to 44 days or ipsilateral ischemic stroke from 45 days up to four years of follow-up. Stroke will be defined according to the World Health Organization as rapidly developing clinical signs of focal disturbance of cerebral function, lasting more than 24 h, with no apparent cause other than that of vascular origin.[12] Outcome is determined by a masked Adjudication Committee.

### *Major and minor stroke*

Stroke is defined as major when the NIHSS is $\geq 6$ at least 30 days after date of stroke onset, and minor

otherwise, or as determined by the Stroke Adjudication Committee based on clinical data.

### *Disabling and non-disabling stroke*

A stroke is classified as disabling if the mRS is 3 or more at least 30 days after onset of stroke, and non-disabling if the mRS is 2 or less. If the mRS was not performed, the score is estimated based on available clinical records.

## Statistical consideration

The sample size in each trial is 1240. Power calculations assumed a 5% cross-over rate, a 2.5% annual dropout rate, and a 0.05 level to declare a significant difference. The anticipated 4-year event rate in the revascularization arms (CEA or CAS) is 3.6%, comprising 2.0% during the 44-day periprocedural period plus 1.6% (0.4% per year) over the four-year post-procedural period. Under these assumptions, there is approximately 85% power to detect a difference if the event rate in the IMM arm is 4.8% greater (a rate of 8.4%) or 2.8% less (a rate of 0.8%) than the anticipated 3.6% rate in the revascularization arm. Analysis will use superiority testing in an intention-to-treat approach. Within each trial, the four-year event rate in both arms will be estimated using Kaplan-Meier methods, and the difference between arms will be assessed with a re-randomization test.

The analysis of cognitive function will also be estimated at the four-year follow-up point using a random-effects regression approach that includes assessments performed at each time point. Additional secondary analyses also include: (1) treatment differences in the area under the Kaplan-Meier event curves, (2) potential effect modification of the difference in event rates by age, sex, severity of stenosis, risk factor profile, and remote ipsilateral symptoms and contralateral symptoms, (3) treatment differences in major stroke and minor stroke, (4) the effect of stenosis progression or restenosis on stroke risk, and (5) effect modifiers and predictors of the pattern of cognitive change. Sensitivity analyses will assess the impact of participant withdrawal from the study and the level of risk factor control.

## Imaging Core

The Imaging Core oversees examination and interpretation for DU, CT, MRA and catheter-based angiography, and brain CT and MR imaging. The Core has a standardized carotid DU protocol and certifies each ultrasound laboratory's equipment, personnel, and testing technique. The Core reviews and re-reads all imaging tests performed on CREST-2 patients. Accordingly, exclusion of patients without high grade stenosis will be maximized and accurate imaging characterization of brain lesions associated with clinical strokes during the trial will be accomplished. Important secondary endpoints such as restenosis/occlusion after revascularization and stenosis progression/occlusion during medical therapy will be detected.

## Site selection and ongoing site management

Careful selection and timely activation of clinical sites in multicenter clinical trials is critical for successful enrollment, subject safety, and generalizability of results. The first potential clinical sites were identified from the sites in CREST that provided the highest number of randomizations as well as high-quality data.[13] Additional sites were invited to apply through submission of a data form containing extensive information on experience with the trial procedures, and clinical trials (see Table 7). Sites from StrokeNet, a centrally coordinated US network of 25 regional centers, were especially invited to apply.[14] Information was reviewed and sites were scored as high, medium or low. The initial target was 120 sites in North America. By the end of January 2017, 153 sites had been approved by the Site Selection and Management Committee. Of these, 104 had completed all the training and regulatory requirements and been approved to randomize.

Monitoring assures adequate protection of the rights and safety of human subjects. The trial monitor visits every site, verifies source and study documents, proper informed consent, and patient eligibility. Data quality reports are produced by the Statistical and Data Coordinating Center and protocol deviations and incompleteness of data are addressed for corrective and/or preventive actions by study leadership. An independent, NINDS-appointed Data Safety and Monitoring Board monitors safety and integrity of the trials and advises the funding agency.

## Training and credentialing

Protocol and medical management training is conducted prior to study start-up and annually for site coordinators and Investigators via in-person, teleconferences, webinars, and e-learning platforms.

Multi-disciplinary Surgical and Interventional Management Committees (IMC) credentialed operators. Surgeon candidates not previously credentialed in CREST submitted procedural reports and discharge information on at least 50 consecutive cases.

**Table 7.** Data submitted for site selection consideration

| |
|---|
| 1. Number of carotid endarterectomy and carotid stenting procedures performed at participating hospital for the past two years (including minority and sex distribution) |
| 2. Qualifications and experience of principal investigator |
| 3. Presence of an experienced clinical investigative team (e.g. neurologists, vascular surgeons, neurosurgeons, interventional cardiologists, interventional radiologists, interventional neuroradiologists, medical management physicians, research coordinators, etc.) |
| 4. Presence of affiliate sites |
| 5. Status of vascular ultrasonography laboratory (i.e. whether approved by the Intersocietal Commission on Accreditation of Vascular Laboratories or American College of Radiology Certification) |
| 6. Availability of central institutional ethics review board |
| 7. Receipt of any FDA warning letters |
| 8. Experience in other stroke trials |
| 9. Scientific/publication experience of the investigators |
| 10. StrokeNet site |

Interventionist candidates submitted 25 consecutive cases completed within five years as primary operator out of a required total experience of ≥50 cases (≥20 for operators completing training). Credentialing requires appropriate case selection, technique, and a combined stroke and death rate of <3% for asymptomatic patients.

## Companion registry

A CREST-2 Companion Registry (C2R) (clinicaltrials.gov NCT02240862) was developed to promote rapid enrollment into the CREST-2 CAS trial because many stent operator applicants did not have sufficient experience to apply for credentialing. Once reviewed by the IMC, operators receive conditional approval allowing them to perform CAS procedures within C2R. The registry ensures that procedures are performed by skilled operators at well-resourced sites.

## Summary and conclusions

Building on the recent successes of the CREST trial,[13,15] CREST-2 is uniquely positioned to test the merits of CEA and CAS in the context of IMM. CREST-2 is needed to compare CEA and CAS to IMM in asymptomatic patients primarily because of substantial changes in medical management in the past two decades that may have substantially reduced the risk of asymptomatic carotid stenosis. By using real-world applicable best practices from SAMMPRIS,[7] CREST-2 will achieve substantially better rates of risk factor control than all prior cervical carotid atherosclerosis trials through more active centralized intervention.

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### Authors' contributions

All authors were involved in the study design, protocol preparation, and acquisition of funding. VJH was responsible for first draft and final revision. All authors provided critical revision of the manuscript for important intellectual content. All authors have reviewed and approved the final manuscript.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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