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Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis

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ABSTRACT

BACKGROUND

Previous clinical trials have suggested that carotid-artery stenting with a device to capture and remove emboli ("embolic protection") is an effective alternative to carotid endarterectomy in patients at average or high risk for surgical complications.

METHODS

In this trial, we compared carotid-artery stenting with embolic protection and carotid endarterectomy in patients 79 years of age or younger who had severe carotid stenosis and were asymptomatic (i.e., had not had a stroke, transient ischemic attack, or amaurosis fugax in the 180 days before enrollment) and were not considered to be at high risk for surgical complications. The trial was designed to enroll 1658 patients but was halted early, after 1453 patients underwent randomization, because of slow enrollment. Patients were followed for up to 5 years. The primary composite end point of death, stroke, or myocardial infarction within 30 days after the procedure or ipsilateral stroke within 1 year was tested at a noninferiority margin of 3 percentage points.

RESULTS

Stenting was noninferior to endarterectomy with regard to the primary composite end point (event rate, 3.8% and 3.4%, respectively; P=0.01 for noninferiority). The rate of stroke or death within 30 days was 2.9% in the stenting group and 1.7% in the endarterectomy group (P=0.33). From 30 days to 5 years after the procedure, the rate of freedom from ipsilateral stroke was 97.8% in the stenting group and 97.3% in the endarterectomy group (P=0.51), and the overall survival rates were 87.1% and 89.4%, respectively (P=0.21). The cumulative 5-year rate of stroke-free survival was 93.1% in the stenting group and 94.7% in the endarterectomy group (P=0.44).

CONCLUSIONS

In this trial involving asymptomatic patients with severe carotid stenosis who were not at high risk for surgical complications, stenting was noninferior to endarterectomy with regard to the rate of the primary composite end point at 1 year. In analyses that included up to 5 years of follow-up, there were no significant differences between the study groups in the rates of non–procedure-related stroke, all stroke, and survival. (Funded by Abbott Vascular; ACT I ClinicalTrials.gov number, NCT00106938.)

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Stroke is the fifth leading cause of death and the leading cause of disability among U.S. adults. It affects nearly 800,000 people in the United States annually, resulting in more than 170,000 deaths and causing major disability among the survivors, at a cost estimated to exceed $41 billion annually.[1] Extracranial carotid-artery disease is responsible for up to 20% of these strokes. The Asymptomatic Carotid Atherosclerosis Stenosis (ACAS) and Asymptomatic Carotid Surgery (ACST) trials showed that among asymptomatic patients with carotid-artery stenosis of greater than 60% of the diameter of the artery, the risk of stroke or death was lower when immediate carotid endarterectomy was performed than when surgery was deferred.[1,2] In spite of these data, revascularization for asymptomatic carotid stenosis remains controversial; current medical therapy that combines statins, antiplatelet agents, and antihypertension control has independently led to a reduction in the incidence of stroke, although reductions among patients with established severe carotid stenosis have not been shown in prospective studies. Most carotid revascularization procedures in the United States are carotid endarterectomies performed for the treatment of asymptomatic atherosclerotic disease. Revascularization is also performed by means of stenting with devices to capture and remove emboli ("embolic protection" devices).[3,4] In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), no significant difference was found between carotid endarterectomy and stenting with embolic protection for the treatment of atherosclerotic carotid bifurcation stenosis with regard to the composite end point of stroke, death, or myocardial infarction.[5] CREST included both symptomatic and asymptomatic patients, and it was not sufficiently powered to discern whether the carotid endarterectomy and stenting with embolic protection were equivalent according to symptomatic status. The primary aim of the Asymptomatic Carotid Trial (ACT) I was to compare the outcomes of carotid endarterectomy versus stenting with embolic protection in patients with asymptomatic severe carotid-artery stenosis who were at standard risk for surgical complications.

METHODS

STUDY DESIGN

ACT I was a prospective multicenter trial involving asymptomatic patients with severe stenosis of the carotid-artery bifurcation, caused by atherosclerotic disease, who were at standard risk for surgical complications. Enrolled patients were randomly assigned in a 3:1 ratio to undergo stenting with embolic protection (stenting group) or carotid endarterectomy (endarterectomy group). The investigational study was sponsored by Abbott Vascular, reviewed by the Food and Drug Administration, and approved by the institutional review board at each study site; all patients provided written informed consent. An independent clinical events committee from the Harvard Clinical Research Institute adjudicated all primary endpoint events, and an independent data and safety monitoring board from the Harvard Clinical Research Institute reviewed the accumulating data.

Patients were recruited in clinical practices and referred for possible revascularization of known or suspected carotid stenosis; they were then screened for eligibility on the basis of findings from duplex ultrasonography, contrast angiography, or both. Before enrollment, a study neurologist or neurosurgeon confirmed each patient's asymptomatic status (defined as having been free, in the ipsilateral hemisphere, from stroke, transient ischemic attack, and amaurosis fugax for 180 days before enrollment). A neurologic assessment was performed and data were collected before and on the day after the procedure; at 1, 6, and 12 months; and every year until 5 years after the procedure. For these assessments, study-group assignments could not be concealed because most patients who were randomly assigned to undergo endarterectomy had a neck incision.

Each clinical site had an investigational team that consisted of one or more of the following specialists: an interventionist, a surgeon, and an independent study neurologist or neurosurgeon. Randomization was performed with the use of a Web-based system. The enrolling sites were audited for excess adverse events; the auditors were unaware of the treatment assignments of individual patients. Sites with very high rates of adverse events, according to a predetermined formula, were counseled regarding case selection and technique in the performance of endarterectomy and stenting; two sites were temporarily stopped from enrollment of patients.

The study sites and physicians were selected through a process that included a review of American Board of Medical Specialties certification and training, previous experience (procedural

volumes for stenting or endarterectomy in excess of 25 recent cases for each investigator), and recent outcomes (as determined by case logs, procedure reports, discharge summaries, and images). There was also a lead-in phase during which sites were required to show proficiency with the study devices in at least two cases before they could treat randomly assigned patients. After a patient underwent randomization, the assigned treatment was to be performed within 2 weeks. The trial was designed to include 1658 patients for randomization. Enrollment was initiated on March 30, 2005, and was closed early on January 18, 2013, with 1453 of the planned 1658 participants (88%) enrolled. The study was stopped in February 2013, and no additional follow-up data were collected after this time. The reason for termination of the study was slow enrollment; it was not related to patient safety, futility, or concerns regarding the study devices. The authors vouch for the accuracy and completeness of the findings, wrote and take responsibility for the manuscript, and vouch for the fidelity of the study and of this report to the study protocol, available with the full text of this article at NEJM.org.

PATIENT POPULATION

Eligible patients were candidates for stenting and endarterectomy, were 79 years of age or younger, and were considered not to be at high risk for operative complications. All participating patients were asymptomatic, which was defined as having been free, in the ipsilateral hemisphere, from stroke, transient ischemic attack, and amaurosis fugax for 180 days before enrollment. All the patients had bifurcation carotid stenosis of 70 to 99% of the diameter of the artery, as determined on the basis of strict ultrasonographic or angiographic criteria, in the absence of substantial (>60%) contralateral carotid stenosis. (A complete list of the inclusion and exclusion criteria and definitions is available in the Supplementary Appendix, available at NEJM.org.)

TREATMENT

All patients received aspirin (325 mg) daily starting 3 days before the procedure and indefinitely after the procedure. Patients who underwent stenting received clopidogrel daily for 3 days before the procedure and for 30 days thereafter. For stenting, closed-cell, nitinol stents with a tapering diameter (Xact, Abbott Vascular) were used in conjunction with distal embolic protection (Emboshield, Emboshield Pro, or Emboshield NAV6, Abbott Vascular). For endarterectomy, the type of anesthetic used, the use of patches or shunts, and intraprocedural monitoring were at the surgeon's discretion. For both procedures, patients underwent anticoagulation with either heparin or bivalirudin; for patients undergoing stenting, an activated clotting time of greater than 250 seconds was required.

END POINTS

The primary end point was the composite of death, stroke (ipsilateral or contralateral, major or minor [see the Supplementary Appendix for definitions]), or myocardial infarction during the 30 days after the procedure or ipsilateral stroke during the 365 days after the procedure.

The secondary end points included a prespecified composite measure of complications, which was assessed 30 days after the procedure; the composite included cranial-nerve and peripheral-nerve injury, vascular injury, noncerebral bleeding, wound complications related to the neck incision or femoral puncture site, and other complications (e.g., related to the anesthesia). The secondary end point of freedom from clinically driven target-lesion revascularization (see the Supplementary Appendix) at 6 months and at 12 months was prespecified in the protocol; freedom from clinically driven target-lesion revascularization through 5 years was also assessed. Freedom from death was assessed through 5 years. Freedom from all stroke through 5 years, although not a prespecified end point in the protocol, is an additional outcome included in this report. Prespecified secondary end points also included device success and procedural success for stenting (see the Supplementary Appendix for definitions).

STATISTICAL ANALYSIS

Baseline variables are summarized with the use of descriptive statistics. Continuous variables are summarized as the mean, median, standard deviation, minimum and maximum values, and 95% confidence intervals. Categorical variables are summarized as counts, percentages, and exact 95% Clopper–Pearson confidence intervals. For time-to-event variables, Kaplan–Meier estimates were used. The starting day was the day of the procedure; if no procedure was attempted, the day of randomization was used. Data are summarized for the intention-to-treat population.

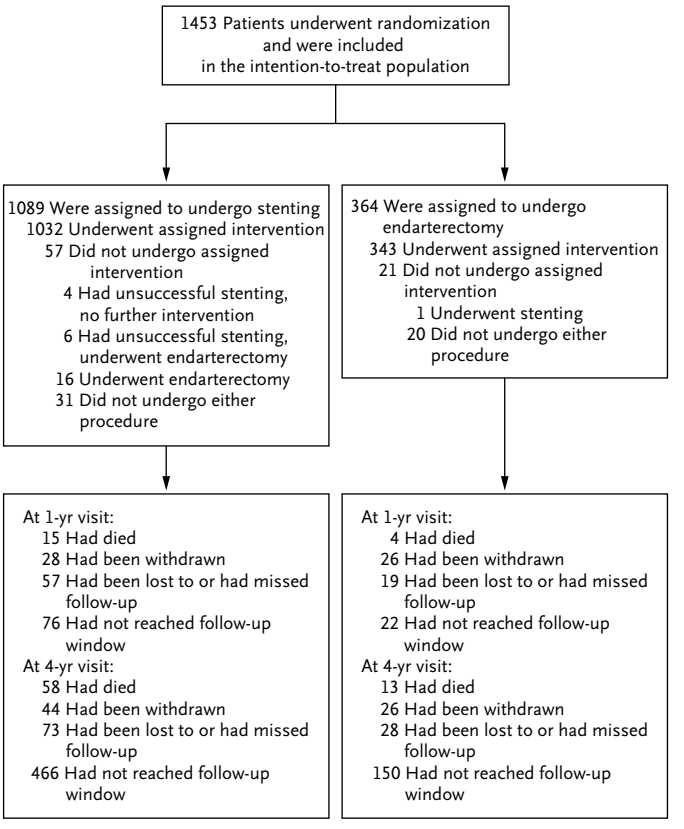


Figure 1. Randomization and Treatment.

The primary end-point analysis was a between-group comparison of the rate of death, stroke, or myocardial infarction within 30 days or of an ipsilateral stroke within 365 days after the index procedure. Kaplan–Meier analysis was used to estimate the primary end-point event rates in the test of the noninferiority hypothesis, which took into consideration a patient's duration of participation in the study.

If the upper limit of the one-sided 95% confidence interval of the difference in event rates between stenting and endarterectomy was 3 percentage points or lower (prespecified noninferiority margin), stenting was considered to be noninferior to endarterectomy.[6] The study was originally designed to enroll 1658 patients, with 80% power to detect the noninferiority margin at P=0.05. Before the results were unmasked and enrollment was stopped, the power analysis was recalculated on the basis of the final enrollment of 1453 randomly assigned patients, resulting in a revised power of 75%. No formal hypothesis testing was planned for the secondary end points. Nominal P values are reported and should be interpreted in the context of the multiple comparisons. All P values are two-sided, with the exception of P values from noninferiority testing, which are one-sided.

RESULTS

PATIENT POPULATION

Between 2005 and 2013, a total of 1453 patients were randomly assigned to undergo stenting or endarterectomy; 1089 were assigned to the stenting group, and 364 were assigned to the endarterectomy group (Fig. 1). Follow-up was completed for 1391 patients at 30 days after the procedure, 1206 patients at 1 year, 1024 patients at 2 years, 802 patients at 3 years, 544 patients at 4 years, and 328 patients at 5 years. At 1 year, 19 patients had died, 54 had withdrawn, and 7 had been lost to follow-up. At 1 year, 1275 patients were eligible for their visit, and 98 had not reached their visit window; of the 1275 eligible patients, 53 had a missed visit, 16 did not complete their visit but were within the visit window, and 1206 completed their 1-year visit.

There were no significant differences in the baseline demographic or medical history characteristics between patients randomly assigned to the stenting group and those randomly assigned to the endarterectomy group (Table 1). The mean age in both study groups was 68 years, with the majority of patients 65 years of age or older. Contralateral stenosis was noted in 40.5% of the patients in the stenting group and in 44.5% of the patients in the endarterectomy group. In seven instances (four in the stenting group and three in the endarterectomy group), patients who had had symptoms during the previous 180 days were inadvertently enrolled (protocol violations). Other patients had a history of transient ischemic attacks (6.1% in the stenting group and 7.4% in the endarterectomy group), amaurosis fugax (1.7% and 1.4%), or stroke (6.7% and 4.7%) more than 180 days before enrollment (Table 1).

Available baseline angiographic data for patients randomly assigned to each study group are provided in Table 1, and in Table S1 in the Supplementary Appendix. The mean degree of stenosis was 74% in both groups.

PRIMARY END POINT

At 1 year, the event rate (±SE) estimated by the Kaplan–Meier method for the primary end point

Table 1. Baseline Demographic, Clinical, and Lesion Characteristics.*

Characteristic	Stenting (N=1089)	Endarterectomy (N=364)
Patient demographic and clinical characteristics		
Age — yr		
Mean	67.7±7.0	67.9±6.9
Range	44.4–79.9	43.3–80.0
Age ≥65 yr — no. (%)	764 (70.2)	261 (71.7)
Male sex — no. (%)	666 (61.2)	207 (56.9)
White race — no. (%)†	985 (90.4)	327 (89.8)
Hypertension — no. (%)	987 (90.6)	326 (89.6)
Hyperlipidemia requiring medication — no. (%)	980 (90.0)	320 (87.9)
History of cigarette smoking — no. (%)	803 (73.7)	259 (71.2)
Current cigarette smoking — no. (%)	266 (24.4)	71 (19.5)
Diabetes mellitus — no. (%)	388 (35.6)	118 (32.4)
Coronary artery disease — no. (%)	581 (53.4)	186 (51.1)
Myocardial infarction >30 days before the index procedure — no. (%)	209 (19.2)	64 (17.6)
Left ventricular dysfunction — no. (%)	86 (7.9)	30 (8.2)
Cardiac arrhythmia — no. (%)	115 (10.6)	33 (9.1)
Valvular heart disease — no. (%)	95 (8.7)	30 (8.2)
Other peripheral vascular disease — no. (%)	391 (35.9)	124 (34.1)
Current contralateral carotid disease — no. (%)	441 (40.5)	162 (44.5)
History of stroke — no. (%)‡	73 (6.7)	17 (4.7)
History of ipsilateral stroke — no. (%)‡	18 (1.7)	5 (1.4)
History of transient ischemic attack — no. (%)‡	66 (6.1)	27 (7.4)
History of amaurosis fugax — no. (%)‡	18 (1.7)	5 (1.4)
Chronic obstructive pulmonary disease — no. (%)	130 (11.9)	34 (9.3)
History of renal insufficiency — no. (%)§	92 (8.4)	24 (6.6)
Lesion characteristics		
Stenosis — % of vessel diameter¶‖		
Mean	73.7±8.8	73.9±10.2
Range	33.8–98.6	34.7–96.0
Lesion length — mm‖		
Mean	19.0±5.8	18.0±6.2
Range	2.5–40.0	4.9–41.1
Ulcerated — no./total no. (%)	172/1062 (16.2)	37/255 (14.5)
Thrombus — no./total no. (%)	10/1061 (0.9)	7/254 (2.8)

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the study groups (Student's t-test), with the exception of lesion length and number of patients with thrombus, which differed significantly at P<0.05 (Fisher's exact test).

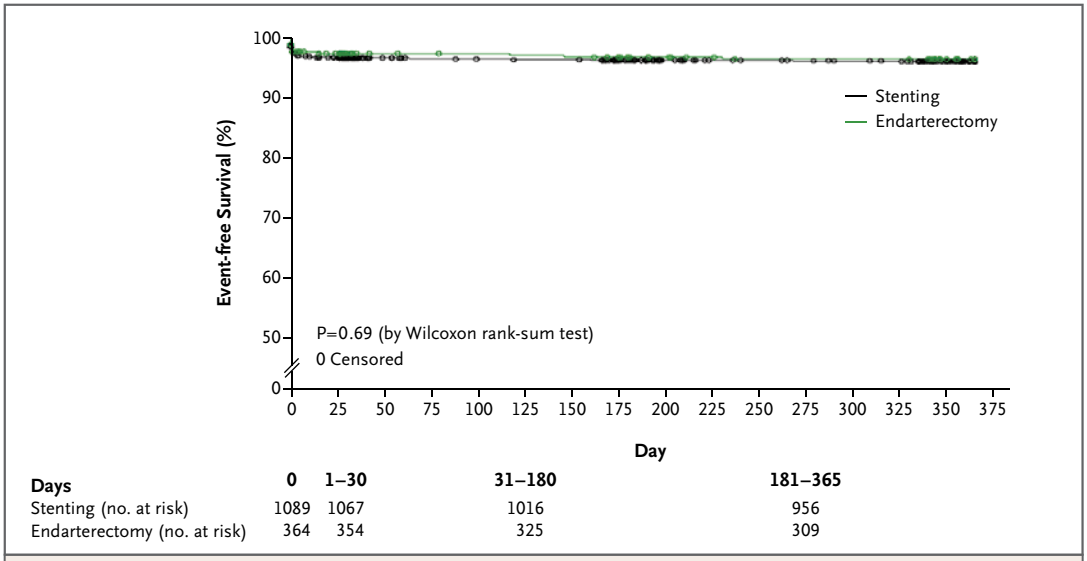
† Race was self-reported.

‡ Patients with a history of this event were included in the study only if the event had occurred more than 180 days before enrollment.

§ Data on history of renal insufficiency were reported by the study sites. Patients with a creatinine level of 2.5 mg per deciliter (221 μmol per liter) or greater were not included in the study.

¶ Patients were enrolled by investigators on the basis of the percent stenosis determined during preprocedure noninvasive testing; however, data in this table reflect the degree of stenosis determined by means of angiographic core laboratory analysis. These degrees of stenosis are commonly discrepant, with the angiographic evaluation showing a lower percent stenosis.

‖ A total of 1061 lesions were evaluated in the stenting group, and 255 lesions were evaluated in the endarterectomy group.



Days	0	1–30	31–180	181–365
Stenting (no. at risk)	1089	1067	1016	956
Endarterectomy (no. at risk)	364	354	325	309

Figure 2. Kaplan–Meier Analysis of Freedom from the Primary Composite End Point.
Shown is the Kaplan–Meier survival curve for freedom from death, stroke, and myocardial infarction within 30 days and from ipsilateral stroke within 365 days after the procedure in the intention-to-treat population.

was 3.8±0.59% (1089 patients) in the stenting group and 3.4±0.98% (364 patients) in the endarterectomy group, with a between-group difference of 0.4 percentage points. The upper limit of the one-sided 95% confidence interval for the difference was 2.27 percentage points (P=0.01 for noninferiority), which is below the prespecified 3-percentage-point noninferiority margin for the primary end point, leading to the conclusion that stenting was noninferior to endarterectomy. Figure 2 shows the Kaplan–Meier analysis of freedom from death, stroke, and myocardial infarction within 30 days and from ipsilateral stroke within 365 days in the stenting group (96.2%) and the endarterectomy group (96.6%). The periprocedural event rates through 30 days after the procedure are shown in Table 2. The 30-day rate of death or major stroke was low in both groups (0.6%). The 30-day rate of minor stroke was numerically higher in the stenting group than in the endarterectomy group (2.4% vs. 1.1%, P=0.20), which resulted in a 30-day rate of death or any stroke of 2.9% in the stenting group and 1.7% in the endarterectomy group (P=0.33).

SECONDARY END POINTS

The analysis of the composite measure of complications through 30 days after the procedure is shown in Table 2. The overall event rate for this composite measure was 2.8% in the stenting group and 4.7% in the endarterectomy group (P=0.13); the rate of cranial-nerve injury was 0.1% in the stenting group and 1.1% in the endarterectomy group (P=0.02). The rates of acute device success and procedural success in the stenting group were 98.4% and 95.6%, respectively. The rate of freedom from clinically driven target-lesion revascularization at 6 months was 99.8% in the stenting group and 99.7% in the endarterectomy group (P=0.72); at 1 year, the rates were 99.4% and 97.4%, respectively (P=0.005).

The estimated survival rate at 5 years was 87.1% in the stenting group and 89.4% in the endarterectomy group (P=0.21) (Fig. 3B). The rate of freedom from non–procedure-related ipsilateral stroke through 5 years was 97.8% in the stenting group and 97.3% in the endarterectomy group (P=0.51) (Fig. 3A). The rate of freedom from any stroke (ipsilateral or contralateral) through 5 years was 93.1% in the stenting group and 94.7% in the endarterectomy group (P=0.44) (Fig. 3C).

DISCUSSION

Several multicenter, randomized clinical trials of carotid endarterectomy have provided data showing the usefulness of surgical revascularization for the treatment of patients with asymptomatic

Table 2. Death, Stroke, or Myocardial Infarction and Composite Measure of Complications within 30 Days after Index Procedure.*

Outcome	Stenting (N=1089)	Endarterectomy (N=364)	P Value†
	no. of patients/total no. (%)		
Death, stroke, or myocardial infarction	35/1072 (3.3)	9/348 (2.6)	0.60
Death or stroke	31/1072 (2.9)	6/348 (1.7)	0.33
Death or major stroke	6/1072 (0.6)	2/348 (0.6)	1.00
Death	1/1072 (0.1)	1/348 (0.3)	0.43
All stroke	30/1072 (2.8)	5/348 (1.4)	0.23
Major stroke	5/1072 (0.5)	1/348 (0.3)	1.00
Ipsilateral	4/1072 (0.4)	1/348 (0.3)	1.00
Nonipsilateral	1/1072 (0.1)	0/348	1.00
Minor stroke	26/1072 (2.4)	4/348 (1.1)	0.20
Ipsilateral	22/1072 (2.1)	4/348 (1.1)	0.36
Nonipsilateral	4/1072 (0.4)	0/348	0.58
Myocardial infarction	5/1072 (0.5)	3/348 (0.9)	0.41
Composite measure of complications	31/1089 (2.8)	17/364 (4.7)	0.13
Cranial-nerve injury	1/1089 (0.1)‡	4/364 (1.1)	0.02
Peripheral-nerve injury	0/1089	0/364	NA
Vascular injury	8/1089 (0.7)	3/364 (0.8)	1.00
Noncerebral bleeding	21/1089 (1.9)	6/364 (1.6)	0.83
Endarterectomy incision or puncture-site bleeding	3/1089 (0.3)	4/364 (1.1)	0.07
Other complications	0/1089	0/364	NA

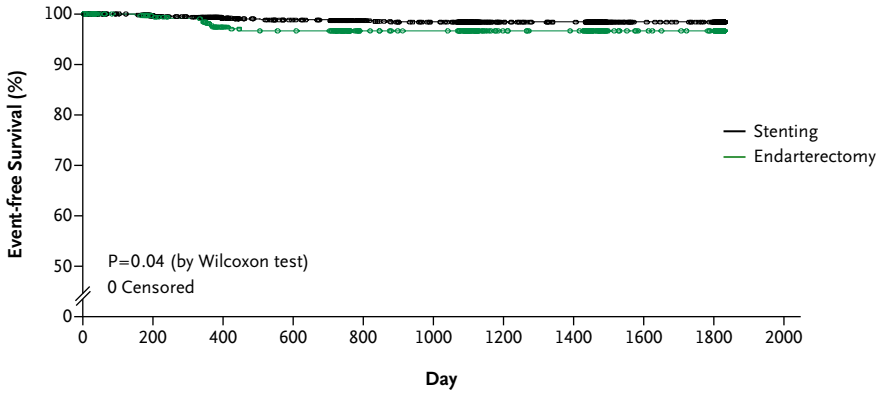
* The data in the table are for the intention-to-treat population; they include only the most serious event for each patient and only each patient's first occurrence of the event. Patients who did not complete 30-day follow-up and did not have any death, stroke, or myocardial infarction events are not included. NA denotes not applicable.
† P values were calculated with Fisher's exact test.
‡ One patient who was randomly assigned to the stenting group crossed over to the endarterectomy group.

carotid stenosis. The results of these pivotal studies established the indications for endarterectomy in selected patients with asymptomatic stenosis of 60% or greater.[1,2,7]

Carotid-artery stenting has emerged as a therapeutic alternative to endarterectomy for the treatment of severe cervical carotid-artery stenosis. The results of randomized trials comparing stenting and endarterectomy in symptomatic patients have been conflicting, and no completed multicenter randomized trials have focused exclusively on asymptomatic patients, which is the largest group of patients undergoing carotid procedures in the United States.[3,4,8-10] In the current trial, with regard to the primary composite end point of death, stroke, or myocardial infarction by 30 days after the procedure or ipsilateral stroke by 1 year, stenting was noninferior to endarterectomy (event rates, 3.8% and 3.4%, respectively). The 30-day rate of stroke was numerically higher in the stenting group than in the endarterectomy group (2.8 vs. 1.4%, P=0.23), and the 30-day rate of death or stroke was 2.9% in the stenting group and 1.7% in the endarterectomy group. Current guidelines state that it is reasonable to perform revascularization in asymptomatic patients with stenosis greater than 70% of the diameter of the artery "if the risk of perioperative stroke, MI [myocardial infarction], and death is low."[11]

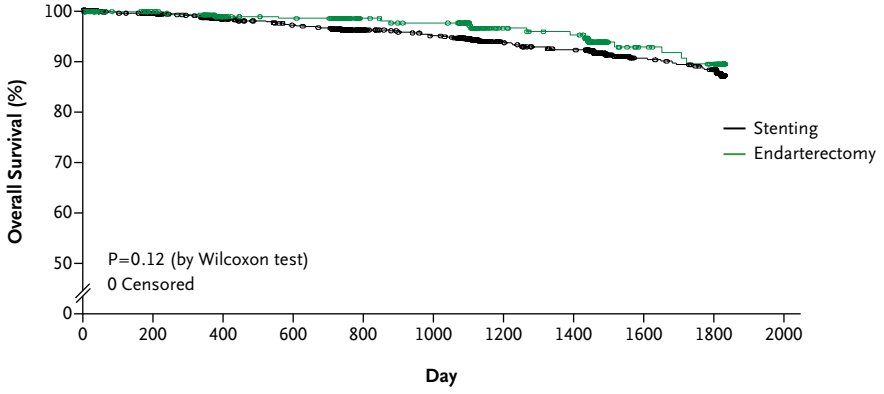
We did not find significant differences in long-term outcomes between the study groups in this large randomized trial. Similarly, CREST, a randomized trial of stenting versus endarterectomy in a combined cohort of symptomatic and asymptomatic patients with severe carotid steno-

A **Freedom from Clinically Driven Target-Lesion Revascularization through 5 Yr**



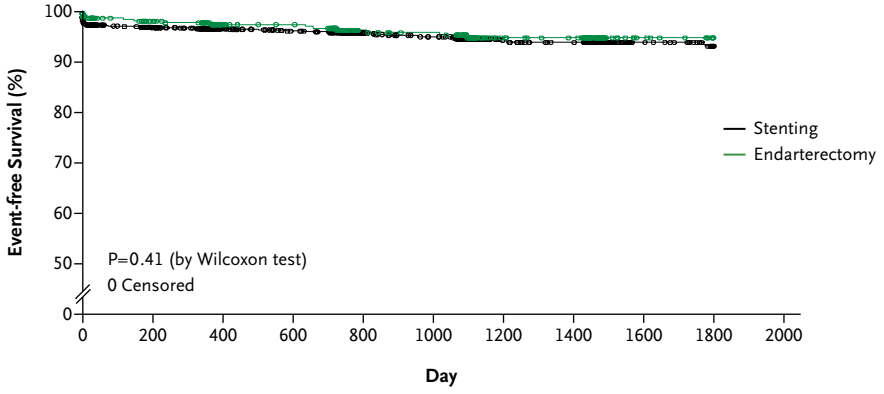
Days	0	1–180	181–365	366–730	731–1095	1096–1460	1461–1825
Stenting (no. at risk)	1089	1082	987	886	745	555	375
Endarterectomy (no. at risk)	364	357	317	286	244	180	111

B **Overall Survival through 5 Yr**



Days	0	1–365	366–730	731–1095	1096–1460	1461–1825
Stenting (no. at risk)	1089	1082	892	756	567	381
Endarterectomy (no. at risk)	364	357	294	254	189	116

C **Freedom from All Stroke through 5 Yr**



Days	0	1–365	366–730	731–1095	1096–1460	1461–1825
Stenting (no. at risk)	1089	1068	865	730	541	363
Endarterectomy (no. at risk)	364	355	287	244	180	112

sis, showed no significant difference in the rate of the primary end point between the stenting group and the endarterectomy group either over 4 years (hazard ratio, 1.11; 95% confidence interval [CI], 0.81 to 1.51)[5] or, as now reported in the *Journal*,[12] over 10 years (hazard ratio, 1.10; 95% CI, 0.83 to 1.45). ACT I used a qualification path for physician investigators that was similar to that used in CREST and, as in CREST, did not include specific subgroups of patients who were at high risk for complications from endarterectomy or stenting. At the time of the inception and initiation of ACT I, CREST was designed to evaluate only symptomatic patients. ACT I was designed to complement CREST by comparing stenting and endarterectomy in asymptomatic patients who were not older than 79 years of age and who were at standard risk for complications from both procedures, when the procedures were performed by interventionists and surgeons with adequate skill and experience and when routine embolic protection and dual antiplatelet therapy were used. CREST was later modified to include asymptomatic patients. It is widely recognized that the skill and experience of the physician is important in achieving acceptable outcomes both with endarterectomy and with stenting, particularly in asymptomatic patients, for whom the absolute risk reduction associated with the intervention is small.[9,13] The results of our study reinforce the findings of CREST, again suggesting that short-term and long-term outcomes with respect to the prevention of stroke are similar with stenting and endarterectomy. Furthermore, as in CREST, we found that the rates of stroke, death, and myocardial infarction overall were low with each intervention.[5]

A limitation of the current study, which was designed and began enrollment a decade ago, is the lack of a treatment group that received contemporary medical therapy only. Current multispecialty guidelines and the existing evidence support the use of carotid revascularization for treatment in selected patients.[1,11] However, advances in medical treatment have resulted in a reduction in stroke risk in selected populations with neurologic symptoms.[14-16] Observational studies have shown that the annual risk of a stroke among asymptomatic patients is probably less than 1% per year with modern medical therapy.[15,17-19] Improved medical therapy may also mitigate the benefits of intervention in patients with intracranial and coronary atherosclerotic disease.[20,21] Risk-stratification techniques may assist in the identification of high-risk and low-risk patients.[22] Although ACT I does not address a comparison between revascularization and contemporary medical therapy alone, the declining rate of stroke and resultant variation in clinical practice has led to important new randomized trials, such as CREST 2 (ClinicalTrials.gov number, NCT02089217), that will reassess the relative benefit.[23-25]

A second limitation of this study is the lack of characterization of the population that was screened but not enrolled. The most common reasons for nonenrollment were an unwillingness of the patient to undergo randomization and a reluctance regarding the long follow-up period that was required. A third limitation of the study is the extended period of enrollment over 8 years and the early termination of the trial. Because of lower-than-expected losses to follow-up, the actual change in power owing to early termination was a reduction from 80% to 75%. A fourth limitation is the inclusion of periprocedural myocardial infarction in the primary composite end point, which created the potential for the higher risk of minor stroke associated with stenting to be offset by the higher risk of myocardial infarction associated with endarterectomy. Our composite end point was selected a priori on the basis of data suggesting that long-term survival rates after endarterectomy are lower among patients with procedure-related myocardial infarction.[26,27] It should be noted that the rate of myocardial infarction was low in both study groups in ACT I (0.5% in the stenting group and 0.9% in the endarterectomy group).

In conclusion, in this multicenter trial involving patients 79 years of age or younger with asymptomatic severe carotid stenosis, carotid-artery stenting was noninferior to carotid endarterectomy at 1 year with regard to the primary composite end point of death, stroke, and myocardial infarction within 30 days or ipsilateral

Figure 3 (facing page). Clinical Outcomes at 5 Years after the Procedure.

Shown are the Kaplan–Meier survival curves for freedom from clinically driven target-lesion revascularization (Panel A), overall survival (Panel B), and freedom from all stroke (Panel C).

stroke within 365 days after the procedure. The rates of stroke and survival after the procedure did not differ significantly between the two study groups over a period of 5 years.

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