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## Protected Carotid-Artery Stenting versus Endarterectomy in High-Risk Patients

Jay S. Yadav, M.D., Mark H. Wholey, M.D., Richard E. Kuntz, M.D., M.Sc., Pierre Fayad, M.D., Barry T. Katzen, M.D., Gregory J. Mishkel, M.D., Tanvir K. Bajwa, M.D., Patrick Whitlow, M.D., Neil E. Strickman, M.D., Michael R. Jaff, D.O., Jeffrey J. Popma, M.D., David B. Snead, Ph.D., Donald E. Cutlip, M.D., Brian G. Firth, M.D., Ph.D., and Kenneth Ouriel, M.D., for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators\*

### ABSTRACT

#### BACKGROUND

Carotid endarterectomy is more effective than medical management in the prevention of stroke in patients with severe symptomatic or asymptomatic atherosclerotic carotid-artery stenosis. Stenting with the use of an emboli-protection device is a less invasive revascularization strategy than endarterectomy in carotid-artery disease.

#### METHODS

We conducted a randomized trial comparing carotid-artery stenting with the use of an emboli-protection device to endarterectomy in 334 patients with coexisting conditions that potentially increased the risk posed by endarterectomy and who had either a symptomatic carotid-artery stenosis of at least 50 percent of the luminal diameter or an asymptomatic stenosis of at least 80 percent. The primary end point of the study was the cumulative incidence of a major cardiovascular event at 1 year — a composite of death, stroke, or myocardial infarction within 30 days after the intervention or death or ipsilateral stroke between 31 days and 1 year. The study was designed to test the hypothesis that the less invasive strategy, stenting, was not inferior to endarterectomy.

#### RESULTS

The primary end point occurred in 20 patients randomly assigned to undergo carotid-artery stenting with an emboli-protection device (cumulative incidence, 12.2 percent) and in 32 patients randomly assigned to undergo endarterectomy (cumulative incidence, 20.1 percent; absolute difference, -7.9 percentage points; 95 percent confidence interval, -16.4 to 0.7 percentage points;  $P=0.004$  for noninferiority, and  $P=0.053$  for superiority). At one year, carotid revascularization was repeated in fewer patients who had received stents than in those who had undergone endarterectomy (cumulative incidence, 0.6 percent vs. 4.3 percent;  $P=0.04$ ).

#### CONCLUSIONS

Among patients with severe carotid-artery stenosis and coexisting conditions, carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy.

From the Cleveland Clinic Foundation, Cleveland (J.S.Y., P.W., K.O.); Pittsburgh Vascular Institute, Pittsburgh (M.H.W.); the Department of Cardiology (R.E.K.) and the Angiographic Core Laboratory (J.J.P.), Brigham and Women's Hospital, Boston; Harvard Medical School, Boston (R.E.K., D.E.C.); University of Nebraska, Omaha (P.F.); Miami Vascular Institute, Miami (B.T.K.); Prairie Cardiovascular Institute, Springfield, Ill. (G.J.M.); St. Luke's Medical Center, Milwaukee (T.K.B.); Texas Heart Institute, Houston (N.E.S.); Vascular Ultrasound Core Laboratory, Morristown, N.J. (M.R.J.); Cordis, Warren, N.J. (D.B.S., B.G.F.); and Beth Israel Deaconess Medical Center, Boston (D.E.C.). Address reprint requests to Dr. Yadav at Cardiovascular Medicine, Desk F25, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195, or at yadavj@ccf.org.

\*The investigators in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial are listed in the Appendix.

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SEVERAL TRIALS HAVE SHOWN CAROTID endarterectomy to be superior to medical management for the prevention of stroke in patients with symptomatic or asymptomatic carotid-artery stenosis.<sup>1-3</sup> The patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and those in the Asymptomatic Carotid Atherosclerosis Study (ACAS) were carefully selected and had low rates of surgical complications.<sup>1,3</sup> Many patients for whom surgery poses a high risk, however, routinely undergo carotid endarterectomy in clinical practice and were excluded from these trials, and such patients have outcomes that are substantially worse than those reported in these trials.<sup>4</sup>

During the past decade, carotid angioplasty with stenting has been used to treat patients at high surgical risk, but its use has been limited by the risks of compression of the stent and embolization of plaque debris to the brain.<sup>5-8</sup> Nickel-titanium (nitinol) crush-resistant stents and emboli-protection devices have been developed to address these problems.<sup>9</sup> We conducted the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial to determine a revascularization strategy for patients with severe carotid-artery stenosis and coexisting conditions that would have excluded them from previous trials of carotid endarterectomy.

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## METHODS

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### INVESTIGATORS

Our multicenter, randomized trial complied with the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review boards at the 29 centers where patients were enrolled for the trial, and all patients provided written informed consent. Prospective investigators were required to submit accounts of their surgical experience and their experience with percutaneous interventional procedures to an executive review committee composed of a neurologist, a cardiologist, a vascular surgeon, and two interventional radiologists. The experience of surgeons had to meet the criteria of the American Heart Association with respect to acceptable rates of complications during and after carotid endarterectomy, and the experience of interventional physicians had to be equal to or superior to the published results of carotid stenting (i.e., an incidence of periprocedural stroke or death of less than 6 percent).<sup>10,11</sup> Surgical investi-

gators had a median annual volume of 30 endarterectomies (range, 15 to 100). Because carotid-artery stenting is a relatively new procedure, the total experience of interventional physicians with this procedure (median, 64 procedures; range, 20 to 700), instead of the annual volume, was reviewed by the committee. Each center was required to assemble a multidisciplinary team of physicians comprising a neurologist, either a vascular surgeon or a neurosurgeon, and an interventional physician.

### PATIENTS

Patients were randomly assigned to a procedure only if all members of the team were in agreement that the patient was a suitable candidate for either endarterectomy or stenting. If the surgeon assessing the patient concluded that endarterectomy could not be safely performed but the interventional physician judged that stenting was feasible, the patient was not randomly assigned to a procedure but instead was entered into a stent registry. Likewise, if the surgeon deemed the patient suitable for surgery but the interventional physician did not think that stenting was feasible, the patient was entered into a surgical registry.

The major eligibility criteria are listed in Table 1. All patients were required to have at least one coexisting condition that potentially increased the risk posed by carotid endarterectomy. Neurologic symptoms were assessed by the neurologist. Patients with symptomatic carotid-artery stenosis were required to have a stenosis of at least 50 percent of the luminal diameter, and patients with asymptomatic carotid-artery stenosis were required to have a stenosis of at least 80 percent on color duplex ultrasonography. Each center had a vascular laboratory that was fully accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories. The analyses of all measurements obtained with the use of carotid ultrasonography were performed by a core laboratory (Vascular Ultrasound Core Laboratory, Morristown, N.J.), according to published criteria.<sup>12</sup> Eligible patients were randomly assigned in a 1:1 ratio to endarterectomy or stenting, with stratification according to the clinical center and according to whether the patient had symptomatic or asymptomatic disease. Randomization was performed with the use of a pseudo-random-number generator, and the numbers were distributed by an automated, centralized telephone-response system. After randomization, patients who were assigned to undergo endarterectomy did

not also undergo angiography, so that the surgical group was not subjected to the risks associated with angiography.

#### ENDARTERECTOMY AND STENTING

Treatment with aspirin at a dose of 81 or 325 mg per day was begun at least 72 hours before stenting or endarterectomy and was continued indefinitely in both study groups. Both groups received intra-procedural heparin to maintain a therapeutic activated partial-thromboplastin time of 250 to 300 seconds. Patients undergoing stenting received clopidogrel (75 mg per day) starting 24 hours before the procedure and continuing for two to four weeks thereafter. Patients undergoing endarterectomy did not receive clopidogrel because of the potential increase in the risk of perioperative bleeding. Surgeons performed endarterectomy according to their customary techniques.

The stent used was a self-expanding, nitinol stent (Smart or Precise, Cordis) with an emboli-protection device (Angioguard or Angioguard XP, Cordis). The device consists of a guidewire with a 0.04 cm (0.014 in.) diameter and an expandable filter basket with a pore size of 100  $\mu\text{m}$ .<sup>9</sup> The guidewire was used to cross the carotid-artery stenosis, and then the filter was expanded before the stent was deployed. At the end of the procedure, the filter containing the captured emboli was collapsed and removed.

#### DATA COLLECTION AND FOLLOW-UP

All data were submitted to the data-coordinating center (Harvard Clinical Research Institute, Harvard Medical School, Boston), which performed the analysis. The investigators had full access to the data. Cerebral angiography was performed before carotid stenting, and the results were submitted to the angiographic core laboratory (Angiographic Core Laboratory, Brigham and Women's Hospital, Boston), where they were analyzed with the use of a computerized system. The study design, all analyses, and the decision to publish were determined solely by the principal investigators and the study investigators.

Follow-up visits were scheduled to take place 30 days and 6 and 12 months after the procedure and annually thereafter for 3 years. Color duplex ultrasonography was repeated before hospital discharge and at each follow-up visit, except at 30 days. Follow-up angiography was indicated when the findings on carotid ultrasonography suggested that

restenosis (i.e., more than 50 percent stenosis) had developed. A neurologic examination, including assessment according to the National Institutes of Health Stroke Scale, and monitoring for adverse clinical events were performed within 24 hours after the procedure and daily thereafter until hospital discharge and at all follow-up visits. Neurologic deficits lasting longer than 48 hours were evaluated with the use of brain imaging. Major adverse clinical events were adjudicated by an independent, blinded clinical-events committee appointed by the data-coordinating center and composed of neurologists, surgeons, and cardiologists. An independent data and safety monitoring board, not affiliated with the study sponsor or the study investigators, reviewed the data periodically to identify safety concerns.

#### END POINTS

The primary end point of the trial was the cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. The secondary end points included target-vessel revascularization at one year, cranial-nerve palsy,

**Table 1. Major Eligibility Criteria.**

#### Inclusion criteria

##### General criteria

- Age  $\geq 18$  yr
- Unilateral or bilateral atherosclerotic or restenotic lesions in native carotid arteries
- Symptoms plus stenosis of more than 50 percent of the luminal diameter
- No symptoms plus stenosis of more than 80 percent of the luminal diameter

##### Criteria for high risk (at least one factor required)

- Clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery)
- Severe pulmonary disease
- Contralateral carotid occlusion
- Contralateral laryngeal-nerve palsy
- Previous radical neck surgery or radiation therapy to the neck
- Recurrent stenosis after endarterectomy
- Age  $> 80$  yr

#### Exclusion criteria

- Ischemic stroke within previous 48 hr
- Presence of intraluminal thrombus
- Total occlusion of target vessel
- Vascular disease precluding use of catheter-based techniques
- Intracranial aneurysm  $> 9$  mm in diameter
- Need for more than two stents
- History of bleeding disorder
- Percutaneous or surgical intervention planned within next 30 days
- Life expectancy  $< 1$  yr
- Ostial lesion of common carotid artery or brachiocephalic artery

and complications at the surgical site or the vascular access site. Stroke was defined as an ischemic neurologic deficit that persisted for more than 24 hours. Myocardial infarction was defined as a creatine kinase level higher than two times the upper limit of normal with a positive MB fraction. Neurologic complications were quantified with the use of the National Institutes of Health Stroke Scale, the Barthel index of functional levels in activities of daily living, and the Rankin scale of functional disability.<sup>13-15</sup>

#### STATISTICAL ANALYSIS

The randomized trial was designed to show that carotid stenting was not inferior to carotid endarterectomy. Data were analyzed with the use of the triangular sequential-monitoring method, which allows flexibility in sample size (as many as 2400 patients could be enrolled) and in the timing of the interim analyses.<sup>16</sup> An interim analysis according to this method (i.e., comparison between the monitoring end point, which is a combination of the 30-day component of the primary end point in all patients, and the 1-year primary end point in patients with 1-year follow-up) was planned to determine whether enrollment in the trial should be terminated. The condition for termination was based on the upper boundary of the 95 percent confidence interval for the difference in the monitoring end point between the two groups, calculated as the monitoring end point in the stenting group minus the monitoring end point in the surgery group. If the upper boundary was calculated to be less than 3 percent, which was the definition of noninferiority used in the trial, enrollment was to be terminated. A final noninferiority test of the primary end point was to be repeated after all patients had been followed for one year, with appropriate adjustment according to the triangular method.<sup>16</sup>

In early 2002, the pace of enrollment in the trial abruptly slowed, because several nonrandomized carotid-stent registries had become available. The trial was therefore terminated because of the decrease in enrollment, and the primary end point was analyzed with respect to the noninferiority of carotid-artery stenting as compared with endarterectomy with the use of interval-censored survival data at one year.<sup>16</sup> The prespecified secondary analysis at one year compared the cumulative incidence of the primary end point between the two groups for all patients who underwent randomization (i.e., intention-to-treat analysis) and between patients

who actually received one of the two assigned treatments (i.e., actual-treatment analysis). The rates of the secondary end points were estimated with the use of the Kaplan–Meier method,<sup>17</sup> and differences between the groups were estimated with the use of the log-rank test. The length of the hospital stay among patients in the protocol sample was calculated for both the stenting group and the endarterectomy group and was compared with the use of the Wilcoxon two-sample test. Computations were performed with the use of SAS software (version 6.12).

#### RESULTS

Between August 2000 and July 2002, 747 patients were enrolled in the study, and 334 patients underwent randomization. Of the 413 patients who were not randomly assigned to treatment, 406 were entered into the stent registry and 7 were entered into the surgical registry. Of the 167 patients randomly assigned to stenting, 159 received the assigned treatment; 8 patients were not treated owing to deterioration of their condition (3), inability to meet the enrollment criteria (2), and withdrawal of consent (3). Of the 167 patients assigned to surgery, 151 received the assigned treatment; 16 patients were not treated owing to deterioration of their condition (4), inability to meet the enrollment criteria (4), and withdrawal of consent (8). All 334 patients were followed. The baseline clinical characteristics of the patients in the two treatment groups were similar (Table 2), with the exception of a significantly higher frequency of coronary disease and previous percutaneous transluminal coronary angioplasty among those assigned to receive a stent than among those assigned to undergo endarterectomy. The emboli-protection device was successfully used in 95.6 percent of the patients assigned to stenting.

The primary end point occurred in 20 of the 167 patients randomly assigned to stenting (cumulative incidence, 12.2 percent) and in 32 of the 167 patients randomly assigned to surgery (cumulative incidence, 20.1 percent), for an absolute difference of  $-7.9$  percentage points (95 percent confidence interval,  $-16.4$  to  $0.7$  percentage points;  $P=0.004$  for noninferiority). The analysis of the primary end point by the triangular method showed that carotid-artery stenting was not inferior to endarterectomy, since the 0.6 percent upper boundary of the absolute difference between the groups in the incidence of the primary end point at one year was less than 3 percent. The secondary analysis of the cumulative

incidence of the primary end point at one year showed a nearly significant difference between carotid-artery stenting and endarterectomy among all 334 patients randomly assigned to treatment (intention-to-treat analysis,  $P=0.053$ ) and among the 310 treated patients (cumulative incidence, 12.0 percent in patients who received a stent vs. 20.1 percent in patients who underwent endarterectomy;  $P=0.048$ ) (Table 3 and Fig. 1). The estimated rate of cranial-nerve palsy at one year was higher among those who were assigned to undergo endarterectomy than among those who were assigned to receive a carotid stent (4.9 percent vs. 0 percent,  $P=0.004$ ) as was the estimated rate of target-vessel revascularization (4.3 percent vs. 0.6 percent,  $P=0.04$ ) (Table 3).

In the periprocedural period (up to 30 days), the cumulative incidence of stroke, myocardial infarction, or death was 4.8 percent among patients as-

signed to receive a stent and 9.8 percent among those assigned to undergo endarterectomy in the intention-to-treat analysis ( $P=0.09$ ) and 4.4 percent among patients who actually received a stent and 9.9 percent among those who underwent endarterectomy ( $P=0.06$ ) (Table 4). The mean ( $\pm$ SD) length of the hospital stay was  $1.84\pm 1.75$  days among patients who received a stent and  $2.85\pm 3.67$  days among those who underwent surgery ( $P=0.002$ ).

In the analysis of patients with symptomatic carotid-artery stenosis, the cumulative incidence of the primary end point at one year was 16.8 percent among those who received a stent, as compared with 16.5 percent among those who underwent endarterectomy ( $P=0.95$ ). In the postprocedural period, the cumulative incidence of the primary end point at 30 days among these patients was 2.1 percent among those who received a stent and 9.3 percent among those who underwent endarterectomy

**Table 2. Characteristics of Patients Randomly Assigned to Treatment Groups.**

Characteristic	Stent (N=167)	Endarterectomy (N=167)
Age (yr)		
Mean $\pm$ SD	72.5 $\pm$ 8.3	72.6 $\pm$ 8.9
Range	49.0–89.0	46.0–91.0
Male sex (%)	66.9	67.1
Diabetes mellitus (%)	25.3	27.5
History of dyslipidemia (%)	78.5	76.9
History of hypertension (%)	85.5	85.1
Current smoking (%)	16.9	16.4
Coronary artery disease (%)	85.8	75.5
Class 3 or 4 angina (%)*	24.1	14.7
Previous Q-wave or non-Q-wave myocardial infarction (%)	29.7	35.3
Previous percutaneous transluminal angioplasty (%)	34.8	23.4
Renal insufficiency (%)	6.0	7.5
Chronic obstructive pulmonary disease (%)	17.0	13.8
Previous coronary-artery bypass grafting (%)	43.4	30.8
Previous endarterectomy (%)	28.3	26.7
History of transient ischemic attack (%)	31.1	34.0
History of stroke (%)	27.1	23.8
Symptomatic stenosis (%)	29.9	27.7
Congestive heart failure (%)	17.1	19.6
Coexisting severe coronary artery disease (%)	15.9	16.5
Contralateral carotid occlusion (%)	23.6	25.3
Recurrent stenosis after endarterectomy (%)	22.6	22.2
Age >80 yr (%)	19.3	20.5
One risk factor (%)	67.9	63.9

\* The severity of angina was classified according to the guidelines of the Canadian Cardiovascular Society.

( $P=0.18$ ). For patients with asymptomatic carotid-artery stenosis, the cumulative incidence of the primary end point at one year was lower among those who received a stent (9.9 percent) than among those who underwent endarterectomy (21.5 percent,  $P=0.02$ ); however, a test for interaction between asymptomatic stenosis and receipt of a carotid-artery stent was negative ( $P=0.55$ ). In the periprocedural period, the cumulative incidence of death, myocardial infarction, or stroke among patients with asymptomatic carotid-artery stenosis was 5.4 percent among those who received a stent, as compared with 10.2 percent among those who underwent endarterectomy ( $P=0.20$ ).

### DISCUSSION

In this randomized trial, carotid stenting with an emboli-protection device was compared with carotid endarterectomy. The findings showed that stenting was not inferior to surgery, and the rate of the primary end point (a composite of death, stroke, or

myocardial infarction within 30 days) was 39 percent lower among patients who were randomly assigned to protected carotid-artery stenting than among those who were assigned to undergo endarterectomy. Stenting resulted in rates of complications for all adverse events (death, stroke, or myocardial infarction) that were statistically equivalent to or lower than those among patients who underwent endarterectomy both in the overall study population and in the subgroups with asymptomatic or symptomatic stenosis. The rates of bleeding complications were similar in the two groups, and the rates of cranial-nerve palsy and revascularization and the duration of the hospital stay were greater among those in the carotid-endarterectomy group than among those in the stenting group.

We studied patients for whom the risk posed by surgery was high, because when our trial was designed, clinical equipoise did not exist for the random assignment of patients at low risk to a percutaneous interventional treatment.<sup>18,19</sup> Although patients with the types of coexisting conditions

**Table 3. Cumulative Incidence of Adverse Events within One Year.\***

Event	Intention-to-Treat Analysis			Actual-Treatment Analysis		
	Stenting (N=167) no. (%)	Endarterectomy (N=167) no. (%)	P Value	Stenting (N=159) no. (%)	Endarterectomy (N=151) no. (%)	P Value
Death	12 (7.4)	21 (13.5)	0.08	11 (7.0)	19 (12.9)	0.08
Stroke	10 (6.2)	12 (7.9)	0.60	9 (5.8)	11 (7.7)	0.52
Major ipsilateral	1 (0.6)	5 (3.3)	0.09	0	5 (3.5)	0.02
Major nonipsilateral	1 (0.6)	2 (1.4)	0.53	1 (0.6)	1 (0.7)	0.97
Minor ipsilateral	6 (3.7)	3 (2.0)	0.34	6 (3.8)	3 (2.2)	0.37
Minor nonipsilateral	3 (1.9)	4 (2.7)	0.64	3 (2.0)	3 (2.1)	0.89
Myocardial infarction	5 (3.0)	12 (7.5)	0.07	4 (2.5)	12 (8.1)	0.03
Q-wave	0	2 (1.2)	0.15	0	2 (1.3)	0.15
Non-Q-wave	5 (3.0)	10 (6.2)	0.17	4 (2.5)	10 (6.7)	0.08
Cranial-nerve palsy	0	8 (4.9)	0.004	0	8 (5.3)	0.003
Target-vessel revascularization	1 (0.6)	6 (4.3)	0.04	1 (0.7)	6 (4.6)	0.04
Conventional end point (stroke or death at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 yr)	9 (5.5)	13 (8.4)	0.36	8 (5.1)	11 (7.5)	0.40
Primary end point (death, stroke, or myocardial infarction at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 yr)	20 (12.2)	32 (20.1)	0.05	19 (12.0)	30 (20.1)	0.05

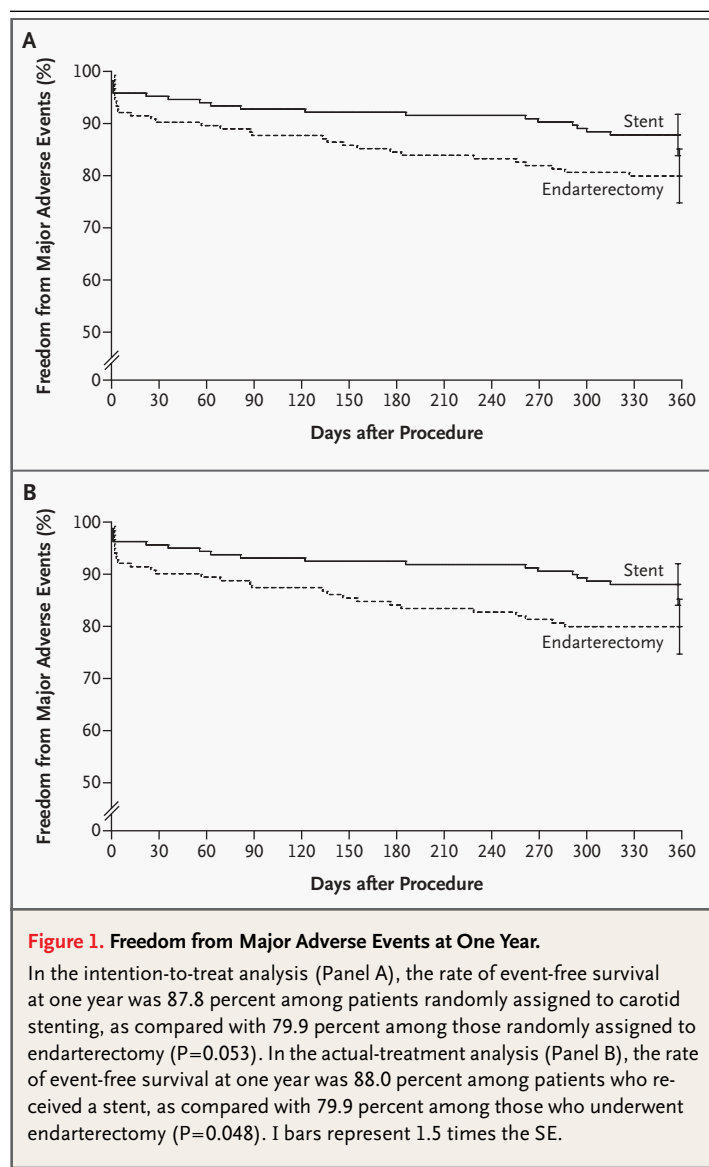
\* Patients may have had more than one event. P values were determined by the log-rank test. Rates of adverse events were estimated with the use of the Kaplan–Meier method.

present in our study population have been excluded from randomized trials of carotid endarterectomy, they do frequently undergo surgery and therefore represent a substantial proportion of the patients undergoing carotid endarterectomy.<sup>4,20</sup> In a study of more than 100,000 Medicare patients undergoing endarterectomy, Wennberg et al. found that the overall perioperative mortality rate at hospitals participating in NASCET and ACAS was 1.4 percent.<sup>4</sup> Since the mortality rate in NASCET was 0.6 percent and that in ACAS was 0.1 percent, Wennberg et al. concluded that the patients enrolled were not representative of patients routinely treated with endarterectomy. In a review of Medicare patients in Ohio who underwent carotid endarterectomy, one in six patients was 80 years of age or older and on that basis would have been excluded from both NASCET and ACAS.<sup>21</sup> In the Cleveland Clinic's prospective surgical registry of more than 3000 patients who have undergone carotid endarterectomy, the rate of perioperative death, stroke, and myocardial infarction among those at high risk has been reported to be 7.4 percent, as compared with 2.9 percent among those at low risk.<sup>19</sup>

Because the surgical investigators made the final decision regarding the patients' suitability for surgery and randomization, our trial provides systematic information on the types of patients for whom, according to practicing vascular surgeons, the risk associated with carotid endarterectomy is high. The surgeons in this study had considerably more experience with endarterectomy than the typical vascular surgeon has in the United States.<sup>21-24</sup> The volume of procedures is an important predictor of outcomes.<sup>22-26</sup> Even though many of the patients had previously undergone endarterectomy, radical neck surgery, or radiation therapy, the rate of cranial-nerve palsy among patients who underwent endarterectomy in our trial was lower than that in NASCET (5.3 percent vs. 7.6 percent). This supports the technical excellence of the surgeons in this study.

The primary end point in our trial — including death from all causes within 1 year after the intervention and myocardial infarction within 30 days — was broader than that in previous trials of carotid-artery surgery. The primary end point in ACAS was death or stroke within 30 days after the procedure and ipsilateral stroke within 5 years. The primary end point in NASCET was fatal or nonfatal ipsilateral stroke. In addition, in our trial all patients were assessed by the study neurologist within 24 hours

after the procedure and daily thereafter until discharge, potentially resulting in an increase in the detection of small strokes. We included myocardial infarction in the primary end point because patients with atherosclerotic vascular disease who undergo either stenting or endarterectomy are at a substantial risk for myocardial infarction, and the occurrence of either a Q-wave or a non-Q-wave infarction in the perioperative period increases the risk of future complications and death.<sup>27-31</sup> A perioperative non-Q-wave infarction confers an increase in the risk of death by a factor of 6 and an increase in the risk of myocardial infarction by a factor of 27 in the subsequent six months.<sup>30</sup> The



**Table 4. Cumulative Incidence of Adverse Events at 30 Days.\***

Event	Intention-to-Treat Analysis			Actual Treatment Analysis		
	Stent (N=167)	Endarterectomy (N=167)	P Value	Stent (N=159)	Endarterectomy (N=151)	P Value
	no. (%)			no. (%)		
Death	2 (1.2)	4 (2.5)	0.39	1 (0.6)	3 (2.0)	0.29
Stroke	6 (3.6)	5 (3.1)	0.77	5 (3.1)	5 (3.3)	0.94
Major ipsilateral	1 (0.6)	2 (1.2)	0.55	0	2 (1.3)	0.15
Major nonipsilateral	1 (0.6)	1 (0.6)	1.00	1 (0.6)	1 (0.7)	0.97
Minor ipsilateral	4 (2.4)	1 (0.6)	0.18	4 (2.5)	1 (0.7)	0.20
Minor nonipsilateral	1 (0.6)	1 (0.6)	1.00	1 (0.6)	1 (0.7)	0.97
Myocardial infarction	4 (2.4)	10 (6.1)	0.10	3 (1.9)	10 (6.6)	0.04
Q-wave	0	2 (1.2)	0.15	0	2 (1.3)	0.15
Non-Q-wave	4 (2.4)	8 (4.9)	0.23	3 (1.9)	8 (5.3)	0.11
Death, stroke, or myocardial infarction	8 (4.8)	16 (9.8)	0.09	7 (4.4)	15 (9.9)	0.06
Major vascular complications	2 (1.2)	1 (0.6)	0.57	2 (1.3)	1 (0.7)	0.60

\* P values were determined by the log-rank test. Rates of adverse events were estimated with the use of the Kaplan–Meier method.

increasing divergence at the one-year follow-up between the survival curves for patients who received stents and those who underwent endarterectomy may be due to the delayed effect of perioperative myocardial infarctions (Fig. 1).

In ACAS, which involved patients with asymptomatic carotid-artery stenosis of greater than 60 percent of the luminal diameter, the rate of perioperative stroke and death at 30 days among patients who underwent endarterectomy (2.3 percent) was similar to the annual rate of ipsilateral stroke in the group that received medical treatment (2.2 percent).<sup>3</sup> Patients with asymptomatic carotid-artery stenosis in the SAPPHERE trial had severe stenosis (80 percent to 99 percent of the luminal diameter), which carries a 5 to 6 percent annual risk of stroke with medical therapy.<sup>32</sup> In that trial, the rates of death or stroke at 30 days among the patients with asymptomatic carotid-artery stenosis who received a carotid-artery stent and those who underwent endarterectomy (5.4 percent and 4.6 percent, respectively) were similar to the annual risk of stroke among such patients who received medical therapy. These increased rates of periprocedural events may be acceptable among such patients, given that their annual risk of stroke is higher than that among patients with moderate stenosis.

The trial was terminated early, because the recruitment of patients slowed after nonrandomized stent registries were established. Although the sta-

tistical power of our study might have been enhanced with the use of a larger sample, our finding of the noninferiority of stenting as compared with surgery met the intended goal of the primary analysis. A larger sample might have provided more support for the secondary finding of the superiority of stenting.

The main finding of our randomized trial is that carotid-artery stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy in the prevention of stroke, death, or myocardial infarction among patients for whom surgery poses an increased risk. In the secondary analysis, the cumulative incidence of stroke, death, and myocardial infarction, as well as the cumulative incidence of cranial-nerve palsy and revascularization and the length of the hospital stay, were lower among patients who received a stent than among those who underwent surgery. The results of our study are not generalizable to patients at low surgical risk, and studies are under way to assess the appropriateness of stenting in such patients.

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Dr. Yadav is the inventor of the Angioguard emboli-protection device used in the SAPPHERE trial and was a shareholder in Angioguard at the time of its purchase by Johnson & Johnson in 1999; he does not now own any shares of stock in Johnson & Johnson. Drs. Kuntz and Popma report having received educational grant support from Cordis; Dr. Mishkel grant support from Cordis; Dr. Whitlow support from Abbott, Kerberos, and Cordis; Drs. Wholey, Katzen, and Strickman consulting fees from Cordis, Guidant, and Boston Scientific; and Dr. Ouriel lecture fees from Cordis. Dr. Jaff reports being a consultant to Cordis. Drs. Snead and Firth are employees of Cordis.

## APPENDIX

The investigators and institutions participating in the SAPHIRE trial were as follows: *Executive Committee*: J.S. Yadav, M. Wholey, K. Ouriel, B. Katzen, P. Fayad, D. Donohoe. *Clinical Events Committee*: Harvard Clinical Research Institute (Harvard Medical School, Boston). *Data and Safety Monitoring Board*: L. Wechsler (chair), F. Pomposelli, J. Orav, J. Carozza, D. Cutlip. *Principal investigators*: P. Whitlow, Cleveland Clinic Foundation, Cleveland; M. Wholey and G. Eles, Shadyside Hospital, Pittsburgh; G. Mishkel, St. John's Hospital, Springfield, Ill.; T.K. Bajwa and A. Ahuja, St. Luke's Medical Center, Milwaukee; N.E. Strickman, Texas Heart Institute, Houston; G.M. Ansel, Riverside Methodist Hospital, Columbus, Ohio; K. Rosenfield, R. Shainfeld, and P. Soukas, St. Elizabeth's Hospital, Boston; F.J. Criado, Union Memorial Hospital and MedStar Health, Baltimore; S. Myla, Hoag Hospital and Fountain Valley Hospital, Newport Beach, Calif.; R. Raabe, Heart Institute of Spokane, Spokane, Wash.; M. Bacharach, North Central Heart Institute, Sioux Falls, S.D.; R.J. Hye, Kaiser Permanente Medical Center, San Diego, Calif.; B.T. Katzen, Baptist Hospital of Miami, Miami; D. McCormick, Hahnemann Hospital, Philadelphia; D. Allie and C. Walker, Cardiovascular Institute of the South, Lafayette, La.; F.A. Shawl, Washington Adventist Hospital, Takoma Park, Md.; J. Belville, Mission Hospital Vascular Institute and Stroke Center, Mission Viejo, Calif.; C. Gomez, M. Liu, and S. Saddekni, University of Alabama at Birmingham, Birmingham; R.R. Heuser, St. Luke's Medical Center, Phoenix, Ariz.; H. Madyoon, St. Joseph's Medical Center, Stockton, Calif.; T.M. Sullivan and B. Gray, Greenville Hospital System, Greenville, S.C.; G. Roubin, Lenox Hill Hospital Center, New York; P.M. Davis, Our Lady of the Lake Regional Medical Center, Baton Rouge, La.; G. Petrossian, St. Francis Medical Center Hospital, Roslyn, N.Y.; L.N. Hopkins, Millard Fillmore Hospital, Buffalo, N.Y.; W. Gray, Swedish Heart Hospital, Seattle; S.R. Ramee, Ochsner Clinic, New Orleans; M. Myers and D. Tubman, Abbott Northwestern Hospital, Minneapolis; T. Ohki, Montefiore Medical Center, Bronx, N.Y.

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