

EDITORIALS



Carotid-Artery Stenting in Stroke Prevention

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Stroke is a massive medical and societal challenge. It is the third most common cause of death among adults and the leading cause of long-term disability. We need better ways to treat acute stroke — and this need has been addressed by the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST; ClinicalTrials.gov number, NCT00004732), the results of which are reported by Brott and colleagues in this issue of the *Journal*.¹

The CREST results have been eagerly awaited, since they follow a series of reports of trials that indicate either a trend toward inferiority or significant inferiority of carotid-artery stenting as compared with carotid endarterectomy for the treatment of carotid-artery stenosis. The treatment of acute stroke has been derived in part from similar advances in cardiac treatment. For example, strategies for primary and secondary prevention of stroke are broadly similar to those used for cardiac disease, including blood-pressure reduction and use of antiplatelet therapy or statins. Carotid endarterectomy is a proven method of stroke prevention in patients with severe carotid stenosis, as is coronary-artery bypass surgery for patients with coronary artery disease. The confirmation of thrombolysis as a preventive measure for ischemic stroke followed research on its efficacy in patients with acute coronary syndromes. It therefore seems plausible that carotid-artery stenting might be the next incarnation of the already-widespread use of stenting in the management of coronary artery disease.

Though previous, small trials have suggested that carotid-artery stenting is equivalent to carotid endarterectomy,² or even superior in high-risk patients,³ more recent, larger trials either have in-

dicated that the periprocedural risks of carotid-artery stenting are significantly higher than those of carotid endarterectomy^{4,5} or have failed to establish the noninferiority of carotid-artery stenting.⁶ Guidelines have indicated that carotid endarterectomy is the preferred option for patients with symptomatic carotid stenosis.⁷ So, the critical question is whether the CREST results — with the headline finding of equivalence of stenting and endarterectomy regarding the primary composite end point of stroke, myocardial infarction, or death — are different from, or broadly similar to, the results of the previous trials. This is the debate that will follow publication of the CREST findings.

In comparing the CREST findings with those of the earlier trials, the most important issue is the choice of the primary end point. Two of the three earlier trials used the composite end point of stroke or death.^{4,6} The French trial Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S; NCT00190398), involving 527 patients, was stopped prematurely for reasons of safety and futility; the rates of death or stroke at 1 and 6 months were lower with carotid endarterectomy than with carotid-artery stenting.⁴ In the German trial, Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE; Current Controlled Trials number, ISRCTN57874028), with 1183 symptomatic patients, there was a failure to prove noninferiority of carotid-artery stenting.⁶ More recently, the investigators of the International Carotid Stenting Study (ICSS; ISRCTN25337470), enrolling 1713 patients, reported on an interim safety analysis of the composite of stroke, death, or periprocedural myocardial infarction, which

showed a clear superiority of carotid endarterectomy over carotid-artery stenting.⁵ This finding reflected increased risks of stroke and death, as in the EVA-3S and SPACE trials, with similarly low rates of myocardial infarction.⁵

The timing of the primary end point is another important issue. In CREST, the primary end point was the composite of any stroke, myocardial infarction, or death during the periprocedural period and subsequent ipsilateral stroke within 4 years after randomization. In contrast, the European trials reported adjudication of end points at between 30 days, in the EVA-3S and SPACE trials,^{4,6} and 120 days, in the ICSS,⁵ although the ICSS investigators will be reporting longer-term outcomes. In CREST, there was no significant difference in the risk of the composite primary end point between the two treatment groups; however, the rate of stroke or death was still significantly higher in the stenting group than in the endarterectomy group, both during the periprocedural period and at 4 years. This is true despite the low rates of periprocedural stroke and death in both treatment groups as compared with the other trials. For example, the rate of periprocedural stroke among symptomatic patients treated by carotid-artery stenting was 6.0% in CREST but 9.6% in the EVA-3S trial.^{1,4} These results underline the importance of training, credentialing, and auditing of proceduralists. In CREST, the increased risk of stroke associated with carotid-artery stenting was offset by a reduced risk of myocardial infarction (1.1%, vs. 2.3% with carotid endarterectomy). The rate of myocardial infarction was lower in some of the earlier trials, for example, 0.8% with carotid endarterectomy in the EVA-3S trial⁴ and 0.5% in the ICSS,⁵ perhaps in part reflecting differing definitions of the condition but also reflecting the high proportion of patients in CREST who had preexisting coronary artery disease.

The crux of the debate about the CREST results is this: Can periprocedural stroke and myocardial infarction be considered equivalent events in terms of longer-term health implications? We think not. Indeed, post hoc analyses in CREST of health status at 1 year (according to the 36-Item Short-Form Health Survey summary scales) showed that although major stroke and minor stroke had an effect on physical health, and minor stroke on mental health, the

effect of periprocedural myocardial infarction was not significant.

In CREST, carotid-artery stenting provided embolic protection in the large majority of patients (96.1%), but this did not obviate the clear-cut superiority of carotid endarterectomy over carotid-artery stenting with respect to the secondary end point of stroke or death. A substudy of the ICSS involving magnetic resonance imaging showed an increase in the rate of new lesions on diffusion-weighted imaging after carotid-artery stenting as compared with carotid endarterectomy, with an even higher rate, paradoxically, in centers that used distal cerebral-protection devices.⁸ A fascinating finding in CREST is the interaction between age and the efficacy of therapy. Stenting tended to have greater efficacy at younger ages (below approximately 70 years) and carotid endarterectomy in older subjects (above approximately 70 years). This trend has been seen in an earlier trial⁶ and may reflect some of the increased technical challenges of stenting in older patients, such as the atherosclerotic burden in the internal carotid artery and aortic arch and increased arterial tortuosity.

What can we conclude from CREST? It is among the largest of the randomized trials of carotid-artery stenting, with impressively low complication rates, but the results are broadly consistent with those in previous trials. Namely, carotid-artery stenting is associated with a higher periprocedural risk of stroke or death, a difference that was still significant at 4 years. A recent meta-analysis of 11 randomized trials performed through 2009 (not including CREST) showed that carotid endarterectomy was superior to carotid-artery stenting with regard to short-term outcomes but not longer-term outcomes.⁹ Clearly, more long-term data are needed before a full appreciation of the relative risks and benefits of the two procedures can be made.¹⁰ In addition, we look forward to more information concerning the intriguing effect of age, which may indicate greater equipoise in the choice of interventions in younger patients. Local complications, particularly cranial-nerve palsies, are mainly associated with carotid endarterectomy. Though it appears that the increased risk of stroke with carotid-artery stenting is offset by an increased risk of myocardial infarction with carotid endarterectomy, stroke has greater long-

term health consequences than myocardial infarction. The risk–benefit issue is complex and should be discussed with patients. We conclude that until more data are available, carotid endarterectomy remains the preferred treatment for most patients with symptomatic carotid stenosis; treatment for asymptomatic stenosis remains controversial. However, given the lack of significant difference in the rate of long-term outcomes, the individualization of treatment choices is appropriate.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Prognostic Implications of HPV in Oropharyngeal Cancer

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Identification of human papillomavirus (HPV) as the etiologic agent of cervical cancer has led to its identification in other cancers, with oropharyngeal squamous-cell carcinoma the most common of these.^{1,2} In this issue of the *Journal*, Ang and colleagues³ report findings from their study (ClinicalTrials.gov number, NCT00047008) that contribute to the growing body of evidence that HPV-positive oropharyngeal squamous-cell carcinoma represents a distinct clinicopathological entity associated with a better prognosis than HPV-negative oropharyngeal squamous-cell carcinoma.^{4,5} In a randomized trial of patients with oropharyngeal squamous-cell carcinoma, the overall survival was substantially better among patients with HPV-positive cancer than among patients with HPV-negative cancer. The size of the

sample — 323 patients with oropharyngeal squamous-cell carcinoma and known HPV status, of whom 64% had HPV-positive tumors — enabled the authors to control for many variables and to conclude that HPV status was a critical independent prognostic determinant.

The two classes of oropharyngeal squamous-cell carcinoma appear to have distinct causes. HPV-positive cases are associated with sex-related risk factors that have also been linked to cervical cancer and an increased likelihood of orogenital activity, whereas tobacco and alcohol consumption are the key risk factors for HPV-negative cases. Epidemiologic studies suggest little interaction between the two sets of risk factors, suggesting that HPV-positive cancer and HPV-negative cancer may each have a distinct pathogenesis.

Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis

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ABSTRACT

BACKGROUND

Carotid-artery stenting and carotid endarterectomy are both options for treating carotid-artery stenosis, an important cause of stroke.

METHODS

We randomly assigned patients with symptomatic or asymptomatic carotid stenosis to undergo carotid-artery stenting or carotid endarterectomy. The primary composite end point was stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization.

RESULTS

For 2502 patients over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary end point between the stenting group and the endarterectomy group (7.2% and 6.8%, respectively; hazard ratio with stenting, 1.11; 95% confidence interval, 0.81 to 1.51; $P=0.51$). There was no differential treatment effect with regard to the primary end point according to symptomatic status ($P=0.84$) or sex ($P=0.34$). The 4-year rate of stroke or death was 6.4% with stenting and 4.7% with endarterectomy (hazard ratio, 1.50; $P=0.03$); the rates among symptomatic patients were 8.0% and 6.4% (hazard ratio, 1.37; $P=0.14$), and the rates among asymptomatic patients were 4.5% and 2.7% (hazard ratio, 1.86; $P=0.07$), respectively. Periprocedural rates of individual components of the end points differed between the stenting group and the endarterectomy group: for death (0.7% vs. 0.3%, $P=0.18$), for stroke (4.1% vs. 2.3%, $P=0.01$), and for myocardial infarction (1.1% vs. 2.3%, $P=0.03$). After this period, the incidences of ipsilateral stroke with stenting and with endarterectomy were similarly low (2.0% and 2.4%, respectively; $P=0.85$).

CONCLUSIONS

Among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing carotid-artery stenting and the group undergoing carotid endarterectomy. During the periprocedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy. (ClinicalTrials.gov number, NCT00004732.)

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CAROTID-ARTERY ATHEROSCLEROSIS IS AN important cause of ischemic stroke.¹ Carotid endarterectomy has been established as effective treatment for both symptomatic patients and asymptomatic patients.²⁻⁴ Carotid-artery stenting is another option for treatment. The results of randomized trials comparing carotid-artery stenting and carotid endarterectomy for use in symptomatic patients are conflicting.⁵⁻⁷ The primary aim of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) was to compare the outcomes of carotid-artery stenting with those of carotid endarterectomy among patients with symptomatic or asymptomatic extracranial carotid stenosis.

METHODS

STUDY DESIGN

CREST is a randomized, controlled trial with blinded end-point adjudication. Ethics review boards at all participating centers approved the protocol. All patients provided written informed consent. The authors designed the study, gathered and analyzed the data, wrote the manuscript, made the decision to publish the findings, vouch for the completeness and accuracy of the data, and attest to the fidelity of the report to the study protocol. Abbott Vascular Solutions (formerly Guidant) donated the Accunet and Acculink systems to all CREST centers in Canada and to CREST centers in the United States that were at Veterans Affairs sites. Abbott has a nonvoting seat on the CREST Executive Committee and reviewed the final draft of the manuscript before submission. Abbott assisted with CREST site monitoring and was responsible for all site monitoring of the Canadian centers. The full protocol and statistical analysis plan can be found in the Supplementary Appendix with the full text of this article at NEJM.org.

CENTERS AND INVESTIGATORS

We enrolled patients at 108 centers in the United States and 9 in Canada. Centers were required to have a team consisting of a neurologist, an interventionist, a surgeon, and a research coordinator. Patients could not be randomly assigned to a treatment group until the operators performing carotid-artery stenting and carotid endarterectomy had been certified. Certification was achieved by 477 surgeons, whose clinical results were audited by

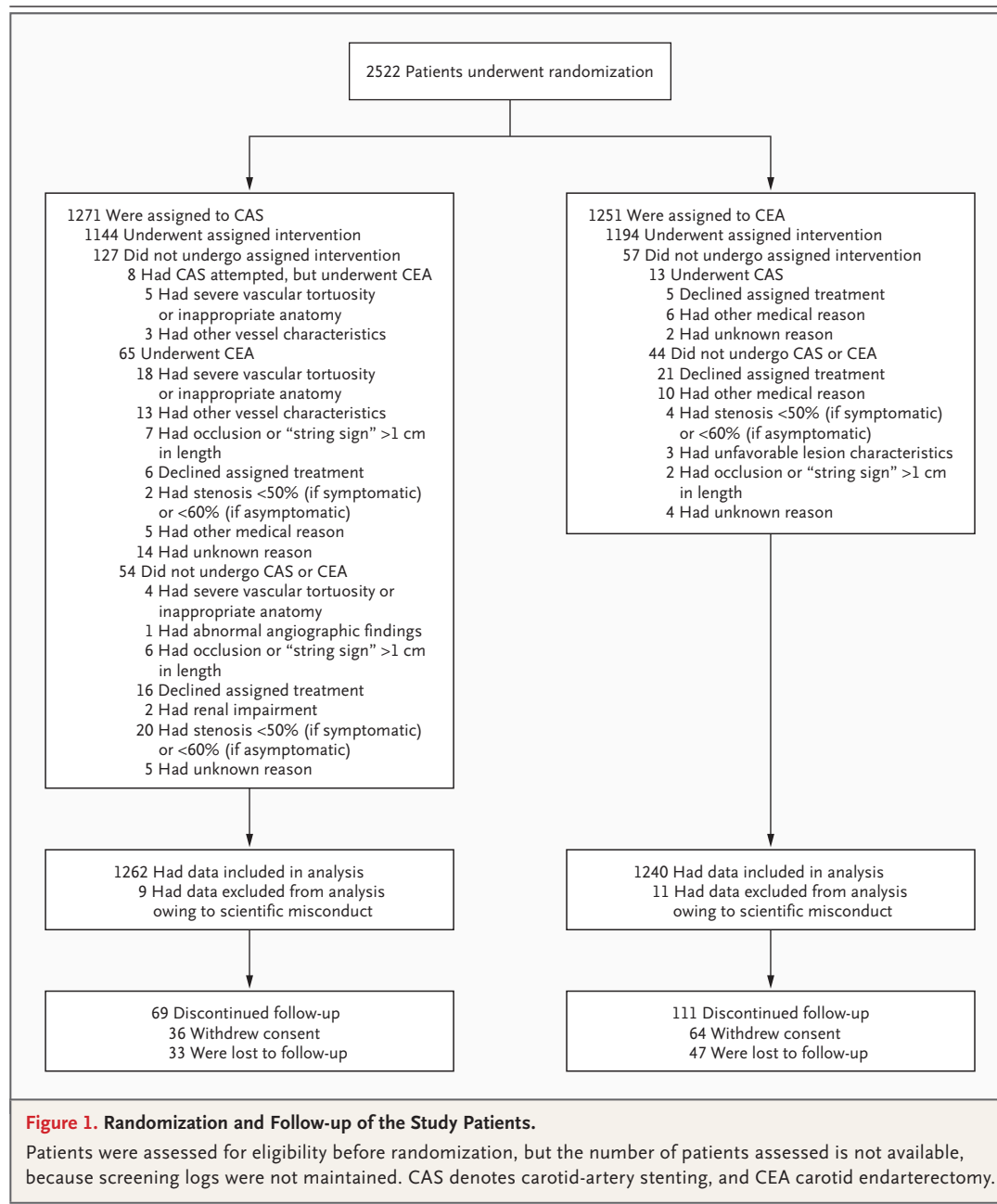
means of a validated selection process⁸ documenting that they performed more than 12 procedures per year and that the rates of complications and death were less than 3% among asymptomatic patients and less than 5% among symptomatic patients. The 224 interventionists were certified after satisfactory evaluation of their endovascular experience, carotid-stenting results, participation in hands-on training, and participation in a lead-in phase of training (see additional details in the Supplementary Appendix).⁹

SELECTION OF STUDY PATIENTS

Patients were considered to be symptomatic if they had had a transient ischemic attack, amaurosis fugax, or minor nondisabling stroke involving the study carotid artery within 180 days before randomization. Eligibility criteria were stenosis of 50% or more on angiography, 70% or more on ultrasonography, or 70% or more on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50 to 69%. Eligibility was extended in 2005 to include asymptomatic patients, for whom the criteria were stenosis of 60% or more on angiography, 70% or more on ultrasonography, or 80% or more on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50 to 69%. Patients were excluded if they had had a previous stroke that was sufficiently severe to confound the assessment of end points or if they had chronic atrial fibrillation, paroxysmal atrial fibrillation that had occurred within the preceding 6 months or that necessitated anticoagulation therapy, myocardial infarction within the previous 30 days, or unstable angina. Additional eligibility criteria were clinical and anatomical suitability, before randomization, for management by means of either of the study revascularization techniques. The full eligibility criteria have been published elsewhere.¹⁰

RANDOMIZATION

Eligible patients were randomly assigned, with the use of a Web-based system, to undergo either carotid-artery stenting or carotid endarterectomy. Randomization was based on a permuted-block design (with random block sizes of 2, 4, or 6), was stratified according to center and symptomatic status, and was performed after the patient, surgeon, and interventionist could arrange for a date for the procedure within 2 weeks.



STENTING AND ENDARTERECTOMY

Carotid-artery stenting and carotid endarterectomy were performed according to published guidelines.^{9,11,12} For carotid-artery stenting, the protocol specified use of the RX Acculink stent and, whenever feasible, the RX Accunet embolic-protection device. At least 48 hours before carotid-artery stenting, patients received aspirin, at a dose of 325 mg twice daily, and clopidogrel at a dose of 75 mg twice daily. When carotid-artery stenting

was scheduled for within 48 hours after randomization, 650 mg of aspirin and 450 mg of clopidogrel were given 4 or more hours before the procedure. After the procedure, patients received one or two 325-mg doses of aspirin daily for 30 days and either clopidogrel, 75 mg daily, or ticlopidine, 250 mg twice daily, for 4 weeks. The continuation of antiplatelet therapy for more than 4 weeks after the procedure was recommended for all patients who had undergone carotid-artery stenting. At

least 48 hours before carotid endarterectomy, patients received 325 mg of aspirin daily and continued to receive that dose for a year or more. Alternatives to this regimen were ticlopidine given at a dose of 250 mg twice daily, clopidogrel at a dose of 75 mg daily, aspirin at a dose of 81 mg daily, or aspirin and extended-release dipyridamole twice daily (Table 1 in the Supplementary Appendix). Patients undergoing either study procedure received medical therapy that was consistent with the current standard of care, including treatment of hypertension and hyperlipidemia.

FOLLOW-UP ASSESSMENTS OF END POINTS

Neurologic evaluation was performed at baseline and 18 to 54 hours after the study procedure, 1 month afterward, and every 6 months thereafter. The evaluation consisted of the use of the National Institutes of Health (NIH) Stroke Scale (NIHSS),¹³ the modified Rankin scale, and the Transient Ischemic Attack (TIA)–Stroke Questionnaire.¹⁴ The

NIHSS is a 15-item neurologic-impairment scale, with possible scores ranging from 0 (no deficit) to 42 (quadriplegia and coma). The modified Rankin scale is a disability scale on which scores can range from 0 (no symptoms) to 6 (death). The TIA–Stroke Questionnaire consists of a question about whether there is a history of TIA, one about whether there is a history of stroke, and six questions about whether there was a sudden onset of any of various focal neurologic symptoms consistent with TIA or stroke.

Cardiac-enzyme levels were measured before the study procedure and 6 to 8 hours after the procedure. Electrocardiography (ECG) was performed before stenting or endarterectomy, as well as 6 to 48 hours and 1 month afterward. Carotid ultrasonography was performed before the study procedure; 1, 6, and 12 months afterward; and annually thereafter.¹⁰ A follow-up telephone interview, including administration of the TIA–Stroke Questionnaire,¹⁴ was conducted at 3 months and

Table 1. Baseline Characteristics of the Study Population, According to Treatment Group.*

Characteristic	Carotid-Artery Stenting (N=1262)	Carotid Endarterectomy (N=1240)
Age (yr)	68.9±9.0	69.2±8.7
Male sex (% of patients)	63.9	66.4
White race (% of patients)†	92.9	93.5
Asymptomatic arteries (% of patients)	47.1	47.3
Risk factors (% of patients)		
Hypertension	85.8	86.1
Diabetes	30.6	30.4
Dyslipidemia‡	82.9	85.8
Current smoker	26.4	26.1
Previous cardiovascular disease	42.4	45.0
Previous coronary-artery bypass	19.9	21.5
Blood pressure (mm Hg)		
Systolic	141.6±20.2	141.2±20.5
Diastolic	74.0±11.6	73.9±11.5
Percent stenosis at randomization		
Moderate (<70%)	13.1	14.9
Severe (≥70%)	86.9	85.1
Stenosis characteristics (% of patients)		
Left carotid artery treated	50.6	52.3
Contralateral occlusion	2.7	3.2
Time from randomization to treatment (no. of days)		
Median	6	7
Interquartile range	9	9

Table 1. (Continued.)

Characteristic	Carotid-Artery Stenting (N=1262)	Carotid Endarterectomy (N=1240)
Procedural characteristics		
Target-lesion length (mm)	17.8±8.5	—
Total length of stented segment (mm)	34.4±7.3	—
Balloon angioplasty before stenting (% of patients)	67.7	—
Embololic protection (% of patients)	96.1	—
Medical treatment (% of patients)		
Antiplatelet therapy 48 hr before stenting	97.7	—
During procedure		
Heparin	86.4	—
Bivalirudin	13.6	—
Vasopressors	29.9	—
After procedure		
Any antiplatelet therapy	99.0	—
Aspirin plus either clopidogrel or ticlopidine for 4 wk	87.9	—
General anesthesia (% of patients)	—	90.0
Surgical technique (% of patients)		
Patch	—	62.4
Shunt	—	56.7
Medical treatment (% of patients)		
Aspirin 48 hr before endarterectomy	—	92.1
Vasopressors during endarterectomy	—	61.0
Antiplatelet therapy after endarterectomy	—	91.1

* Plus-minus values are means ±SD. Dashes indicate not applicable.

† Race was self-reported.

‡ P=0.05 for the difference in the baseline rate of dyslipidemia between the two groups.

every 6 months thereafter. General health status was assessed at baseline, at 2 weeks, 1 month after the procedure, and 1 year after randomization, with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), which evaluates eight dimensions of health, with scores for each ranging from 0 to 100, and higher scores indicating better health status. The SF-36 provides summary scales for overall physical and mental health, with norm-based standardization of the scores to a mean of 50 and a standard deviation of 10.^{15,16}

The primary end point was the composite of any stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization. When the procedure was performed within 30 days after randomization, the periprocedural period was defined as the period from randomization through

30 days after the procedure. When the procedure was not performed within 30 days after randomization, the periprocedural period was defined as the period from randomization through 36 days after randomization. Study committees unaware of the treatment assignments adjudicated stroke and myocardial infarction.

Stroke was defined as an acute neurologic event with focal symptoms and signs, lasting for 24 hours or more, that were consistent with focal cerebral ischemia. The adjudication process was initiated after a clinically significant neurologic event, any positive response on the TIA–Stroke Questionnaire, or an increase by 2 points or more in the NIHSS score. Stroke was defined as major stroke on the basis of clinical data or if the NIHSS score was 9 or higher 90 days after the procedure. Myocardial infarction was defined by a creatine kinase MB or troponin level that was twice the up-

Table 2. Primary End Point, Components of the Primary End Point, and Other Events, According to Treatment Group.*

End Point			Periprocedural Period		P Value
	CAS (N=1262)	CEA (N=1240)	Absolute Treatment Effect of CAS vs. CEA (95% CI)	Hazard Ratio for CAS vs. CEA (95% CI)	
	no. of patients (% ±SE)		percentage points		
Death	9 (0.7±0.2)	4 (0.3±0.2)	0.4 (−0.2 to 1.0)	2.25 (0.69 to 7.30)†	0.18†
Stroke					
Any	52 (4.1±0.6)	29 (2.3±0.4)	1.8 (0.4 to 3.2)	1.79 (1.14 to 2.82)	0.01
Major ipsilateral	11 (0.9±0.3)	4 (0.3±0.2)	0.5 (−0.1 to 1.2)	2.67 (0.85 to 8.40)	0.09
Major nonipsilateral‡	0	4 (0.3±0.2)	NA	NA	NA
Minor ipsilateral	37 (2.9±0.5)	17 (1.4±0.3)	1.6 (0.4 to 2.7)	2.16 (1.22 to 3.83)	0.009
Minor nonipsilateral	4 (0.3±0.2)	4 (0.3±0.2)	0.0 (−0.4 to 0.4)	1.02 (0.25 to 4.07)	0.98†
Myocardial infarction	14 (1.1±0.3)	28 (2.3±0.4)	−1.1 (−2.2 to −0.1)	0.50 (0.26 to 0.94)	0.03
Any periprocedural stroke or postprocedural ipsilateral stroke	52 (4.1±0.6)	29 (2.3±0.4)	1.8 (0.4 to 3.2)	1.79 (1.14 to 2.82)	0.01
Major stroke	11 (0.9±0.3)	8 (0.6±0.2)	0.2 (−0.5 to 0.9)	1.35 (0.54 to 3.36)	0.52
Minor stroke	41 (3.2±0.5)	21 (1.7±0.4)	1.6 (0.3 to 2.8)	1.95 (1.15 to 3.30)	0.01
Any periprocedural stroke or death or postprocedural ipsilateral stroke	55 (4.4±0.6)	29 (2.3±0.4)	2.0 (0.6 to 3.4)	1.90 (1.21 to 2.98)	0.005
Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)	66 (5.2±0.6)	56 (4.5±0.6)	0.7 (−1.0 to 2.4)	1.18 (0.82 to 1.68)	0.38

* The periprocedural period was defined, according to the study protocol, as the 30-day period after the procedure (for all patients who underwent the assigned procedure within 30 days after randomization) or the 36-day period after randomization (for all patients who did not undergo the assigned procedure within 30 days after randomization). Because the periprocedural period was relatively short, which minimized the need for censoring, event proportions and the absolute differences in event proportions were calculated as the percentage of patients with events. For the 4-year study period, proportions reflecting the absolute efficacy of carotid-artery stenting (CAS) over that of carotid endarterectomy (CEA) were based on Kaplan–Meier survival estimates at the end of the 4 years. Hazard ratios for the periprocedural period were based on data for all patients, censored at the end of the periprocedural period. All hazard ratios were adjusted for age, symptomatic status, and sex. P values were calculated on the basis of the significance of the hazard ratio (per study protocol). For death, stroke, and myocardial infarction end points, patients may have had more than one event (e.g., fatal stroke was counted as both a death and a stroke, and patients may have had an ipsilateral stroke followed by a nonipsilateral stroke).

† Because of the small number of events, a univariate proportional-hazards model was used to estimate the hazard ratio for death during the periprocedural period, the P value for minor nonipsilateral stroke during the periprocedural period, and the P value for major nonipsilateral stroke during the 4-year study period.

‡ Absolute treatment effect, hazard ratio, and P value for major nonipsilateral stroke were not available (NA) because of the small number of events, resulting in unreliable estimates.

per limit of the normal range or higher according to the center's laboratory, in addition to either chest pain or symptoms consistent with ischemia or ECG evidence of ischemia, including new ST-segment depression or elevation of more than 1 mm in two or more contiguous leads according to the core laboratory.¹⁷

STATISTICAL ANALYSES

Analyses were aimed at testing for superiority. The null hypothesis was that the two study treatments are equivalent; the alternative hypothesis was that the treatments differ. A sample size of 2500 patients was selected to provide a statistical power of 90% to detect a hazard ratio for the primary

end point of less than 0.54 or more than 1.49 with stenting as compared with endarterectomy, approximating an absolute difference of 1.2 percentage points per year in the rate of the primary end point between the two treatment groups. Intention-to-treat survival analysis was used, and Kaplan–Meier survival curves were plotted. Two interim analyses were performed with the use of O'Brien–Fleming boundaries,¹⁸ the first after approximately one fifth of the patients had been recruited, and the second after approximately half the patients had been recruited. Multiple-imputation techniques¹⁹ were used to assess bias from differential rates of withdrawal from the study in the two groups.

4-Yr Study Period (Including Perioperative Period)				
CAS (N=1262)	CEA (N=1240)	Absolute Treatment Effect of CAS vs. CEA (95% CI)	Hazard Ratio for CAS vs. CEA (95% CI)	P Value
<i>no. of patients (% ± SE)</i>		<i>percentage points</i>		
94 (11.3±1.2)	83 (12.6±1.5)	-1.3 (-5.1 to 2.5)	1.12 (0.83 to 1.51)	0.45
105 (10.2±1.1)	75 (7.9±1.0)	2.3 (-0.6 to 5.2)	1.40 (1.04 to 1.89)	0.03
16 (1.4±0.3)	6 (0.5±0.2)	0.8 (0.1 to 1.6)	2.56 (1.00 to 6.54)	0.05
6 (0.9±0.4)	8 (0.8±0.3)	0.1 (-0.9 to 1.1)	0.73 (0.25 to 2.11)	0.56†
52 (4.5±0.6)	36 (3.5±0.6)	1.0 (-0.7 to 2.7)	1.43 (0.94 to 2.19)	0.10
33 (4.0±0.8)	29 (3.8±0.9)	0.2 (-2.1 to 2.4)	1.11 (0.67 to 1.82)	0.69
72 (6.2±0.7)	50 (4.7±0.7)	1.5 (-0.4 to 3.4)	1.44 (1.00 to 2.06)	0.049
16 (1.4±0.3)	10 (0.8±0.3)	0.6 (-0.2 to 1.4)	1.55 (0.70 to 3.42)	0.28
56 (4.8±0.6)	40 (3.8±0.6)	1.0 (-0.8 to 2.7)	1.39 (0.93 to 2.09)	0.11
75 (6.4±0.7)	50 (4.7±0.7)	1.7 (-0.2 to 3.7)	1.50 (1.05 to 2.15)	0.03
85 (7.2±0.8)	76 (6.8±0.8)	0.4 (-1.7 to 2.6)	1.11 (0.81 to 1.51)	0.51

Secondary aims included estimating the modification of the treatment effect by symptomatic status, sex, and age, which were assessed through inclusion of the interaction terms in the proportional-hazards models (as a single indicator variable for sex and symptomatic status and a linear term for age). The analyses of age were planned before data analysis began but were not described in the study protocol. Longitudinal random-effect growth-curve models²⁰ were used to evaluate the effect of perioperative events on health status at 1 year, as assessed with the use of the SF-36 physical and mental health scales. These models were adjusted for symptomatic status, sex, age, and baseline health status.

RESULTS

STUDY POPULATION AND TREATMENTS

From December 2000 through July 2008, a total of 2522 patients were randomly assigned to one of the two treatments (Fig. 1). After randomization, among the 1271 patients randomly assigned to undergo carotid-artery stenting, 36 (2.8%) withdrew consent, 73 (5.7%) underwent carotid endarterectomy, and 33 (2.6%) were lost to follow-up; among the 1251 patients assigned to carotid

endarterectomy, 64 (5.1%) withdrew consent, 13 (1.0%) underwent carotid-artery stenting, and 47 (3.8%) were lost to follow-up.

Quality-control and site-monitoring activities resulted in the detection of irregular data from one center. The principal investigator and the Office of Research Integrity of the Department of Health and Human Services were notified and subsequently determined that some data were fabricated. All data from this center (which had enrolled 9 patients undergoing carotid-artery stenting and 11 undergoing carotid endarterectomy) were excluded before any analyses were performed, resulting in a cohort of 2502 patients for all analyses.

Dyslipidemia was more common among patients in the endarterectomy group than among those in the stenting group (85.8% vs. 82.9%, $P=0.048$), both groups had high rates of vascular risk factors, and more than 80% of patients had severe stenosis (Table 1). Baseline characteristics are reported according to symptomatic status in Tables 2 and 3 in the Supplementary Appendix.

The median time from randomization to the procedure was 6 days for carotid-artery stenting and 7 days for carotid endarterectomy. Stenting was performed with embolic protection in 96.1% of patients assigned to the stenting group, and

endarterectomy was performed with the use of general anesthesia in 90.0% of patients assigned to the endarterectomy group. The median duration of follow-up was 2.5 years. During that time, the level or prevalence of selected risk factors remained similar between the two treatment groups, except for current smoking, the prevalence of which was similar at baseline (26.4% with stenting and 26.1% with endarterectomy) but for which differences developed during follow-up (21.8% with stenting vs. 13.8% with endarterectomy, $P=0.03$) (Table 4 in the Supplementary Appendix).

PRIMARY END POINT

There was no significant difference in the estimated 4-year rates of the primary end point between carotid-artery stenting and carotid endarterectomy (7.2% and 6.8%, respectively; hazard ratio for stenting, 1.11; 95% confidence interval [CI], 0.81 to 1.51; $P=0.51$) (Table 2 and Fig. 2A). Findings from the multiple-imputation analysis suggested that the withdrawal of patients in each group did not introduce bias. Of the end-point events, 13 strokes were fatal (7 in the stenting group and 6 in the endarterectomy group), and 1 myocardial infarction was fatal (in the endarterectomy group). During the periprocedural period, the incidence of the primary end point was similar with carotid-artery stenting and carotid endarterectomy (5.2 and 4.5%, respectively; hazard ratio for stenting, 1.18; 95% CI, 0.82 to 1.68; $P=0.38$), although the rates of the individual end points differed between the stenting group and the endarterectomy group (death, 0.7% vs. 0.3%; $P=0.18$; stroke, 4.1% vs. 2.3%; $P=0.01$; myocardial infarction, 1.1% vs. 2.3%; $P=0.03$) (Table 2, and Fig. 1 in the Supplementary Appendix). After the periprocedural period, the incidence of ipsilateral stroke was similarly low with carotid-artery stenting and with carotid endarterectomy (2.0% and 2.4%, respectively; $P=0.85$).

Prespecified analyses did not show a modification of the treatment effect by symptomatic status ($P=0.84$) or by sex ($P=0.34$) (Table 5 in the Supplementary Appendix). However, an interaction between age and treatment efficacy was detected ($P=0.02$) (Fig. 2B and 2C), with a crossover at an age of approximately 70 years; carotid-artery stenting tended to show greater efficacy at younger ages, and carotid endarterectomy at older ages.

PRESPECIFIED SECONDARY ANALYSES

During the periprocedural period, rates of the primary end point did not differ significantly be-

tween the stenting group and the endarterectomy group among symptomatic patients (6.7% vs. 5.4%; hazard ratio for stenting, 1.26; 95% CI, 0.81 to 1.96) or among asymptomatic patients (3.5% vs. 3.6%; hazard ratio, 1.02; 95% CI, 0.55 to 1.86) (Table 3). Cranial-nerve palsies were less frequent during the periprocedural period with carotid-artery stenting (0.3%, vs. 4.7% with carotid endarterectomy; hazard ratio, 0.07; 95% CI, 0.02 to 0.18). Additional serious adverse events are detailed in Table 6 in the Supplementary Appendix. The 4-year rate of stroke or death was 6.4% in the stenting group as compared with 4.7% in the endarterectomy group (hazard ratio, 1.50; 95% CI, 1.05 to 2.15; $P=0.03$); the respective rates were 8.0% and 6.4% among symptomatic patients (hazard ratio, 1.37; 95% CI, 0.90 to 2.09; $P=0.14$) and 4.5% and 2.7% among asymptomatic patients (hazard ratio, 1.86; 95% CI, 0.95 to 3.66; $P=0.07$).

POST HOC ANALYSES

Longitudinal growth-curve models were used to estimate the effect of periprocedural stroke and myocardial infarction on health status at 1 year (Fig. 2 and 3 in the Supplementary Appendix). Major stroke and minor stroke were found to have an effect on physical health at 1 year, according to the SF-36 physical component scale (mean effect estimates, -15.8 points [95% CI, -25.1 to -6.4] and -4.5 points [95% CI, -7.9 to -1.2], respectively), whereas the effect of periprocedural myocardial infarction was less certain (mean effect estimate, -3.0 points [95% CI, -7.1 to 1.1]). Minor stroke had a significant effect on mental health at 1 year, as measured on the SF-36 mental component scale (mean effect estimate, -3.4 points [95% CI, -6.3 to -0.5]). The likelihood of the primary end point was not significantly affected by the medical specialty of the interventionist performing the carotid-artery stenting ($P=0.51$) (Table 7 in the Supplementary Appendix).⁹

DISCUSSION

Our CREST results indicate that carotid-artery stenting and carotid endarterectomy were associated with similar rates of the primary composite outcome — periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke — among men and women with either symptomatic or asymptomatic carotid stenosis. However, the incidence of periprocedural stroke was lower in the endarterectomy group than in the stenting

group, whereas the incidence of periprocedural myocardial infarction was lower in the stenting group. These countervailing effects during the periprocedural period resulted in similar rates of the primary outcomes because the rates of events after the periprocedural period were similar in the two groups. Although previous studies have indicated that both stroke and myocardial infarction are associated with substantial morbidity and mortality,^{21,22} quality-of-life analyses among survivors at 1 year in our trial indicate that stroke had a greater adverse effect on a broad range of health-status domains than did myocardial infarction.

The selection of patients for either carotid-artery stenting or carotid endarterectomy may require attention to age, with younger patients having a slightly better outcome with carotid-artery stenting and older patients having a better outcome with carotid endarterectomy.²³ The association between older age and increased risk of adverse events after carotid-artery stenting was seen in our lead-in cohort,⁹ the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial (Current Controlled Trials number, ISRCTN57874028),⁶ and the International Carotid Stenting Study (ICSS; ISRCTN25337470).²⁴ An effect of age on differences between carotid-artery stenting and carotid endarterectomy was found in the SPACE trial²⁵ as well as in our study. Mechanisms underlying the increased risk with carotid-artery stenting in very elderly patients probably include vascular tortuosity and severe vascular calcification.²³

The periprocedural outcomes for carotid-artery stenting and carotid endarterectomy reported here are the best reported from a randomized, carotid-revascularization study that incorporated pre- and postprocedural medical, neurologic, ECG, and biomarker evaluations (Table 3). The rate of stroke or death among our symptomatic patients after carotid-artery stenting (6.0%) was lower than the corresponding rates in the SPACE trial (6.8%, not including nonipsilateral stroke), the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial (ClinicalTrials.gov number, NCT00190398) (9.6%), and ICSS (7.4%). The rate of stroke or death among our symptomatic patients after carotid endarterectomy (3.2%) was also lower than the corresponding percentage in SPACE (6.3%) and was similar to the corresponding percentage in EVA-3S (3.9%) as well as that in ICSS (3.4%); in ICSS,

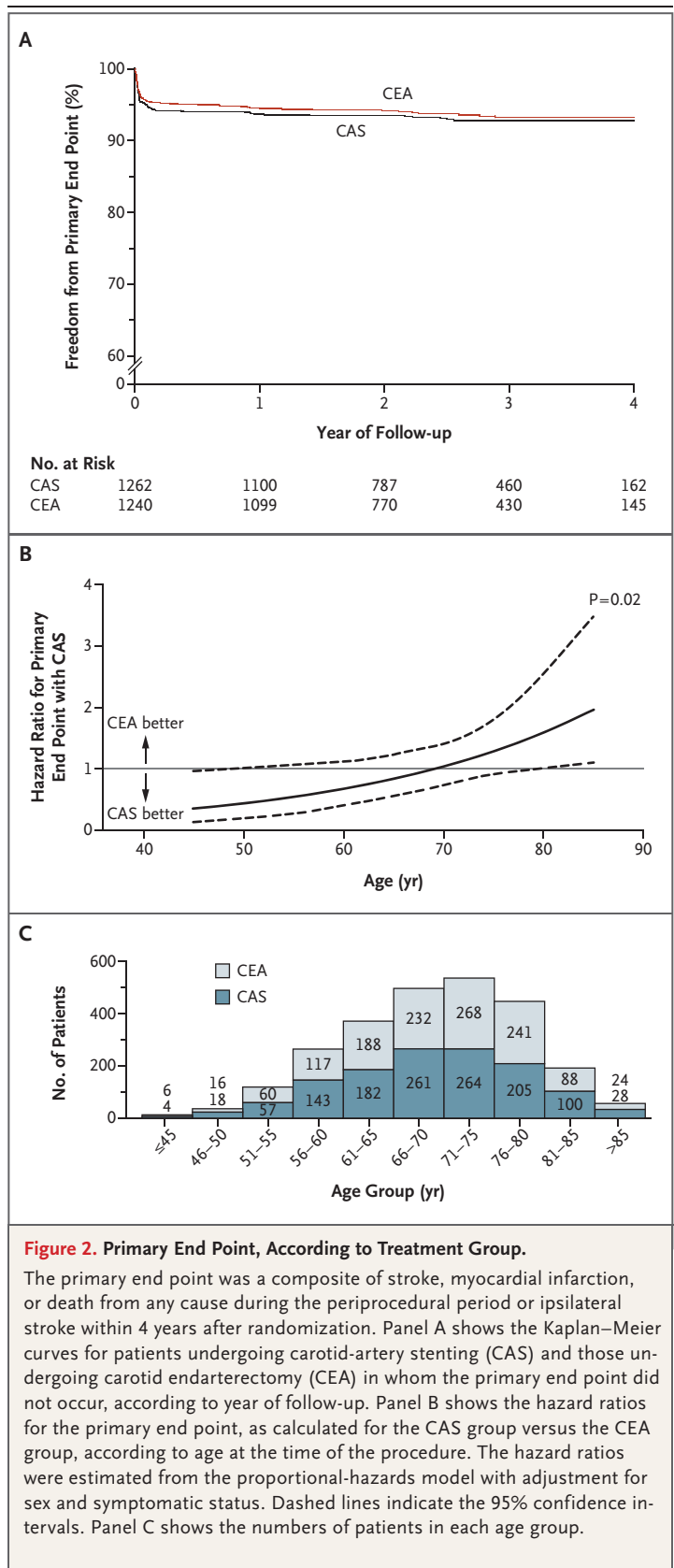


Figure 2. Primary End Point, According to Treatment Group.

The primary end point was a composite of stroke, myocardial infarction, or death from any cause during the periprocedural period or ipsilateral stroke within 4 years after randomization. Panel A shows the Kaplan–Meier curves for patients undergoing carotid-artery stenting (CAS) and those undergoing carotid endarterectomy (CEA) in whom the primary end point did not occur, according to year of follow-up. Panel B shows the hazard ratios for the primary end point, as calculated for the CAS group versus the CEA group, according to age at the time of the procedure. The hazard ratios were estimated from the proportional-hazards model with adjustment for sex and symptomatic status. Dashed lines indicate the 95% confidence intervals. Panel C shows the numbers of patients in each age group.

Table 3. Primary End Point and Its Individual Components among the 1181 Asymptomatic and the 1321 Symptomatic Patients, According to Treatment Group.*

End Point	Periprocedural Period				4-Yr Study Period (Including Periprocedural Period)					
	CAS <i>no. of patients (% ±SE)</i>	CEA <i>no. of patients (% ±SE)</i>	Absolute Treatment Effect of CAS vs. CEA (95% CI) <i>percentage points</i>	Hazard Ratio for CAS vs. CEA (95% CI) <i>percentage points</i>	P Value	CAS <i>no. of patients (% ±SE)</i>	CEA <i>no. of patients (% ±SE)</i>	Absolute Treatment Effect of CAS vs. CEA (95% CI) <i>percentage points</i>	Hazard Ratio for CAS vs. CEA (95% CI) <i>percentage points</i>	P Value
Myocardial infarction										
Asymptomatic patients	7 (1.2±0.4)	13 (2.2±0.6)	-1.0 (-2.5 to 0.4)	0.55 (0.22 to 1.38)	0.20					
Symptomatic patients	7 (1.0±0.4)	15 (2.3±0.6)	-1.2 (-2.6 to 0.1)	0.45 (0.18 to 1.11)	0.08					
Any periprocedural stroke or postprocedural ipsilateral stroke										
Asymptomatic patients	15 (2.5±0.6)	8 (1.4±0.5)	1.2 (-0.4 to 2.7)	1.88 (0.79 to 4.42)	0.15	24 (4.5±0.9)	13 (2.7±0.8)	1.9 (-0.5 to 4.3)	1.86 (0.95 to 3.66)	0.07
Symptomatic patients	37 (5.5±0.9)	21 (3.2±0.7)	2.3 (0.1 to 4.5)	1.74 (1.02 to 2.98)	0.04	48 (7.6±1.1)	37 (6.4±1.1)	1.2 (-1.8 to 4.1)	1.29 (0.84 to 1.98)	0.25
Any periprocedural stroke or death or postprocedural ipsilateral stroke										
Asymptomatic patients	15 (2.5±0.6)	8 (1.4±0.5)	1.2 (-0.4 to 2.7)	1.88 (0.79 to 4.42)	0.15	24 (4.5±0.9)	13 (2.7±0.8)	1.9 (-0.5 to 4.3)	1.86 (0.95 to 3.66)	0.07
Symptomatic patients	40 (6.0±0.9)	21 (3.2±0.7)	2.8 (0.5 to 5.0)	1.89 (1.11 to 3.21)	0.02	51 (8.0±1.1)	37 (6.4±1.1)	1.6 (-1.4 to 4.6)	1.37 (0.90 to 2.09)	0.14
Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)										
Asymptomatic patients	21 (3.5±0.8)	21 (3.6±0.8)	0.0 (-2.2 to 2.1)	1.02 (0.55 to 1.86)	0.96	30 (5.6±1.0)	26 (4.9±1.0)	0.7 (-2.1 to 3.4)	1.17 (0.69 to 1.98)	0.56
Symptomatic patients	45 (6.7±1.0)	35 (5.4±0.9)	1.4 (-1.2 to 3.9)	1.26 (0.81 to 1.96)	0.30	55 (8.6±1.1)	50 (8.4±1.2)	0.2 (-3.0 to 3.4)	1.08 (0.74 to 1.59)	0.69

* The 1181 asymptomatic patients consisted of 594 patients in the carotid-artery stenting (CAS) group and 587 in the carotid endarterectomy (CEA) group. The 1321 symptomatic patients consisted of 668 in the CAS group and 653 in the CEA group. The periprocedural period was defined, according to the study protocol, as the 30-day period after the procedure (for all patients who underwent the assigned procedure within 30 days after randomization) or the 36-day period after randomization (for all patients who did not undergo the assigned procedure within 30 days after randomization). Because the periprocedural period is relatively short, which minimizes the need for censoring, event proportions and the absolute differences in event proportions were calculated as the percentage of patients with events. For the 4-year study period, proportions reflecting the absolute efficacy of CAS over that of CEA were based on Kaplan–Meier survival estimates at the end of the 4 years. Hazard ratios for the periprocedural period were based on data for all patients, censored at the end of the periprocedural period. All hazard ratios were adjusted for age, symptomatic status, and sex. P values were calculated on the basis of the significance of the hazard ratio (per study protocol). For death, stroke, and myocardial infarction end points, patients could have had more than one event (e.g., fatal stroke was counted as both a death and a stroke, and patients may have had an ipsilateral stroke followed by a nonipsilateral stroke).

patients were not formally examined per protocol before or after the procedure or at 30 days. Among asymptomatic patients, the rate of stroke or death in the carotid-artery stenting group in our trial (2.5%) was similar to that in the Asymptomatic Carotid Atherosclerosis Study (ACAS) (2.3%, excluding patients older than 79 years)⁸ and was lower than that in the Asymptomatic Carotid Surgery Trial (ACST; ISRCTN26156392) (3.1%),²⁶ and the rate of stroke and death in our carotid-endarterectomy group (1.4%) was lower than that in ACAS and ACST.

The improved periprocedural outcomes in CREST as compared with previous trials may reflect the effective surgeon credentialing, assimilation of evolving endovascular technology, and rigorous training and credentialing of carotid-artery stenting operators.⁹ The differential results for myocardial infarction and stroke offer opportunities for improvement. To reduce the risk of stroke after carotid-artery stenting, improvements in training and technique, embolic protection and stent design, and patient selection (especially among patients older than 70 years of age) hold promise.^{23,27} To reduce the risk of myocardial infarction after carotid endarterectomy, more detailed preoperative cardiovascular evaluation and the use of dual antiplatelet therapy, statins,²⁸ cardioprotective pharmacotherapy,²⁹ or local anesthesia could be investigated.

The clinical durability of carotid-artery stenting and carotid endarterectomy is important. The rates of ipsilateral stroke during our follow-up period — 2.0% with carotid-artery stenting and 2.4% with carotid endarterectomy — are similar to the rates in the SPACE trial and EVA-3S, suggesting excellent durability for up to 4 years. Because the life expectancy of our average-aged patient is 15 years after the procedure,³⁰ outcomes are being assessed in CREST out to 10 years.

The CREST study does have limitations. The certification requirements were important for patient safety, but they limit the generalizability of the results and conclusions to similarly qualified operators. One interventional carotid-artery stenting system was used. Improvements were incorporated into that system as technology evolved. Although the use of one system facilitated standardization, external validity may have been affected by our prohibition on the use of other stent systems. The addition of asymptomatic patients and the anticipated lower event rate for that group

had the potential to compromise the statistical power. However, that lower event rate was offset by the higher number of events associated with the extended enrollment and follow-up periods. The use of medical therapy alone was not studied, sharply limiting our ability to generalize the results. For example, the rates of ipsilateral and contralateral stroke were similar in the two groups after the periprocedural period. For asymptomatic patients, this similarity could indicate that revascularization is durable or that asymptomatic carotid stenosis is benign if treated medically.

In conclusion, carotid revascularization performed by highly qualified surgeons and interventionists is effective and safe. Stroke was more likely after carotid-artery stenting. Myocardial infarction was more likely after carotid endarterectomy, but the effect on the quality of life was less than the effect of stroke. Younger patients had slightly fewer events after carotid-artery stenting than after carotid endarterectomy; older patients had fewer events after carotid endarterectomy. The low absolute risk of recurrent stroke suggests that both carotid-artery stenting and carotid endarterectomy are clinically durable and may also reflect advances in medical therapy.

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APPENDIX

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