ORIGINAL ARTICLE

Medical Management and Revascularization for Asymptomatic Carotid Stenosis

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ABSTRACT

BACKGROUND

Improvements in medical therapy, carotid-artery stenting, and carotid endarterectomy call into question the preferred management of asymptomatic carotid stenosis. Whether adding revascularization to intensive medical management would provide greater benefit than intensive medical management alone is unclear.

METHODS

We conducted two parallel, observer-blinded clinical trials that enrolled patients with high-grade (≥70%) asymptomatic carotid stenosis across 155 centers in five countries. The stenting trial compared intensive medical management alone (medical-therapy group) with carotid-artery stenting plus intensive medical management (stenting group); the endarterectomy trial compared intensive medical management alone (medical-therapy group) with carotid endarterectomy plus intensive medical management (endarterectomy group). The primary outcome was a composite of any stroke or death, assessed from randomization to 44 days, or ipsilateral ischemic stroke, assessed during the remaining follow-up period up to 4 years.

RESULTS

A total of 1245 patients underwent randomization in the stenting trial and 1240 in the endarterectomy trial. In the stenting trial, the 4-year incidence of primary-outcome events was 6.0% (95% confidence interval [CI], 3.8 to 8.3) in the medical-therapy group and 2.8% (95% CI, 1.5 to 4.3) in the stenting group (P=0.02 for the absolute difference). In the endarterectomy trial, the 4-year incidence of primary-outcome events was 5.3% (95% CI, 3.3 to 7.4) in the medical-therapy group and 3.7% (95% CI, 2.1 to 5.5) in the endarterectomy group (P=0.24 for the absolute difference). From day 0 to 44, in the stenting trial, no strokes or deaths occurred in the medical-therapy group and seven strokes and one death occurred in the stenting group; in the endarterectomy trial, three strokes occurred in the medical-therapy group and nine strokes occurred in the endarterectomy group.

CONCLUSIONS

Among patients with high-grade stenosis without recent symptoms, the addition of stenting led to a lower risk of a composite of perioperative stroke or death or ipsilateral stroke within 4 years than intensive medical management alone. Carotid endarterectomy did not lead to a significant benefit. (Funded by the National Institute of Neurological Disorders and Stroke and others; CREST-2 ClinicalTrials.gov number, NCT02089217.)

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*A list of the CREST-2 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The treatment of high-grade carotid-artery stenosis varies considerably internationally. Some countries limit revascularization primarily to patients with symptoms, whereas others more commonly recommend that asymptomatic patients undergo revascularization.[1] In the United States, 75 to 80% of patients who undergo carotid-artery stenting or endarterectomy are asymptomatic.[2] Randomized trials from the 1990s and early 2000s showed that carotid endarterectomy led to a lower risk of stroke among asymptomatic patients with high-grade stenosis than medical therapy.[3] Improvements in carotid endarterectomy, carotid-artery stenting, and medical therapy and the results of two recent small trials have challenged our understanding of appropriate treatments.[4-6] Here, we present results from the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trials (CREST-2), which tested whether carotid-artery stenting or carotid endarterectomy plus intensive medical management would be superior to intensive medical management alone for preventing stroke in patients with high-grade carotid stenosis without recent stroke symptoms.[7]

Methods

Trial Design

We conducted CREST-2, which comprised two parallel, observer-blinded trials: a stenting trial, in which patients were randomly assigned to receive either intensive medical management alone (medical-therapy group) or carotid-artery stenting plus intensive medical management (stenting group); and an endarterectomy trial, in which patients were randomly assigned to receive either intensive medical management alone (medical-therapy group) or endarterectomy plus intensive medical management (endarterectomy group). The ethics committees for all the trial centers approved the protocol, which is available with the full text of this article at NEJM.org. All the patients provided written informed consent. The authors designed the trial, gathered and analyzed the data, wrote the manuscript, and made the decision to submit the manuscript for publication. The authors vouch for accuracy and completeness of the data and for the fidelity of the trials to the protocol.

Centers and Investigators

Patients were enrolled at 155 centers in Australia, Canada, Israel, Spain, and the United States. Operators performing carotid-artery stenting and carotid endarterectomy were required to have certification by means of a validated process.[8] Interventionists submitted carotid-artery stenting cases from the preceding 12 months. Depending on case numbers and results, interventionists submitted procedural reports and angiograms for 3 to 25 additional prospective nonurgent cases. Surgeons submitted their preceding 50 consecutive cases and were required to have documentation of a periprocedural stroke and death rate of less than 3%.

Patient Selection and Randomization

Patients 35 years of age or older were eligible if they had no history of stroke, transient ischemic attack (TIA), or amaurosis fugax in the carotid-artery territory within 180 days before randomization. Also required were stenosis of at least 70% as assessed by Doppler ultrasonography showing a peak systolic velocity of at least 230 cm per second and any of the following findings: an end diastolic velocity of at least 100 cm per second, a peak systolic velocity ratio of the internal to common carotid artery of at least 4.0, or at least 70% stenosis on computed tomographic angiography (CTA) or magnetic resonance angiography (MRA); or at least 70% stenosis on catheter angiography alone.[9] Patients were excluded if they had a previous disabling stroke, unstable angina, or atrial fibrillation prompting anticoagulation. Patient eligibility and trial assignment were established by the trial site, guided by differences in eligibility criteria specific to carotid-artery stenting or carotid endarterectomy.[7] Patients underwent randomization by means of a Web-based system, with stratification according to trial and center.

Intensive Medical Management

The intensive medical management protocol was the same for all the patients, except for the period of antiplatelet use before and after carotid-artery stenting and carotid endarterectomy.[10] Site investigators managed cardiovascular risk factors with protocol-driven central oversight.[10] Primary targets were a systolic blood pressure of less than 130 mm Hg (the initial target of <140 mm Hg was reduced in 2018 after guideline changes)[11] and a low-density lipoprotein (LDL) cholesterol level of less than 70 mg per deciliter (1.80 mmol per liter). Elevated levels of glucose and glycated hemoglobin and lifestyle factors (cigarette smok-

ing, excess body weight, and physical inactivity) were also monitored and managed. Health coaching was provided by telephone.[10] If requested by the patient, medications to address risk factors were provided at no cost, including alirocumab, which was donated by the manufacturer (Regeneron Pharmaceuticals) after 2018.

STENTING AND ENDARTERECTOMY

Revascularization procedures were performed in accordance with guidelines[12,13] and operators' standard procedures. Carotid-artery stenting was performed with local anesthesia for femoral access, with or without conscious sedation. Embolic protection was required. Starting 48 hours before the procedure, patients who underwent carotid-artery stenting received aspirin at a dose of 325 mg daily and clopidogrel at a dose of 75 mg twice daily. After the stenting procedure, patients received clopidogrel at a dose of 75 mg daily and aspirin at a dose of 75 to 325 mg daily for 30 days, followed by a dose of 70 to 325 mg daily thereafter. Alternative antiplatelet regimens were used when clopidogrel or aspirin could not be used. Patients who underwent carotid endarterectomy received aspirin at a dose of 325 mg daily for at least 48 hours before the procedure and 70 to 325 mg daily thereafter; periprocedural anticoagulation with either heparin or bivalirudin was required.

FOLLOW-UP ASSESSMENTS

In-person follow-up occurred at 12 to 36 hours after the revascularization procedure; at 44 days; at 4, 8, and 12 months; and every 6 months thereafter to 48 months. This follow-up included a medical history, the Questionnaire Verifying Stroke Free Status,[14] the modified Rankin scale score (range, 0 [no symptoms] to 6 [death]), the National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating greater neurologic deficit),[15] vital signs, and laboratory studies. Magnetic resonance imaging (MRI) or computed tomography (CT) of the head was recommended in patients who had an increase in the NIHSS score of at least 2 points from baseline. If stroke or TIA was suspected during follow-up, an additional visit was scheduled, which included CT (or CTA) or MRI (or MRA) and other testing as indicated. For patients unable to return to the clinic and during the coronavirus disease 2019 pandemic, telephone and virtual visits were conducted.[16] The last patient who was randomly assigned to each treatment group was followed for 1 year. All the adverse events were reported by the sites to the independent medical monitor, with serious unexpected events reported within 24 hours. Results of Doppler ultrasonography were obtained annually, overseen by the imaging core (University of Maryland).[17]

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was a 4-year composite of any stroke (ischemic or hemorrhagic) or death, assessed from randomization to 44 days (periprocedural period), or ipsilateral ischemic stroke, assessed during the remaining follow-up period up to 4 years (postprocedural period). The primary outcome was analyzed according to the intention-to-treat principle (i.e., in all the patients who had undergone randomization).

Stroke was defined according to the World Health Organization (WHO) as the rapid development of clinical signs of focal (or global) disturbance of cerebral function, lasting at least 24 hours, with no apparent cause other than of cardiovascular origin.[18] A stroke-adjudication committee, whose members were unaware of the treatment assignments, reviewed all potential stroke events and classified them as major or minor, disabling or nondisabling, and ischemic or hemorrhagic. Stroke was considered to be major if the NIHSS score was 6 or higher; stroke was considered to be disabling if the modified Rankin scale score was 3 or higher at least 30 days after onset. Ischemic and hemorrhagic strokes were diagnosed according to tissue-based definitions.[19] Prespecified secondary stroke outcomes included the following: the primary outcome plus contralateral WHO stroke occurring after 44 days up to 4 years; tissue-based cerebral infarction, intracerebral hemorrhage, or subarachnoid hemorrhage in any distribution or death in the periprocedural period plus an ipsilateral central nervous system (CNS) tissue–based infarction that occurred in the postprocedural period; and the same as the preceding outcome plus contralateral CNS tissue–based infarction, intracerebral hemorrhage, or subarachnoid hemorrhage that occurred in the postprocedural period.

STATISTICAL ANALYSIS

Treatment differences were assessed at 4 years. Analyses were performed according to intention-to-treat principles. The percentage of patients with an event in each of the four trial groups (two

medical-therapy groups, stenting group, and endarterectomy group) was estimated with the use of Kaplan–Meier curves, with a supporting analysis that used the cumulative-incidence function to account for the competing risk from death. Asymptotic normality may not be supported given a relatively small number of events; therefore, the significance of the treatment differences was assessed by means of an assumption-free re-randomization test with 10,000 replications.

The trial sample-size simulation calculations assumed a 4-year event rate of 3.6% for each of the revascularization groups and provided the trial with 85% power at an alpha level of 0.05 to detect rates below 0.8% or above 8.4% in the medical-therapy groups (with accounting for 5% crossover between treatments in each direction and for a 2.5% annual withdrawal rate). A prespecified interim analysis was performed with the use of O'Brien–Fleming boundaries after approximately one third of the patients reached the 4-year follow-up point, with an adjustment to the alpha level for the final assessment to 0.047.

For the primary and secondary outcomes, the 95% confidence intervals for the estimated rates and differences in rates were estimated by the 2.5th and 97.5th percentiles of the distributions developed with the use of bootstrap methods with 100,000 replications. Treatment effects within prespecified subgroups were estimated with the use of similar methods. Annual event rates during the postprocedural period and differences in these rates were estimated by means of Poisson regression. Because treatment differences in secondary outcomes and in subgroups were not corrected for multiplicity, results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. The multiple imputation method that was specified in the statistical analysis plan was not implemented because it was not compatible with the resampling approaches used for testing. Missing data were not imputed. Details are provided in the statistical analysis plan, which is available with the protocol.

RESULTS

TRIAL POPULATIONS

In the stenting trial, 1245 patients underwent randomization and were followed for a median of 3.6 years (interquartile range, 1.6 to 4.0). The first patient underwent randomization on December 10, 2014, and the last follow-up visit was completed on July 31, 2025.

In the endarterectomy trial, 1240 patients underwent randomization and were followed for a median of 4.0 years (interquartile range, 2.0 to 4.0). The first patient underwent randomization on December 9, 2014, and the last follow-up visit was completed on September 30, 2024.

The cohorts in both trials had generally similar demographic and risk-factor profiles, and these profiles were also similar to those of the general population of persons with asymptomatic carotid stenosis (Table 1 and Table S1 in the Supplementary Appendix, available at NEJM.org). In the stenting trial, 106 patients (17%) who had been assigned to the medical-therapy group eventually underwent revascularization (78 patients underwent carotid-artery stenting, and 28 underwent carotid endarterectomy), and 41 patients (7%) who had been assigned to the stenting group did not receive any procedure (Fig. S1A). The corresponding numbers in the endarterectomy trial were 111 (18%), with 94 patients undergoing carotid endarterectomy and 17 undergoing carotid-artery stenting, and 24 (4%), with 22 not receiving any procedure and 2 receiving carotid-artery stenting (Fig. S1B). Across the trials and treatment groups, the proportions of patients who had primary risk-factor values in the target range increased in the first few months after randomization and were generally sustained (Fig. 1 and Figs. S2A through S6B). The use of antiplatelet and anticoagulant agents was similar across all the treatment groups (Table S2).

PRIMARY OUTCOME

In the stenting trial, the 4-year rate of the composite primary outcome was 6.0% (95% confidence interval [CI], 3.8 to 8.3) in the medical-therapy group and 2.8% (95% CI, 1.5 to 4.3) in the stenting group. The absolute risk difference was 3.2 percentage points (95% CI, 0.6 to 5.9; P=0.02), and the relative risk in the medical-therapy group as compared with the stenting group was 2.13 (95% CI, 1.15 to 4.39) (Fig. 2A and Table 2). From day 0 through 44, no strokes or deaths occurred in the medical-therapy group, and seven strokes and one death occurred in the stenting group (in 1.3% of patients; 95% CI, 0.6 to 2.5) (Fig. 2B and Table 2). Beyond 44 days, 28

Table 1. Demographic and Clinical Characteristics of the Patients in the Two Trials, According to Treatment Assignment.*

Characteristic	Stenting Trial (N=1245)		Endarterectomy Trial (N=1240)	
	Medical Therapy Alone (N=629)	Stenting (N=616)	Medical Therapy Alone (N=623)	Endarterectomy (N=617)
Age — yr	69.7±7.7	69.3±8.1	70.4±7.6	70.7±7.8
Female sex — %	38.2	36.9	39.0	35.3
Race — %†				
White	90.1	92.9	88.3	90.0
Black	6.2	5.7	6.9	6.0
Other, not reported, or missing data	3.7	1.5	4.8	4.1
Hispanic ethnic group — %†	4.7	4.8	3.9	4.4
Previous stroke or TIA on target lesion >180 days before randomization — %	4.9	8.0	8.4	8.9
Risk factors — %				
Hypertension	87.4	88.0	84.9	85.1
Diabetes	37.8	40.7	38.0	34.4
Dyslipidemia	93.3	92.0	90.0	91.5
Current smoking	21.0	18.8	21.2	21.1
Previous cardiovascular disease or CABG	54.5	53.7	43.3	44.3
Blood pressure — mm Hg				
Systolic	138.8±20.2	138.2±20.2	137.9±19.8	139.3±20.2
Diastolic	73.2±10.8	73.1±11.2	72.6±10.2	73.1±10.7
LDL cholesterol — mg/dl‡	76.7±34.6	77.1±36.5	81.3±33.9	80.3±33.6
Body-mass index§	28.7±5.6	29.3±5.5	28.5±5.4	28.7±5.3
Stenosis at randomization — %				
Index artery				
≥70% stenosis	97.6	97.7	97.1	97.4
Peak systolic velocity ≥389 cm/sec¶	33.5	31.1	32.9	37.2
Nonindex artery: ≥50% stenosis	34.4	37.0	37.2	35.7
Modified Rankin scale score of 0 — %‖	87.8	88.8	87.9	87.0
CHA_2DS_2-VASc score of ≥4 — %**	56.9	60.1	53.8	55.9
Current treatment with any antiplatelet agent before procedure — %	—	100	—	99.2
Carotid-artery stenting procedure				
Median target-lesion length (IQR) — mm	—	18 (12–20)	—	—
Embolic protection placed — %	—	99.6	—	—
Carotid endarterectomy procedure: general anesthesia — %	—	—	—	89.0

* Plus–minus values are means ±SD. The stenting trial compared intensive medical management (medical therapy alone) with carotid-artery stenting plus intensive medical management (stenting), and the endarterectomy trial compared intensive medical management (medical therapy alone) with carotid endarterectomy plus intensive medical management (endarterectomy). CABG denotes coronary-artery bypass grafting, IQR interquartile range, LDL low-density lipoprotein, and TIA transient ischemic attack.

† Race and ethnic group were determined by the investigator.

‡ To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ A peak systolic velocity of 389 cm per second or greater indicates stenosis of approximately 80% or more of the artery.

‖ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability and a score of 6 indicating death. A score of 0 indicates no symptoms.

** The CHA_2DS_2-VASc scale is used to assess the risk of stroke among patients with atrial fibrillation; scores range from 0 to 9, with higher scores indicating a greater risk of stroke.

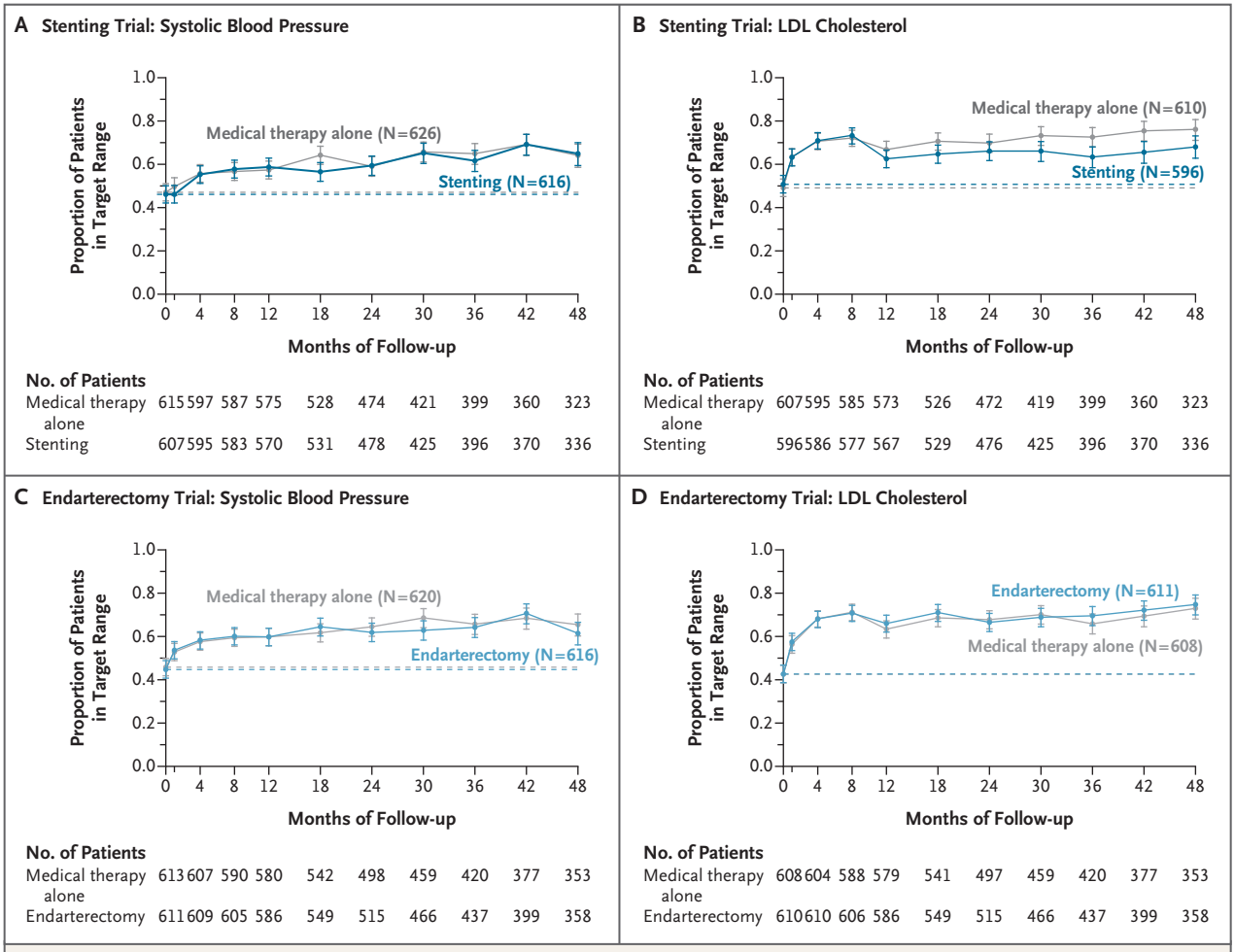


Figure 1. Proportion of Patients with Risk-Factor Values in Target Range over Time.

The stenting trial compared intensive medical management (medical therapy alone) with carotid-artery stenting plus intensive medical management (stenting), and the endarterectomy trial compared intensive medical management (medical therapy alone) with carotid endarterectomy plus intensive medical management (endarterectomy). Shown are changes in risk-factor values (systolic blood pressure and low-density lipoprotein [LDL] cholesterol) from baseline to 48 months for the stenting trial (Panels A and B) and the endarterectomy trial (Panels C and D). The target systolic blood pressure was less than 130 mm Hg (changed from <140 mm Hg in 2018). The target LDL cholesterol level was less than 70 mg per deciliter (1.80 mmol per liter). Dashed lines represent the proportion of patients meeting the treatment threshold goals in each group at baseline; these values overlap in Panel D. The first postbaseline assessment was conducted at 44 days after randomization. Patients were followed beyond the occurrence of a primary-outcome event for risk-factor control. In all panels, I bars indicate 95% confidence intervals.

ipsilateral ischemic strokes occurred among 600 patients followed for 1686 person-years in the medical-therapy group, for an annual event rate of 1.7% (95% CI, 1.1 to 2.4); in the stenting group, 7 ipsilateral ischemic strokes occurred among 582 patients followed for 1714 person-years, for an annual event rate of 0.4% (95% CI, 0.2 to 0.9), with a relative risk of 4.07 (95% CI, 1.78 to 9.31) (Fig. 2C and Table 2).

A supporting analysis that accounted for the competing risk of death showed results similar to those of the primary analysis (Table S3). A tipping-point analysis suggested that the significance for the stenting trial would be retained unless four or more events were removed from the medical-therapy group or unless three or more events were added to the stenting group (see the Supplementary Appendix).

In the endarterectomy trial, the 4-year rate of the primary outcome was 5.3% (95% CI, 3.3 to 7.4)

in the medical-therapy group and 3.7% (95% CI, 2.1 to 5.5) in the endarterectomy group. The absolute risk difference was 1.6 percentage points (95% CI, −1.1 to 4.3; P=0.24), and the relative risk in the medical-therapy group as compared with the endarterectomy group was 1.43 (95% CI, 0.78 to 2.72) (Fig. 2A and Table 2). From day 0 through 44, three strokes occurred in the medical-therapy group (in 0.5% of patients; 95% CI, 0.1 to 1.4), and nine strokes occurred in the endarterectomy group (in 1.5% of patients; 95% CI, 0.7 to 2.8) (Fig. 2B and Table 2). Beyond 44 days, 23 ipsilateral ischemic strokes occurred among 600 patients followed for 1761 person-years in the medical-therapy group, for an annual event rate of 1.3% (95% CI, 0.9 to 2.0); in the endarterectomy group, 10 ischemic strokes occurred among 596 patients followed for 1823 person-years, for an annual event rate of 0.5% (95% CI, 0.3 to 1.0), with a relative risk of 2.38 (95% CI, 1.13 to 5.00) (Fig. 2C and Table 2).

A supporting analysis that accounted for the competing risk of death showed similar results to those of the primary analysis. A tipping-point analysis in the endarterectomy trial suggested that significance would have been achieved if seven or more events were removed from the endarterectomy group or if six or more events were added to the medical-therapy group.

In both trials, imaging of the head that was performed within a 30-day window after a primary-outcome cerebral infarction occurred was available for review for 72 of 85 patients (85%), with volume data available for 70 patients. Imaging was conducted by MRI in 59 patients (82%) and by CT only in 13 patients (18%). The median maximum volume was 1.55 ml (interquartile range, 0.27 to 7.81). The infarct volume appeared to be similar in the two treatment groups in both trials (Fig. S7A and S7B). Differences in the treatment effect for 11 prespecified subgroups are shown in Figure 3.

For the combined periprocedural and postprocedural periods, the annual event rate among patients treated with intensive medical management alone was similar in the two trials. In the stenting trial, 28 events occurred among 629 patients followed for 1759 person-years, for an annual event rate of 1.6% (95% CI, 1.1 to 2.3); in the endarterectomy trial, 26 stroke events occurred among 623 patients followed for 1834 person-years, for an annual event rate of 1.4% (95% CI, 1.0 to 2.1).

SECONDARY OUTCOMES

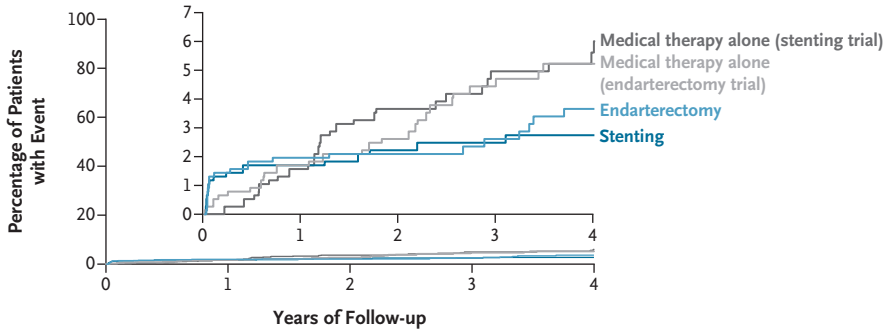
The robustness of the primary findings was assessed by consideration of commonly used alternative outcome definitions (Table S4A through S4J). The results for the 4-year composite primary outcome when the tissue-based definition of stroke was used were similar to the results for the primary outcome with WHO-defined stroke in both the stenting and endarterectomy trials. The results for the nondisabling stroke and minor stroke outcomes were concordant with results for the primary outcome in the stenting and endarterectomy trials. All the treatment groups, including the medical-therapy groups, had low rates of disabling stroke.

Periprocedural and postprocedural serious adverse events are listed in Table S5. In the stenting trial, the most common serious adverse events were carotid revascularization, which occurred in 118 patients (18.8%) in the medical-therapy group and in 29 patients (4.7%) in the stenting group, and death, which occurred in 69 (11.0%) and 48 (7.8%), respectively. In the endarterectomy trial, the most common serious adverse events were carotid revascularization, which occurred in 131 patients (21.0%) in the medical-therapy group and in 44 (7.1%) in the endarterectomy group, and death, which occurred in 60 (9.6%) and 54 (8.8%), respectively. Common reasons that were provided for revascularization were new carotid symptoms, progression of stenosis, and patient preference.

DISCUSSION

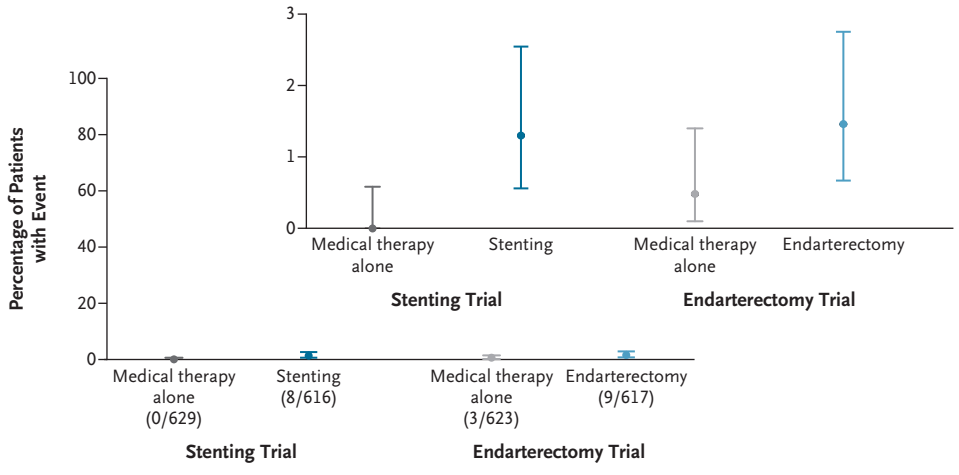
Among participants with asymptomatic high-grade carotid stenosis, the stenting trial showed that the addition of transfemoral carotid-artery stenting to intensive medical management led to a significantly lower risk of the primary composite outcome (periprocedural stroke or death or postprocedural ipsilateral stroke within 4 years) as compared with intensive medical management alone (2.8% vs. 6.0%). The absolute risk difference of 3.2 percentage points was significant, corresponding to a number needed to treat of 31 to prevent one primary-outcome event (Table S6).

A Primary-Outcome Analysis

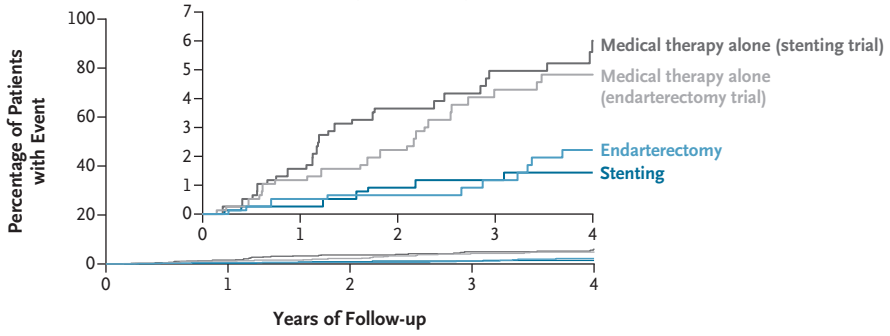


No. of Patients					
Stenting trial					
Medical therapy alone	629	537	428	360	276
Stenting	616	543	431	375	289
Endarterectomy trial					
Medical therapy alone	623	550	461	381	304
Endarterectomy	617	561	482	411	319

B Periprocedural Component of Primary-Outcome Analysis (days 0 to 44)



C Postprocedural Component of Primary-Outcome Analysis (after 44 days)



No. of Patients					
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Medical therapy alone	600	537	428	360	276
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Endarterectomy trial					
Medical therapy alone	600	550	461	381	304
Endarterectomy	596	559	480	409	317

Figure 2 (facing page). Four-Year Event Rates for the Primary Outcome and Individual Components of the Primary Outcome.

Panel A shows Kaplan–Meier estimates of the 4-year incidence of primary-outcome events in the stenting and endarterectomy trials, according to trial group. The primary outcome was a composite of any stroke or death, assessed from randomization to 44 days, or ipsilateral ischemic stroke, assessed during the remaining follow-up period up to 4 years. Panel B shows the periprocedural component of the primary outcome (i.e., stroke or death from randomization [day 0] to 44 days). Numbers in parentheses below the labels on the horizontal axis are the numbers of events and of patients in trial group. I bars indicate 95% confidence intervals. Panel C shows the postprocedural component of the primary outcome (i.e., ipsilateral ischemic stroke during the remaining portion of the 4-year follow-up). In all panels, the inset shows the same data on an expanded y axis.

In the endarterectomy trial, we found no significant difference in the 4-year incidence of primary-outcome events (5.3% in the medical-therapy group and 3.7% in the endarterectomy group). The event rate among patients who had been assigned to a revascularization group appeared to be similar in the two trials (Fig. 2A). Results appeared to be consistent across subgroups in the two trials.

The program of intensive medical management had similar effects on control of risk factors across the treatment groups in the two trials (Fig. 1). The CREST-2 team diligently monitored the risk-factor status of all patients and worked closely with the trial sites to improve control. Furthermore, a commercial company worked directly with patients on risk-factor management.

The results of CREST-2 should be considered in the context of recently completed interventional trials[5,6] and a population-based study of asymptomatic carotid-artery disease.[20] The SPACE-2 trial, which did not show a benefit of revascularization as compared with medical therapy,[21] used the less-stringent criteria of the European Carotid Surgery Trial (ECST) for measuring stenosis.[22] In addition, despite multiple tactics for enrollment,[21] the final cohort in the SPACE-2 trial was less than 16% of the target enrollment, which limited the power of that trial to compare revascularization with medical treatment alone.[5] The ECST-2 trial included patients with stenosis of 50 to 69%, of whom one third had symptoms, and only 10 of 214 patients in the revascularization group underwent carotid-artery stenting.[6]

The Oxford Vascular Study, which involved patients receiving medical therapy, showed a lower annual stroke rate than the medical-therapy groups in CREST-2 but relied on patients with stenosis of 50% or more seeking medical attention for event ascertainment.[20] In CREST-2, but not in the Oxford study, MRI imaging was preferred to CT and was performed for 82% of the primary-outcome cerebral infarctions. MRI has substantially higher sensitivity for detecting infarction than CT, particularly smaller infarcts. Furthermore, we surveilled patients for potential stroke events in a scheduled manner using the Questionnaire Verifying Stroke Free Status.[14] Thus, the two trials in CREST-2 provide more-rigorous evidence than SPACE-2 and ECST-2 about the relative effects of revascularization as compared with medical therapy on stroke outcomes. They also provide more pertinent evidence than the Oxford study about the risk of stroke among asymptomatic patients with stenosis of 70% or more.

As in previous trials involving patients with carotid-artery disease,[5,8,23,24] all the treatment groups, including the medical-therapy groups, had low rates of disabling stroke. Stenosis progression and TIAs are established risk factors for ipsilateral stroke and indications for early intervention. To comply with the standard of care, our trials allowed revascularization in the medical-therapy groups after TIA (urgent) or progression of stenosis (timely). Patients receiving intensive medical therapy should be educated about symptoms of carotid-artery TIA and the importance of urgent presentation for care if such symptoms occur.[25] As in previous trials,[5,8,23,24] both carotid-artery stenting and endarterectomy were durable with regard to low rates of postprocedural strokes.

Our two trials have limitations. First, although stroke adjudicators were unaware of the treatment assignments, patients and treating physicians were not. Second, various changes in medical-therapy practices occurred during the trials that could lower stroke rates and negate any additional benefit of revascularization. For example, guidelines now recommend a lower target for systolic blood pressure, the advent of proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors creates new options for the lowering of LDL cho-

Table 2. Analysis of Primary Outcome and Components.

Variable	Stenting Trial		Endarterectomy Trial	
	Medical Therapy Alone	Stenting	Medical Therapy Alone	Endarterectomy
Primary 4-yr composite outcome*				
Event rate (95% CI) — %	6.0 (3.8 to 8.3)	2.8 (1.5 to 4.3)	5.3 (3.3 to 7.4)	3.7 (2.1 to 5.5)
Absolute difference (95% CI) — percentage points†	3.2 (0.6 to 5.9)		1.6 (–1.1 to 4.3)	
P value for difference	0.02		0.24	
Relative risk (95% CI)†	2.13 (1.15 to 4.39)		1.43 (0.78 to 2.72)	
Components of primary outcome				
Periprocedural period: stroke or death				
No. of events/no. of patients	0/629	8/616	3/623	9/617
Percent of patients with event (95% CI)	0.0 (0.0 to 0.6)	1.3 (0.6 to 2.5)	0.5 (0.1 to 1.4)	1.5 (0.7 to 2.8)
Difference (95% CI) — percentage points	–1.3 (–2.2 to 0.4)		–1.0 (–2.1 to 0.1)	
Postprocedural period: ipsilateral ischemic stroke				
No. of person-yr	1686	1714	1761	1823
No. of events/no. of patients	28/600	7/582	23/600	10/596
Annual event rate per person-yr (95% CI) — %	1.7 (1.1 to 2.4)	0.4 (0.2 to 0.9)	1.3 (0.9 to 2.0)	0.5 (0.3 to 1.0)
Relative risk (95% CI)	4.07 (1.78 to 9.31)		2.38 (1.13 to 5.00)	

* The primary outcome was a composite of any stroke or death in the periprocedural period (randomization through 44 days) or ipsilateral ischemic stroke in the postprocedural period (the remaining portion of the 4-year follow-up).
† These 95% confidence intervals for the 4-year composite outcome were adjusted to 95.3% to account for the reduction in the P value from the interim analysis (i.e., to represent the 2.35% and 97.65% thresholds of the bootstrap distribution).

lesterol levels, and new highly efficacious pharmacotherapies for diabetes and obesity have been adopted widely.[26-28] Third, revascularization was performed only by well-trained and certified high-volume operators, so the results in CREST-2 may not reflect practice more broadly. Fourth, transcarotid-artery revascularization came into frequent use after approximately one half the patients had undergone randomization, and thus this approach could not be incorporated in the trial.[29]

In addition, the tipping-point analysis suggested that significance in the stenting trial could be affected by a change in the outcome of three or four patients (with a larger number being required for the endarterectomy trial to reach significance thresholds). Although the absolute number of patients is relatively small, it represents more than a 10% relative change in the number of events. Finally, carotid-artery revascularization is not designed to prevent strokes of all mechanisms, and some of the postprocedural strokes may not have been causally related to carotid-artery revascularization.

We found that among patients with high-grade stenosis without recent stroke symptoms, carotid-artery stenting with intensive medical management led to a lower risk of a composite outcome of perioperative stroke or death or ipsilateral stroke within 4 years than intensive medical management alone. Carotid endarterectomy plus intensive medical management did not provide a significant benefit as compared with intensive medical management alone. An ongoing long-term post-trial follow-up study, as was done in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) trial,[8] is

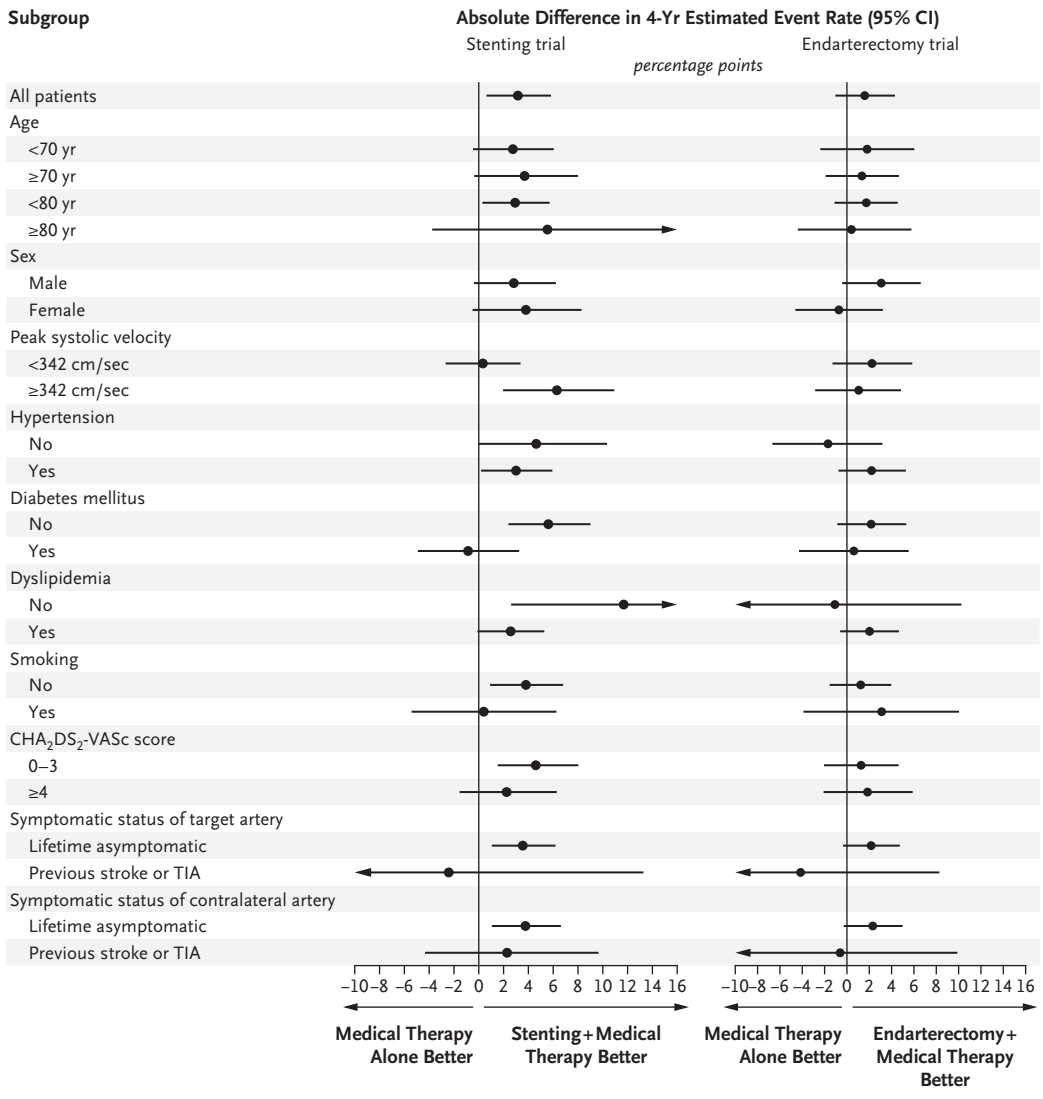

Figure 3. Absolute Between-Group Differences in the 4-Year Estimated Event Rate in the Stenting and Endarterectomy Trials, According to Risk-Factor Subgroups.

Shown are absolute between-group differences in the 4-year incidence of primary-outcome events in the stenting and endarterectomy trials. The CHA_2DS_2-VASc scale is used to assess the risk of stroke among patients with atrial fibrillation; scores range from 0 to 9, with higher scores indicating a greater risk of stroke. Confidence intervals are not adjusted for multiplicity and should not be used to infer treatment effects. Arrows indicate that the 95% confidence interval extends outside the graphed area. Full data regarding the subgroup analyses are provided in Figure S8A through S8K. TIA denotes transient ischemic attack.

evaluating longer-term outcomes for the comparisons of carotid-artery stenting and carotid endarterectomy with intensive medical management.[30] The identification of features of carotid atherosclerosis that may benefit from revascularization warrants future research.[31]

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REFERENCES

1. Vikatmaa P, Mitchell D, Jensen LP, et al. Variation in clinical practice in carotid surgery in nine countries 2005-2010: lessons from VASCUNET and recommendations for the future of national clinical audit. Eur J Vasc Endovasc Surg 2012;44:11-7.
2. Otite FO, Morris NA, Sabra A, et al. Trends in the utilization of different carotid revascularization modalities in the United States over a 17-year period. Neurology 2025;105(8):e214104.
3. Barkat M, Roy I, Antoniou SA, Torella F, Antoniou GA. Systematic review and network meta-analysis of treatment strategies for asymptomatic carotid disease. Sci Rep 2018;8:4458.
4. Naylor R, Rantner B, Ancetti S, et al. Editor's choice — European Society for Vascular Surgery (ESVS) 2023 clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease. Eur J Vasc Endovasc Surg 2023;65:7-111.
5. Reiff T, Eckstein H-H, Mansmann U, et al. Carotid endarterectomy or stenting or best medical treatment alone for moderate-to-severe asymptomatic carotid artery stenosis: 5-year results of a multicentre, randomised controlled trial. Lancet Neurol 2022;21:877-88.
6. Donners SJA, van Velzen TJ, Cheng SF, et al. Optimised medical therapy alone versus optimised medical therapy plus revascularisation for asymptomatic or low-to-intermediate risk symptomatic carotid stenosis (ECST-2): 2-year interim results of a multicentre randomised trial. Lancet Neurol 2025;24:389-99.
7. Howard VJ, Meschia JF, Lal BK, et al. Carotid revascularization and medical management for asymptomatic carotid stenosis: protocol of the CREST-2 clinical trials. Int J Stroke 2017;12:770-8.
8. Brott TG, Hobson RW II, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
9. Gornik HL, Rundek T, Gardener H, et al. Optimization of duplex velocity criteria for diagnosis of internal carotid artery (ICA) stenosis: a report of the Intersocietal Accreditation Commission (IAC) Vascular Testing Division Carotid Diagnostic Criteria Committee. Vasc Med 2021;26:515-25.
10. Turan TN, Voeks JH, Chimowitz MI, et al. Rationale, design, and implementation of intensive risk factor treatment in the CREST2 trial. Stroke 2020;51:2960-71.
11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:1269-324.
12. AbuRahma AF, Avgerinos ED, Chang RW, et al. Society for Vascular Surgery clinical practice guidelines for management of extracranial cerebrovascular disease. J Vasc Surg 2022;75:Suppl 1:4S-22S.
13. White CJ, Brott TG, Gray WA, et al. Carotid artery stenting: JACC state-of-the-art review. J Am Coll Cardiol 2022;80:155-70.
14. Meschia JF, Brott TG, Chukwudelunzu FE, et al. Verifying the stroke-free phenotype by structured telephone interview. Stroke 2000;31:1076-80.
15. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-70.
16. Meschia JF, Barrett KM, Brown RD Jr, et al. The CREST-2 experience with the evolving challenges of COVID-19: a clinical trial in a pandemic. Neurology 2020;95:29-36.
17. Lal BK, Jreij G, Chrencik M, et al. Ca-

rotid plaque characteristics in the CREST-2 trial. JVS Vasc Insights 2024;2:100134.
18. Dirren E, Escribano Paredes JB, Klug J, et al. Stroke incidence, case fatality, and mortality using the WHO International Classification of Diseases 11: the Geneva Stroke Study. Neurology 2025;104(5): e213353.
19. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064-89.
20. Howard DPJ, Gaziano L, Rothwell PM, Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. Lancet Neurol 2021;20:193-202.
21. Eckstein HH, Reiff T, Ringleb P, Jansen O, Mansmann U, Hacke W. SPACE-2: a missed opportunity to compare carotid endarterectomy, carotid stenting, and best medical treatment in patients with asymptomatic carotid stenoses. Eur J Vasc Endovasc Surg 2016;51:761-5.
22. Rothwell PM, Gutnikov SA, Warlow CP, European Carotid Surgery Trialist's Collaboration. Reanalysis of the final results of the European Carotid Surgery Trial. Stroke 2003;34:514-23.
23. Halliday A, Bulbulia R, Bonati LH, et al. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. Lancet 2021;398:1065-73.
24. Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med 2016;374:1021-31.
25. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004;363:915-24.
26. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023;389:2221-32.
27. Banerjee M, Pal R, Mukhopadhyay S, Nair K. GLP-1 receptor agonists and risk of adverse cerebrovascular outcomes in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2023;108: 1806-12.
28. Alammari N, Alshehri A, Al Khalaf A, et al. Effects of GLP-1 receptor agonists on incidence and outcomes of ischemic stroke and myocardial infarction: a systematic review and meta-analysis. Diabetes Obes Metab 2025;27:4387-400.
29. Meschia JF, Lal B, Roubin G, et al. Adapting to evolving technologies and treatment guidelines in a procedural trial: a qualitative review of the CREST-2 experience. Neurology 2023;100:1060-6.
30. Stojadinovic E, Voeks J, Barrett KM, et al. Long-term observational extension study of an international stroke prevention clinical trial: methods and opportunities. Cerebrovasc Dis 2025 July 18 (Epub ahead of print).
31. Paraskevas KI, Mikhailidis DP, Ringleb PA, et al. An international, multispecialty, expert-based Delphi Consensus document on controversial issues in the management of patients with asymptomatic and symptomatic carotid stenosis. J Vasc Surg 2024;79(2):420-435.e1.