Stroke After Carotid Stenting and Endarterectomy in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

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Background—Stroke occurs more commonly after carotid artery stenting than after carotid endarterectomy. Details regarding stroke type, severity, and characteristics have not been reported previously. We describe the strokes that have occurred in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).

Methods and Results—CREST is a randomized, open-allocation, controlled trial with blinded end-point adjudication. Stroke was a component of the primary composite outcome. Patients who received their assigned treatment within 30 days of randomization were included. Stroke was adjudicated by a panel of board-certified vascular neurologists with secondary central review of clinically obtained brain images. Stroke type, laterality, timing, and outcome were reported. A periprocedural stroke occurred among 81 of the 2502 patients randomized and among 69 of the 2272 in the present analysis. Strokes were predominantly minor (81%, n=56), ischemic (90%, n=62), in the anterior circulation (94%, n=65), and ipsilateral to the treated artery (88%, n=61). There were 7 hemorrhages, which occurred 3 to 21 days after the procedure, and 5 were fatal. Major stroke occurred in 13 (0.6%) of the 2272 patients. The estimated 4-year mortality after stroke was 21.1% compared with 11.6% for those without stroke. The adjusted risk of death at 4 years was higher after periprocedural stroke (hazard ratio, 2.78; 95% confidence interval, 1.63–4.76).

Conclusions—Stroke, particularly severe stroke, was uncommon after carotid intervention in CREST, but stroke was associated with significant morbidity and was independently associated with a nearly 3-fold increased future mortality. The delayed timing of major and hemorrhagic stroke after revascularization suggests that these strokes may be preventable.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00004732.

Key Words: stroke ■ carotid stenosis ■ endarterectomy ■ stents ■ randomized controlled trial ■ prevention

Stroke is a more frequent complication of carotid stenting (CAS) than of endarterectomy (CEA).1–4 In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), this greater occurrence of stroke in the CAS arm was offset by the greater occurrence of myocardial infarction (MI) in the CEA arm.5 However, stroke was found to have a greater impact than MI on quality of life based on assessment of the SF-36 physical and mental health subscales. In the International Carotid Stenting Surgery (ICSS) trial, a higher occurrence of minor stroke in the CAS arm was balanced by a higher occurrence of cranial nerve palsy in the CEA arm.4 Furthermore, a magnetic resonance imaging (MRI) substudy of the ICSS confirmed that CAS was associated with a greater number of ischemic cerebral infarctions, both symptomatic and asymptomatic, observed on diffusion-weighted imaging.6 Age and sex may modify this risk, with an observed higher risk of stroke with CAS at older ages7,8 and among women.9

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Prevention of stroke is the goal of carotid revascularization, yet differences in interpretation of periprocedural stroke as an end point in randomized trials of CAS and CEA have generated controversy. Well-informed discussants have advocated MI and cranial neuropathy as important complications of CEA, important enough to consider CAS an equivalent procedure with regard to safety.10 Others have advocated that patients are more affected by stroke than by MI or cranial neuropathy on measures of disability and quality of life and that CEA should therefore be the preferred procedure.11,12

The discussions and guidelines have been limited by a dearth of detailed information describing the strokes.13 European guidelines favor CEA as the primary modality of treatment within 30 days of randomization (n=2272) are included in these analyses. Institutional/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. The primary results and full description of the methodology have been reported previously.5

Patients were enrolled at 108 centers in the United States and 9 in Canada. The CEA surgeons were credentialed by a surgical management committee. The Interventional Management Committee was responsible for training and credentialing the CAS interventionalists. Patients were classified as symptomatic if they had experienced a recent transient ischemic attack, stroke, or transient monocular blindness ipsilateral to the study artery in the preceding 180 days before randomization. Otherwise, they were classified as asymptomatic.

Stroke was defined as an acute neurological event with focal symptoms and signs lasting ≥24 hours that were consistent with focal cerebral ischemia or hemorrhage; stroke was considered a complication of carotid revascularization if it occurred within 30 days of the procedure. Initially, a broad net was cast to try to identify stroke outcome events. One or both of the following could be used as confirmatory evidence of stroke: A 1-point increase on the National Institutes of Health Stroke Scale (NIHSS) or an appropriate score on the transient ischemic attack/stroke questionnaire, or an increase in the NIHSS score of ≥2 points; this second-phase process was more detailed and deterministic. The occurrence and severity of stroke were determined by the Stroke Adjudication Committee. Stroke was minimally defined as major on the NIHSS score if the score was ≥9 at 90 days after the procedure and minor otherwise. Stroke was considered nondiabling if the modified Rankin scale score was ≥2 at 30 days. Transient ischemic attack and amaurosis fugax were not considered in the present analysis; however, the final determination of whether a stroke was major or minor was based on a combination of narrative clinical reports, the NIHSS, imaging reports, and outcome data.

### Methods

**CREST** is a randomized, open-allocation, controlled trial with blinded end-point adjudication comparing CEA to CAS among both symptomatic and asymptomatic patients with atherosclerotic carotid artery stenosis. Stroke was a component of the primary composite outcome for the 2502 patients randomized. The analysis of the stroke outcome was a prespecified analysis. Patients who received their assigned treatment within 30 days of randomization (n=2272) are included in these analyses. Institutional/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. The primary results and full description of the methodology have been reported previously.5

**Table 1. Characteristics of Patients With and Without Periprocedural Stroke**

<table>
<thead>
<tr>
<th></th>
<th>CAS (n=48)</th>
<th>Nonstroke (n=1075)</th>
<th>P</th>
<th>CEA (n=21)</th>
<th>Nonstroke (n=1128)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean±SD</strong></td>
<td>73.0±7.7</td>
<td>68.5±9.0</td>
<td>&lt;0.001</td>
<td>70.2±9.7</td>
<td>69.1±8.7</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>25 (52.1)</td>
<td>700 (65.1)</td>
<td>0.06</td>
<td>14 (66.7)</td>
<td>756 (67.0)</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>White, n (%)</strong></td>
<td>44 (91.7)</td>
<td>1006 (93.6)</td>
<td>0.60</td>
<td>21 (100.0)</td>
<td>1057 (93.7)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Prior cardiovascular disease, n (%)</strong></td>
<td>19 (40.4)</td>
<td>452 (43.7)</td>
<td>0.66</td>
<td>9 (45.0)</td>
<td>482 (44.6)</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Risk factor status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>45 (93.8)</td>
<td>905 (84.3)</td>
<td>0.07</td>
<td>18 (85.7)</td>
<td>970 (86.1)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>18 (37.5)</td>
<td>320 (29.9)</td>
<td>0.26</td>
<td>5 (23.8)</td>
<td>349 (31.0)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>37 (77.1)</td>
<td>902 (84.3)</td>
<td>0.18</td>
<td>18 (85.7)</td>
<td>963 (85.8)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>7 (14.9)</td>
<td>296 (27.9)</td>
<td>0.05</td>
<td>6 (28.6)</td>
<td>289 (26.0)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Symptomatic arteries, n (%)</strong></td>
<td>34 (70.8)</td>
<td>562 (52.3)</td>
<td>0.01</td>
<td>15 (71.4)</td>
<td>597 (52.9)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Type of qualifying event (symptomatic patients), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>16 (47.1)</td>
<td>241 (42.9)</td>
<td>0.61</td>
<td>5 (33.3)</td>
<td>257 (43.1)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td>15 (44.1)</td>
<td>237 (42.2)</td>
<td>0.26</td>
<td>7 (46.7)</td>
<td>243 (40.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Amaurosis fugax</strong></td>
<td>3 (8.8)</td>
<td>84 (14.9)</td>
<td>0.06</td>
<td>3 (20.0)</td>
<td>97 (16.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Medical treatment preprocedure, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiplatelet therapy 48 h</strong></td>
<td>45 (95.7)</td>
<td>1010 (96.4)</td>
<td>0.69</td>
<td>21 (100.0)</td>
<td>1035 (91.8)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Cholesterol medication</strong></td>
<td>33 (94.3)</td>
<td>810 (92.4)</td>
<td>0.67</td>
<td>16 (94.1)</td>
<td>849 (91.0)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; and TIA, transient ischemic attack.

**Clinical Perspective on p 3061**

Prevention of stroke is the goal of carotid revascularization, yet differences in interpretation of periprocedural stroke as an end point in randomized trials of CAS and CEA have generated controversy. Well-informed discussants have advocated MI and cranial neuropathy as important complications of CEA, important enough to consider CAS an equivalent procedure with regard to safety.10 Others have advocated that patients are more affected by stroke than by MI or cranial neuropathy on measures of disability and quality of life and that CEA should therefore be the preferred procedure.11,12

European guidelines favor CEA as the primary modality of choice; North American guidelines allow either procedure.13 The discussions and guidelines have been limited by a dearth of detailed information describing the strokes.

We describe the nature, localization, severity, and outcome of periprocedural stroke in CREST. We also report on the imaging characteristics of these strokes, the timing of stroke after carotid revascularization, and the association of periprocedural stroke with long-term outcomes, including late mortality.
The Stroke Adjudication Committee consisted of 6 board-certified stroke neurologists. All adjudicators were blinded to the randomized procedure. Events were reviewed by at least 2 adjudicators. Enrollment of a third reviewer occurred if the first 2 adjudicators disagreed with 1 or more of the following variables: Stroke outcome, date of occurrence, vascular distribution, or stroke severity. In the event of an ongoing disagreement after the third review, the Stroke Adjudication Committee met via conference call to resolve the disagreement. A total of 300 potential events were screened. Of these, 46 were deemed to be transient ischemic attack or amaurosis fugax (ie, symptoms lasted <24 hours) and per internal protocol were not sent for physician review. Potential periprocedural events were submitted for physician adjudication for 254 suspected events. For events adjudicated as strokes, the laterality, timing, stroke type, and outcome were determined.

Postoperative images of the brain were not collected routinely as part of the study protocol. After publication of the primary outcomes of CREST in 2011, we asked sites to provide digital copies of brain images (computed tomography or MRI) to further characterize the strokes that occurred as periprocedural complications of carotid revascularization. All images were reviewed centrally, blinded to treatment allocation (M.D.H., W.F.M.). Imaging characteristics of stroke are described quantitatively, by stroke type (hemorrhage or ischemia), by arterial territory among ischemic strokes, and qualitatively by imaging pattern of infarction. Where images were unavailable, we requested neuroradiologists’ imaging reports and used these to estimate imaging characteristics. Volumes of strokes were estimated by use of standard planimetry. The brain imaging review was a post hoc analysis; it was not prespecified.

For the present analysis, we primarily considered only the periprocedural period, which lasted 30 days from the date of the procedure. In addition, we considered only patients who underwent a carotid revascularization procedure and only those patients who had a stroke during or after their procedure; therefore, this is a per-protocol analysis and not an intention-to-treat analysis. We conducted a secondary analysis to examine long-term mortality after stroke using an intention-to-treat approach and including all patients by their assigned treatment and all periprocedural strokes that occurred after randomization. Data are reported with standard descriptive statistics. Proportions were compared with Fisher exact test or χ2 test, and normally distributed continuous variables were compared with a t test. We used Kaplan–Meier survival analysis to estimate long-term mortality. Hazard ratios for mortality up to 4 years, adjusted for age, sex, treatment, and symptomatic status, were calculated with a Cox proportional hazards model. For the purposes of this latter analysis, we considered the periprocedural stroke event, which by definition occurred within 30 days of the procedure, as if it had occurred at time 0.

Results

A total of 122 subjects had a stroke; 81 occurred during the periprocedural period. Three subjects had a stroke after randomization but before undergoing CEA or CAS and were excluded from the present analysis. Nine additional subjects did not have their assigned procedure within 30 days of randomization and were excluded. Therefore, 69 (3.0% of 2272) patients who received assigned treatment within 30 days of randomization had a stroke within 30 days of their procedure and comprise the primary cohort for the present analysis. Patients who had a periprocedural stroke compared with those who did not had similar baseline clinical characteristics (Table 1).

Strokes were most commonly minor (81%, n=56). The NIHSS score determined within 1 month after detection of the stroke was available for 57 of the 69 strokes. The median NIHSS was 2 (interquartile range, 6; Figure 1). The median NIHSS was 2 for the minor strokes (available for 50 of 56 minor strokes) and 8 for the major strokes (available for 7 of 13 major strokes). The strokes were overwhelmingly ischemic (90%, n=62), in the anterior circulation (94%, n=65), and ipsilateral to the treated artery (88%, n=61; Table 2). Two in each group involved the posterior circulation and included posterior cerebral artery territory, splenial, and pontine infarcts.

The median time from the date of procedure to stroke was 0 days (interquartile range, 4 days). The median time to minor stroke was 0 days (interquartile range, 3 days) and the median time to major stroke was 3 days (interquartile range, 12 days). Figure 2 shows the distribution of strokes relative to postpro-
procedural time interval for the 2 procedures. Stroke was disabling (modified Rankin Scale score 2 at 30 days) in 23.4% (n=15) of the 64 stroke patients with a modified Rankin Scale score at 1 month. Mortality among all 69 patients who had strokes was 14.5% at 1 year.

Among 59 patients for whom data were reviewed (49 primary imaging data, 10 neuroradiology reports), 40 (68%) had MRIs completed within 1 week of their event, and 19 (32%) had computed tomography only (Table 3). Nine patients had no evidence of a new stroke on imaging. There were 3 common patterns in anterior circulation infarcts, distributed approximately in thirds and equally divided proportionately between the CAS and CEA groups (Figure 3): (1) Scattered or a shower of emboli in the distribution of the revascularized artery, (2) typical wedge-shaped cortical infarcts, and (3) small subcortical and lacunar infarcts. The mean volume of cortical infarcts was 22.5 mL (SD, 28.6 mL). It was judged impractical to attempt to measure the sum of multiple scattered emboli, particularly when MRI was not conducted uniformly. Among the CAS subject images, 1 ischemic stroke was contralateral, 2 were in the brain stem or cerebellum, and 3 were bilateral or multiterritory. Among the CEA subjects with imaging studies, 1 ischemic stroke was contralateral to the treated artery. No bilateral, multiterritory, or posterior ischemic strokes were identified in the CEA subjects on imaging review.

There were 7 intracerebral hemorrhages, 4 in the CAS arm and 3 in the CEA arm. Five of these subjects died within the periprocedural period (online-only Data Supplement Figure I). One of the intracerebral hemorrhages after CEA was...
contralateral and occurred at 14 days. This intracerebral hemorrhage was located in the right posterior parieto-occipital region and resulted in intraventricular rupture, and the patient died on day 16. All other cases were ipsilateral. Intracerebral hemorrhage occurred on days 2, 3, 4, 8, 14, and 21 (2 patients) after intervention.

In the CAS arm, plaque characteristics such as eccentricity and ulceration were numerically more common among patients who had a stroke (Table 4). Intraprocedural factors were different in the CAS arm; patients who had strokes more commonly required blood transfusion. At baseline, within the CAS arm, patients who had a stroke were more likely to be older and recently symptomatic but less likely to be current smokers. Within the CEA arm, there were no substantial differences in baseline characteristics (Table 5).

Figure 1 describes the stroke severity across time for both groups using the NIHSS. Before the procedure, the distribution of the NIHSS was similar ($P_{\text{Wilcoxon}}=0.43$) and uniformly below a score of 5. Stroke was more severe for CAS-treated patients after the procedure ($P_{\text{Wilcoxon}}=0.15$) with the 75th and 90th percentile, respectively, for CEA-treated patients being 3 and 6 compared with 5 and 12 for CAS-treated patients. However, at 1 month and beyond, the majority of stroke patients returned to near-preprocedural neurological deficits. There was little evidence of differences in the severity of strokes between treatment groups ($P_{\text{>0.27}}$). The chance of death after periprocedural strokes was also similar for CEA-treated and CAS-treated patients. Among CEA-treated patients, there were 2 (10.5%) of 19 deaths by 1 month, 3 (17.6%) of 17 by 6 months, and 3 (17.6%) of 17 by 12 months compared with CAS, for which there were 4 (8.7%) of 46, 6 (14.0%) of 43, and 7 (15.6%) of 45 deaths respectively. Hence, although there were slightly more than twice as many strokes among the CAS-treated than the CEA-treated patients, there was not strong evidence that the distribution of severity differed by treatment group.

In the intention-to-treat analysis, during long-term follow-up (median, 2.5 years; range, 1–4 years), there were

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### Table 4. Baseline Characteristics of Carotid Atherosclerotic Lesions for Patients Who Underwent CAS vs CEA

<table>
<thead>
<tr>
<th></th>
<th>Stroke (n=48)</th>
<th>Nonstroke (n=1075)</th>
<th>P</th>
<th>Stroke (n=21)</th>
<th>Nonstroke (n=1128)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal residual lumen, mm, mean±SD* (No. of patients)</td>
<td>1.2±0.6 (46)</td>
<td>1.3±1.8 (1035)</td>
<td>0.76</td>
<td>1.2±0.9 (6)</td>
<td>1.5±5.0 (427)</td>
<td>0.50</td>
</tr>
<tr>
<td>Diameter stenosis, mm, mean±SD* (No. of patients)</td>
<td>76.3±9.4 (47)</td>
<td>76.0±11.2 (1069)</td>
<td>0.84</td>
<td>72.0±16.4 (7)</td>
<td>73.8±10.8 (456)</td>
<td>0.67</td>
</tr>
<tr>
<td>Lesion length, mm, mean±SD (No. of patients)</td>
<td>20.9±7.6 (48)</td>
<td>17.6±8.5 (1070)</td>
<td>0.01</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Eccentric lesion, % (No. of patients)</td>
<td>70.8 (34)</td>
<td>56.8 (608)</td>
<td>0.051</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Ulcerated lesion, % (No. of patients)</td>
<td>54.2 (26)</td>
<td>36.0 (387)</td>
<td>0.01</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Left carotid treated, % (No. of patients)</td>
<td>62.5 (30)</td>
<td>49.4 (531)</td>
<td>0.08</td>
<td>17.1 (12)</td>
<td>52.4 (591)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stenting; CEA, carotid endarterectomy.

*Taken from procedural angiogram for CAS patients and from baseline angiogram for CEA patients (where available).
Table 5. Procedure Information Among Patients Who Underwent CAS vs CEA

<table>
<thead>
<tr>
<th></th>
<th>CAS Stroke (n=48)</th>
<th>CAS Nonstroke (n=1075)</th>
<th>P</th>
<th>CEA Stroke (n=21)</th>
<th>CEA Nonstroke (n=1128)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of procedure, min, mean±SD (No. of patients)*</td>
<td>77.7±30.5 (47)</td>
<td>69.0±41.2 (1072)</td>
<td>0.07</td>
<td>184.9±51.7 (19)</td>
<td>170.9±59.2 (1008)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypertension requiring treatment, % (No. of patients)</td>
<td>4.2 (2)</td>
<td>1.3 (14)</td>
<td>0.15</td>
<td>14.3 (3)</td>
<td>4.2 (47)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypotension requiring treatment, % (No. of patients)</td>
<td>10.4 (5)</td>
<td>4.4 (47)</td>
<td>0.07</td>
<td>0.0 (0)</td>
<td>2.1 (24)</td>
<td>1.00</td>
</tr>
<tr>
<td>Bradycardia requiring treatment*, % (No. of patients)</td>
<td>2.1 (1)</td>
<td>1.4 (15)</td>
<td>0.51</td>
<td>0.0 (0)</td>
<td>0.6 (7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Transfusion, % (No. of patients)</td>
<td>12.5 (6)</td>
<td>1.6 (17)</td>
<td>&lt;0.0001</td>
<td>0.0 (0)</td>
<td>1.0 (11)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stenting; CEA, carotid endarterectomy.

*As reported on procedure form.

177 deaths, with an estimated 4-year mortality of 11.9%. Periprocedural stroke occurred in 81 patients, and long-term mortality was higher if a stroke occurred. Mortality was typically acute, occurring soon after the event. The estimated mortality rate at 4 years was 11.6% in the stroke-free group and 21.2% in the stroke group (age-, sex-, treatment-, and symptomatic status–adjusted hazard ratio, 2.78; 95% confidence interval, 1.63–4.76; Figure 4). We conducted a sensitivity analysis by considering time 0 beginning at 30 days after the procedure and by considering stroke as a time-varying covariate; this resulted in an adjusted hazard ratio that ranged from 2.76 to 2.84.

**Discussion**

Stroke occurred infrequently after carotid intervention in CREST. The rates of periprocedural stroke for symptomatic patients are the lowest reported from recent randomized trials comparing CAS and CEA (online-only Data Supplement Table I). The rates of periprocedural stroke after CAS and CEA compare favorably to those reported in the Asymptomatic Carotid Atherosclerosis Study (ACAS; 1.4%) and the Asymptomatic Carotid Surgery Trial (ACST; 2.5%). The periprocedural strokes in CREST were most commonly minor, ipsilateral to the treated artery, and ischemic in type and occurred twice as frequently in the CAS arm. Major stroke occurred in 0.6% (13/2272), indicative of the very low overall complication rate observed in the trial.

Review of the available computed tomographic data and MRIs suggests 3 patterns of periprocedural stroke: Scattered emboli, cortical, and small subcortical (Table 3). Scattered emboli in the distribution of the treated artery are commonly seen after intervention and may also be seen spontaneously without intervention, which suggests an arteroembolic mechanism. Cortical infarcts, such as wedge-shaped cortical infarcts, may be seen from an arteroembolic source or a cardioembolic source. We do not know whether patients who developed wedge-shaped cortical infarcts had alternate coexistent cardioembolic sources that arose peripheratively. Patients with known chronic or paroxysmal atrial fibrillation were not included in the trial. Furthermore, because we do not have serial MRIs with diffusion-weighted sequences, and because many patients were treated within a few days of randomization, we do not know whether the scattered emboli pattern seen on the postprocedural MRI was spontaneous from the initial stroke or transient ischemic attack event secondary to the symptomatic carotid artery lesion or whether it arose directly from the procedure. The limitations of the present analysis emphasize the importance of conducting preplanned image analysis as a component outcome of stroke clinical trials.

Not all strokes were related to the artery being addressed. Strokes that were posterior, contralateral, or multiterritory occurred in both the CAS and CEA arms but quantitatively more commonly with CAS. It is straightforward to envision catheter-related disruption of aortic arch plaque causing posterior, contralateral, or multiterritory anterior circulation strokes. It is less clear how this occurs with CEA; metachronous atherosclerotic plaque instability in the aortic arch, contralateral carotid artery, intracranial circulation, and an alternate cardioembolic source are possible explanations.

Hemorrhage was severe and devastating and was not more common in the CAS arm. We cannot necessarily conclude that the use of double-antiplatelet therapy in the CAS arm predisposed to hemorrhage. The timing of hemorrhage suggests that these cases may have been related to hyperperfusion syndrome with underlying disordered autoregulation of cerebral blood flow ipsilateral to the revascularized artery. Reperfusion hemorrhage has been proposed as a mechanism of hemorrhage after intracranial artery stenting completed in the SAMMPRIS trial (Stenting and Aggressive Medical
Management for Preventing Recurrent Stroke in Intracranial Stenosis) and after thrombolysis for acute stroke thrombolysis but has been observed too infrequently in randomized trials to justify conclusions. Because the CREST hemorrhages occurred days after intervention, we hypothesize that there is an opportunity to prevent them and speculate that careful and tight blood pressure control could be lifesaving.

The timing of stroke after revascularization is important. Minor strokes occurred early, typically on the same day of the procedure. Qualitatively, we know that few were observed intraprocedurally. Minor stroke was only identified on careful examination later in the day or the following day. Major strokes, including hemorrhages, tended to occur several days after the procedure. Although we do not know the exact mechanism of each of these strokes or the details of postoperative management, we can infer that there is a substantial opportunity for prevention of these major strokes. For example, stringent blood pressure control might conceivably mitigate the risk of both hemorrhage and major ischemic stroke. Unerring use of antiplatelet medication, statins, and good diabetic management, similar to management in SAMMPRIS, could reduce the risk of major ischemic stroke.18

Stroke implied a poorer long-term mortality outcome than for those who underwent revascularization without incident. The risk of death was nearly 3-fold higher (hazard ratio, 2.78; 95% confidence interval, 1.63–4.76), and this relative increase is very similar in magnitude to those who had a perioperative MI (hazard ratio, 3.67; 95% confidence interval, 1.71–7.90; Figure 4).19 The question of whether or not major stroke was the driver of this relationship of periprocedural stroke to long-term mortality could not be addressed. The adjudication of a given stroke as major took place after the occurrence of death, and with knowledge of the death by the adjudicators, in every case. Stratifying the analysis into major and minor stroke and then examining an outcome (death) that was used in part to determine the classification would yield a tautological result.

The present study has limitations. Imaging data were collected and analyzed on a post hoc basis and were not complete, and imaging was performed as indicated clinically rather than at prespecified time points with specified modalities. The number of stroke outcomes was low, which is good for patients but reduced our sample size enough to make some of our conclusions hypothesis-generating.

Overall, stroke, particularly severe stroke, was uncommon after carotid intervention in the CREST trial but was associated with significant morbidity and mortality. The timing of major stroke after revascularization suggests that major stroke is potentially preventable. Minor stroke occurred most commonly and temporally at the time of CAS, which suggests that CAS has potential for further improvement from expected advances in technology, technique, and training.

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References
CLINICAL PERSPECTIVE

Stroke is a feared complication of carotid endarterectomy (CEA) and carotid stenting (CAS). The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and European trials have shown that CAS is associated with a greater risk of stroke than CEA. CREST also showed that CEA was associated with a greater risk of myocardial infarction (MI) than CAS. The greater risk of MI numerically balanced the greater risk of stroke, so that the composite primary outcome (periprocedural stroke, MI, or death and ipsilateral stroke at up to 4 years) was similar for CEA and CAS. This result has invited criticism because of the differing directions of stroke and MI within the composite outcome. To understand further, we examined the strokes that occurred as a complication of the procedure. Stroke was still more common after CAS, but overall the risk of severe stroke was < 1% and was similar for CEA and CAS. The delayed timing of some major strokes, particularly intracerebral hemorrhage that occurred a few days postoperatively, makes it plausible that these postoperative strokes are preventable, perhaps with careful attention to blood pressure control. Minor stroke occurred most commonly on the same day as CAS, which suggests that the technical aspects of the procedure could be improved to minimize stroke as a complication. Previously, we reported that MI, including biomarker-only MI, was associated with an increased risk in long-term mortality. Here we report that stroke, including minor stroke, was also associated with an increased risk in long-term mortality. Carotid intervention with CEA or CAS is safe. Periprocedural stroke incurred significant morbidity and mortality.
Stroke After Carotid Stenting and Endarterectomy in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)


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Supplemental Material

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Stroke after Carotid Stenting and Endarterectomy in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)
Supplemental Figure 1. Intracerebral hemorrhage after carotid intervention. Four cases of severe hemorrhage occurred periprocedurally, all of which were fatal. Intracerebral hemorrhage occurred at 2–21 days post-procedure.
**Supplemental Table 1.** Rates of periprocedural stroke for symptomatic and asymptomatic patients (actual treatment analysis) from selected clinical trials.

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
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<tr>
<td><strong>Symptomatic - %</strong></td>
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<td></td>
</tr>
<tr>
<td>EVA 3-S&lt;sup&gt;1&lt;/sup&gt;</td>
<td>9.2</td>
<td>3.5</td>
</tr>
<tr>
<td>SPACE&lt;sup&gt;2&lt;/sup&gt;</td>
<td>7.2</td>
<td>5.5</td>
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<tr>
<td>ICSS&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>2.5</td>
</tr>
<tr>
<td><strong>Asymptomatic - %</strong></td>
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<td>--</td>
<td>1.4</td>
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<tr>
<td>CREST&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2.7</td>
<td>1.1</td>
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</table>

EVA 3-S=Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial,<sup>1</sup> SPACE=Stent-Protected Angioplasty versus Carotid Endarterectomy trial,<sup>2</sup> ICSS=International Carotid Stenting Study,<sup>3</sup> CREST=Carotid Revascularization Endarterectomy versus Stenting Trial,<sup>4</sup> ACAS=Asymptomatic Carotid Atherosclerosis Study,<sup>5</sup> ACST=Asymptomatic Carotid Surgery Trial.<sup>6</sup>
References


