Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

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Background and Purpose—The safety of carotid artery stenting (CAS) and carotid endarterectomy (CEA) has varied by symptomatic status in previous trials. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) data were analyzed to determine safety in symptomatic and asymptomatic patients.

Methods—CREST is a randomized trial comparing safety and efficacy of CAS versus CEA in patients with high-grade carotid stenoses. Patients were defined as symptomatic if they had relevant symptoms within 180 days of randomization. The primary end point was stroke, myocardial infarction, or death within the periprocedural period or ipsilateral stroke up to 4 years.

Results—For 1321 symptomatic and 1181 asymptomatic patients, the periprocedural aggregate of stroke, myocardial infarction, and death did not differ between CAS and CEA (5.2% versus 4.5%; hazard ratio, 1.18; 95% CI, 0.82 to 1.68; \( P = 0.38 \)). The stroke and death rate was higher for CAS versus CEA (4.4% versus 2.3%; hazard ratio, 1.90; 95% CI, 1.21 to 2.98; \( P = 0.005 \)). For symptomatic patients, the periprocedural stroke and death rates were 6.0% ± 0.9% for CAS and 3.2% ± 0.7% for CEA (hazard ratio, 1.89; 95% CI, 1.11 to 3.21; \( P = 0.02 \)). For asymptomatic patients, the stroke and death rates were 2.5% ± 0.6% for CAS and 1.4% ± 0.5% for CEA (hazard ratio, 1.88; 95% CI, 0.79 to 4.42; \( P = 0.15 \)). Rates were lower for those aged <80 years.

Conclusions—There were no significant differences between CAS versus CEA by symptomatic status for the primary CREST end point. Periprocedural stroke and death rates were significantly lower for CEA in symptomatic patients. However, for both CAS and CEA, stroke and death rates were below or comparable to those of previous randomized trials and were within the complication thresholds suggested in current guidelines for both symptomatic and asymptomatic patients. (Stroke. 2011;42:675-680.)

Key Words: carotid endarterectomy ■ cerebral infarct ■ cerebrovascular disease ■ clinical trials ■ myocardial infarction ■ stenting ■ surgery/endarterectomy

Extracranial atherosclerosis is responsible for up to 10% of all ischemic strokes.¹ Clinical trials demonstrate that carotid endarterectomy (CEA) significantly reduces the risk of stroke in patients with recent stroke or transient ischemic attack and in patients without prior symptoms who have moderate to severe carotid stenoses.² The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) compared CEA and carotid artery stenting (CAS) in symptomatic and asymptomatic patients.³ In this secondary analysis of data from CREST, we compare the periprocedural complications of CEA and CAS in symptomatic and asymptomatic patients. These results are discussed in relationship to prior clinical trials and current clinical practice guidelines.

Methods

CREST is a multicenter randomized clinical trial with blinded end point adjudications that compared the safety and efficacy of CAS versus CEA. Symptomatic patients were required to have ≥50% ipsilateral carotid stenosis by angiography, ≥70% by duplex ultrasound, or ≥70% by CT angiography or MR angiography if the stenosis on ultrasonography was 50% to 69%. Asymptomatic patients had to have ≥60% stenosis by angiography, ≥70% by ultrasound, or ≥80% by CT angiography or MR angiography if the...
Atherosclerotic risk factors were common in both subject groups but more prevalent in the asymptomatic subjects. Asymptomatic subjects were more likely than symptomatic to have severe (≥70%) carotid stenosis (92% versus 80%).

The periprocedural primary end point rates (stroke, MI, or death) for the entire cohort did not differ between CAS and CEA (5.2% versus 4.5%; hazard ratio [HR], 1.18; 95% CI, 0.82 to 1.68; P=0.38). Similarly, there was no difference in the periprocedural primary end point rates for CAS versus CEA for either symptomatic patients (6.7%±1.0% versus 5.4%±0.9%; HR, 1.26; 95% CI, 0.81 to 1.96; P=0.30) or asymptomatic patients (3.5%±0.8% versus 3.6%±0.8%; HR, 1.02; 95% CI, 0.55 to 1.86; P=0.96; Table 2). The periprocedural rate of stroke and death was significantly higher in CAS versus CEA for symptomatic patients (6.0%±0.9% versus 3.2%±0.7%; HR, 1.89; 95% CI, 1.11 to 3.21; P=0.02) but not for asymptomatic patients (2.5%±0.6% versus 1.4%±0.5%; HR, 1.88; 95% CI, 0.79 to 4.42; P=0.15). The rate of MI was lower after CAS versus CEA for symptomatic patients (1.0%±0.4% versus 2.3%±0.6%; HR, 0.45; 95% CI, 0.18 to 1.11; P=0.08) and for asymptomatic patients (1.2%±0.3% versus 2.2%±0.6%; HR, 0.55; 95% CI, 0.22 to 1.38; P=0.20); however, the differences were not significant.

Table 3 reports event rates after removing the oldest patients (≥80 years) and allows the CREST data to be compared with previous clinical trials in which octogenarians were not enrolled or in which the number enrolled was not specified.6–10 For the symptomatic cohort aged <80 years, the 30-day stroke and death rate was 2.6%±0.7% for CEA and 5.6%±1.0% for CAS. For the asymptomatic cohort aged <80 years, the 30-day stroke and death rate was 1.5%±0.5% for CEA and 2.4%±0.7% for CAS.

Other adverse events excluding stroke, MI, and death are outlined in Table 4. Neck hematomas (1.5%), surgical wound

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**Table 1. Description of the Study Population by Treatment Allocation in Symptomatic and Asymptomatic Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=653)</th>
<th>Asymptomatic (n=1321)</th>
<th>Symptomatic (n=1181)</th>
<th>Asymptomatic CAS (n=594)</th>
<th>Symptomatic CAS (n=587)</th>
<th>Asymptomatic CEA (n=668)</th>
<th>Symptomatic CEA (n=653)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>69.3±8.1</td>
<td>68.8±9.5</td>
<td>&lt;0.17</td>
<td>69.0±8.0</td>
<td>69.6±8.1</td>
<td>68.8±9.7</td>
<td>68.8±9.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male, %</td>
<td>65.6</td>
<td>64.7</td>
<td>0.64</td>
<td>63.8</td>
<td>67.5</td>
<td>64.1</td>
<td>65.4</td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>94.9</td>
<td>91.7</td>
<td>0.001</td>
<td>94.4</td>
<td>95.4</td>
<td>91.5</td>
<td>91.9</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>88.0</td>
<td>84.0</td>
<td>0.004</td>
<td>88.2</td>
<td>87.9</td>
<td>83.6</td>
<td>84.4</td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>33.2</td>
<td>28.1</td>
<td>0.006</td>
<td>32.6</td>
<td>33.7</td>
<td>28.7</td>
<td>27.5</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>90.4</td>
<td>79.0</td>
<td>&lt;0.0001</td>
<td>89.7</td>
<td>91.1</td>
<td>76.9</td>
<td>81.1</td>
<td></td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>24.1</td>
<td>28.2</td>
<td>0.02</td>
<td>26.1</td>
<td>22.2</td>
<td>26.8</td>
<td>29.6</td>
<td></td>
</tr>
<tr>
<td>Prior cardiovascular disease, %</td>
<td>49.7</td>
<td>37.9</td>
<td>&lt;0.001</td>
<td>48.6</td>
<td>50.9</td>
<td>36.6</td>
<td>39.3</td>
<td></td>
</tr>
<tr>
<td>Prior coronary artery bypass, %</td>
<td>25.0</td>
<td>16.9</td>
<td>&lt;0.0001</td>
<td>23.5</td>
<td>26.5</td>
<td>16.8</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>Randomization percent stenosis, severe (≥70%)</td>
<td>92.3</td>
<td>80.4</td>
<td>&lt;0.0001</td>
<td>92.8</td>
<td>91.8</td>
<td>81.7</td>
<td>79.0</td>
<td></td>
</tr>
<tr>
<td>Left carotid treated, %</td>
<td>48.9</td>
<td>53.7</td>
<td>0.02</td>
<td>46.3</td>
<td>51.6</td>
<td>54.5</td>
<td>52.8</td>
<td></td>
</tr>
<tr>
<td>Contralateral occlusion, %</td>
<td>2.5</td>
<td>3.5</td>
<td>0.15</td>
<td>2.3</td>
<td>2.7</td>
<td>3.2</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Time from randomization to treatment, median days</td>
<td>8</td>
<td>5</td>
<td>&lt;0.001</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Time from qualifying symptoms to treatment, mean days</td>
<td>36.3±39.6</td>
<td>40.9±42.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Statistical Analyses

Intention-to-treat end point analyses adjusting for major baseline covariates were conducted using standard time-to-event statistical modeling. The periprocedural period was defined as the 30-day period after the procedure for those participants receiving their assigned procedure within 30 days or 36 days after randomization for those participants not receiving their assigned treatment within 30 days. Because the periprocedural period was short, minimizing the need for censoring, event proportion and the absolute differences in event proportions were calculated as the percentage of patients with events. Standard survival techniques were used to estimate hazard ratios as an index of the relative risk of the 2 procedures.

Results

A total of 1321 symptomatic patients and 1181 asymptomatic patients were enrolled in the study. There were no significant differences in age (mean, 69 years) and sex (64% male) between symptomatic and asymptomatic subjects (Table 1). Atherosclerotic risk factors were common in both subject...
target of 2017 http://stroke.ahajournals.org/ Downloaded from 6–17 Furthermore, these rates are within the studies or from large randomized trials of either symptomatic and CEA are the lowest reported from population-based disease. The periprocedural stroke and death rates for CAS safety of CAS and CEA in patients with carotid artery complications (1.6%), and cranial nerve palsies (4.7%) were expected complications of CEA. Femoral bleeding events (3.6% versus 1.2%) and nonhemorrhagic femoral complications (0.8% versus 0.2%) were higher for CAS. Bradycardia requiring a permanent pacemaker occurred in 0.5% of patients who underwent CAS. There were no differences in complication rates between symptomatic and asymptomatic patients.

Discussion

These CREST safety results demonstrate the comparative safety of CAS and CEA in patients with carotid artery disease. The periprocedural stroke and death rates for CAS and CEA are the lowest reported from population-based studies or from large randomized trials of either symptomatic or asymptomatic patients undergoing carotid revascularization (Figure). Furthermore, these rates are within the target of <6% for symptomatic patients suggested in the recent American Heart Association/American Stroke Association guidelines and below the 3% target for asymptomatic patients as recommended by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Periprocedural stroke and death are even lower when the patients aged ≥80 years are excluded (Table 3), the population comparable to those of the North American Symptomatic Carotid Endarterectomy Trial and the Asymptomatic Carotid Atherosclerosis Study, 2 of the landmark studies from which guidelines have been derived.

Unlike the other published carotid revascularization trials, CREST interventionalists were only permitted to use 1 stenting system and the corresponding distal protection device was used in 96% of the stented patients. The high use of embolic protection and the standardization of the stenting system may have contributed to the low periprocedural complication rate in CREST; however, this also limits the generalizability of the study to other stenting systems.

Table 2. Primary End Point and Its Individual Components Among the 1181 Asymptomatic and the 1321 Symptomatic Patients According to Treatment Group in the Periprocedural Period*
The CREST results imply that both CAS and CEA can be done with acceptable periprocedural risks by experienced surgeons and interventionalists. However, in the symptomatic patients, CREST surgeons performed CEA with a significantly lower periprocedural risk of stroke and death as compared with the interventionalists performing CAS. The HRs for CAS versus CEA were almost identical in the symptomatic and asymptomatic patients (1.89 versus 1.88), but the periprocedural stroke and death rate was lower for asymptomatic patients. These HRs, in favor of surgery, continued to improve. The study investigators, although remaining blinded to event rates, worked carefully with the Data and Safety Monitoring Board to ensure that the anticipated lower event rates in the asymptomatic patients included in CREST after 2005 did not endanger the statistical power of the study. The inclusion of asymptomatic patients was considered paramount to ensure the generalizability of findings because it is estimated that ≥70% of patients treated with CEA in the United States are asymptomatic.

Future treatment guidelines will likely call for safety results better than what we report here for CREST. The risk shows that, like the periprocedural risk of stroke related to CEA, the rate has fallen over time. CEA has had a 40-year head start over CAS; patient selection, technique, and technology continue to improve.

CREST is currently the only published randomized clinical trial comparing CAS and CEA that has included conventional risk patients with both symptomatic and asymptomatic carotid disease. The study investigators, although remaining blinded to event rates, worked carefully with the Data and Monitoring Board to ensure that the anticipated lower event rates in the asymptomatic patients included in CREST after 2005 did not endanger the statistical power of the study. The inclusion of asymptomatic patients was considered paramount to ensure the generalizability of findings because it is estimated that ≥70% of patients treated with CEA in the United States are asymptomatic.

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Future treatment guidelines will likely call for safety results better than what we report here for CREST. The risk
of stroke in the medical arms of the past CEA clinical trials has diminished over time, likely as a consequence of improvements in medical treatments for secondary stroke prevention such as better blood pressure control and the widespread use of statins. It is also reasonable to infer that improvements in medical treatments have led to improvements in the safety of CAS and CEA. In addition, improvements in technique and technology will impact both CAS and

Table 4. Serious Adverse Events During the Periprocedural Period, Excluding Stroke, MI, and Death

<table>
<thead>
<tr>
<th>Clinical Status Procedure</th>
<th>Overall (n=2502)</th>
<th>Symptomatic (n=1321)</th>
<th>Asymptomatic (n=1181)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAS (n=1262)</td>
<td>CEA (n=1240)</td>
<td>CAS (n=668)</td>
</tr>
<tr>
<td>Surgical wound complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma requiring treatment</td>
<td>0</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>3*</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Bleeding events†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion required</td>
<td>24</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Hematoma requiring treatment</td>
<td>8</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Retroperitoneal hemorrhage</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding moderate</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding minor</td>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Femoral artery complications, nonhemorrhagic</td>
<td>10</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
<td>4*</td>
<td>58</td>
<td>3</td>
</tr>
<tr>
<td>Hypotension‡</td>
<td>53</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>55</td>
<td>8</td>
</tr>
<tr>
<td>Bradycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requiring permanent pacemaker</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Atropine or no treatment</td>
<td>35</td>
<td>6</td>
<td>18</td>
</tr>
</tbody>
</table>

*Three of these patients were randomized to CAS but underwent endarterectomy.
†Categories not mutually exclusive.
‡Systolic blood pressure ≤80 mm Hg or pressors administered ≥24 hours.

Figure. A, Perioperative stroke and death rate for CEA in symptomatic patients. FIELD11; CINC 198012; CINC 198412; NASCET 1991—North American Symptomatic Carotid Endarterectomy Trial6; NASCET 19987; CAVATAS—Carotid and Vertebral Artery Transluminal Angioplasty Study14; SPACE—Stent-protected Angioplasty versus Carotid Endarterectomy trial15; EVA-3S—Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial16; ICSS—International Carotid Stenting Study17; CREST—Carotid Revascularization Endarterectomy versus Stenting Trial3 B, Perioperative stroke and death rate for CAS in symptomatic patients. CINC 198012; CINC 198412; ACAS—Asymptomatic Carotid Atherosclerosis Study9; ACST—Asymptomatic Carotid Surgery Trial10; CREST—Asymptomatic Carotid Surgery Trial10; CREST. C, Perioperative stroke and death rate for CEA in asymptomatic patients. WALLSTENT13; CAVATAS14; SPACE15; EVA-3S16; ICSS17; CREST. D, Perioperative stroke and death rate for CAS in asymptomatic patients. CREST3.
CEA over the coming decade. By 2020, it may be reasonable to require stroke and death rates <3% to 4% for symptomatic patients and 1% to 2% for asymptomatic patients. Even with these lower complication rates, as the effectiveness of medical therapies improve, additional clinical trials will be needed to demonstrate a benefit of carotid revascularization in asymptomatic patients in whom the risk of stroke is already low.

Summary

CREST has demonstrated that, with experienced surgeons and interventionists, both CEA and CAS are viable options for carotid revascularization because the overall complication rates for both procedures are within current treatment guidelines. Although the primary complication rates (MI, stroke, and death) were similar for CEA and CAS in both symptomatic and asymptomatic patients, the rate of stroke in the peri-procedural period was higher for CAS for symptomatic patients. This difference may currently favor CEA; however, the disparity could potentially be reduced as new stent systems are introduced and as endovascular techniques improve.

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References

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CREST試験における症状の有無別にみた頸動脈ステント留置術と頸動脈内膜剥離術の安全性

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10. University of Alabama at Birmingham, Birmingham, Alabama
11. Mayo Clinic, Jacksonville, Florida

目的および目的：過去の試験で報告されている頸動脈ステント留置術（CAS）および頸動脈内膜剥離術（CEA）の安全性は、症状の有無によって異なっている。本研究ではCREST試験（Carotid Revascularization Endarterectomy Versus Stenting Trial）のデータを分析し、無経験者患者と無経験者患者の安全性を検討した。

方法：CREST試験は、高誘因脳卒中リスク患者を対象に、CASとCEAの安全性および有効性を比較した無作為試験である。無作為割り付けの180日以内に既存の症例が認められた患者を無経験者とみなした。主な評価項目は、周術期の脳卒中、心臓病変、死亡または4年間の間隔例であった。

結果：無経験者患者1,321例、無経験者患者1,181例を比較した結果、周術期の脳卒中、心臓病変、死亡の発生率に関してCASとCEAの間に差はみられなかった（5.2%vs4.5%、ハザード比：1.18、95%CI:0.82–1.65、p=0.38）。脳卒中と生死を併せた発生率には、CEAの方がCEAよりも高かった（44%vs23%、ハザード比：1.96、95%CI:1.21–2.96、p=0.002）。無経験者患者における周術期の脳卒中と死亡の発生率は、CASが6.0±0.9%、CEAが3.2±0.7%であった（ハザード比：1.99、95%CI:1.11–3.21、p=0.02）。無経験者患者における周術期の脳卒中と死亡の発生率は、CASが25.6±0.9%、CEAが14.4±0.5%であった（ハザード比：1.88、95%CI:0.76–4.42、p=0.15）。80歳以上の患者および80歳未満の患者の方が発生率は低かった。

結論：無経験者患者の発症率は無経験者患者でも、CREST試験の主な評価項目に関してCASとCEAの間に差はみられなかった。無経験者患者では、周術期の脳卒中と死亡の発生率はCEAの方が有意に低かった。しかし、無経験者患者でも、CASおよびCEA施行例における脳卒中と死亡の発生率に過去の無作為試験で得られた結果が同様であり、現行のガイドラインに示された合併症の関係性も同様であった。

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