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

Frank L. Silver, MD; Ariane Mackey, MD; Wayne M. Clark, MD; William Brooks, MD; Carlos H. Timaran, MD; David Chiu, MD; Larry B. Goldstein, MD; James F. Meschia, MD; Robert D. Ferguson, MD; Wesley S. Moore, MD; George Howard, DrPH; Thomas G. Brott, MD; for the CREST Investigators

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
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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=2502)</th>
<th>CAS (n=1128)</th>
<th>CEA (n=1374)</th>
<th>Asymptomatic (n=1321)</th>
<th>Symptomatic (n=1181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>69.3±8.1</td>
<td>68.9±8.5</td>
<td>69.7±8.1</td>
<td>68.8±8.0</td>
<td>68.8±9.3</td>
</tr>
<tr>
<td>Male, %</td>
<td>65.6</td>
<td>64.7</td>
<td>65.4</td>
<td>63.8</td>
<td>64.1</td>
</tr>
<tr>
<td>White, %</td>
<td>94.9</td>
<td>91.7</td>
<td>95.4</td>
<td>94.4</td>
<td>91.5</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>80.0</td>
<td>84.0</td>
<td>87.9</td>
<td>88.2</td>
<td>84.4</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>32.2</td>
<td>28.1</td>
<td>33.7</td>
<td>32.6</td>
<td>27.5</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>90.4</td>
<td>79.0</td>
<td>91.1</td>
<td>89.7</td>
<td>81.1</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>24.1</td>
<td>28.2</td>
<td>22.2</td>
<td>26.1</td>
<td>29.6</td>
</tr>
<tr>
<td>Prior coronary artery bypass,</td>
<td>49.7</td>
<td>37.9</td>
<td>50.9</td>
<td>48.6</td>
<td>39.3</td>
</tr>
<tr>
<td>Randomization percent stenosis, severe (≥70%)</td>
<td>92.3</td>
<td>80.4</td>
<td>91.8</td>
<td>92.8</td>
<td>81.7</td>
</tr>
<tr>
<td>Left carotid treated, %</td>
<td>48.9</td>
<td>53.7</td>
<td>51.6</td>
<td>46.3</td>
<td>54.5</td>
</tr>
<tr>
<td>Contralateral occlusion, %</td>
<td>2.5</td>
<td>3.5</td>
<td>2.7</td>
<td>2.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Time from randomization to treatment, mean days</td>
<td>36.3±39.6</td>
<td>40.9±42.9</td>
<td>36.3±39.6</td>
<td>40.9±42.9</td>
<td>36.3±39.6</td>
</tr>
<tr>
<td>Time from qualifying symptoms to treatment, mean days</td>
<td>85</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
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 interventionists 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 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.
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, 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.

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 CEA clinical trials.

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>Surgical wound complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma requiring treatment</td>
<td>0/262 (n=668)</td>
<td>0/68 (n=653)</td>
<td>0/594 (n=587)</td>
</tr>
<tr>
<td>Other</td>
<td>3*/120 (n=668)</td>
<td>3/8 (n=653)</td>
<td>0/12 (n=587)</td>
</tr>
<tr>
<td>Bleeding events†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion required</td>
<td>24/120 (n=668)</td>
<td>16/5 (n=653)</td>
<td>8/7 (n=587)</td>
</tr>
<tr>
<td>Hematoma requiring treatment</td>
<td>8/68 (n=668)</td>
<td>6/0 (n=653)</td>
<td>2/0 (n=587)</td>
</tr>
<tr>
<td>Retropertoneal hemorrhage</td>
<td>4/68 (n=668)</td>
<td>4/0 (n=653)</td>
<td>0/0 (n=587)</td>
</tr>
<tr>
<td>Bleeding moderate</td>
<td>4/68 (n=668)</td>
<td>2/0 (n=653)</td>
<td>2/2 (n=587)</td>
</tr>
<tr>
<td>Bleeding minor</td>
<td>5/68 (n=668)</td>
<td>3/0 (n=653)</td>
<td>2/1 (n=587)</td>
</tr>
<tr>
<td>Femoral artery complications, nonhemorrhagic</td>
<td>10/68 (n=668)</td>
<td>6/2 (n=653)</td>
<td>4/1 (n=587)</td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
<td>4*/58 (n=668)</td>
<td>3/33 (n=653)</td>
<td>1/25 (n=587)</td>
</tr>
<tr>
<td>Hypotension‡</td>
<td>53/24 (n=668)</td>
<td>30/13 (n=653)</td>
<td>23/11 (n=587)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17/55 (n=668)</td>
<td>8/32 (n=653)</td>
<td>9/23 (n=587)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requiring permanent pacemaker</td>
<td>6/0 (n=668)</td>
<td>2/0 (n=653)</td>
<td>4/0 (n=587)</td>
</tr>
<tr>
<td>Atropine or no treatment</td>
<td>35/6 (n=668)</td>
<td>18/4 (n=653)</td>
<td>17/2 (n=587)</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. FIELDS; CINC 1980; CINC 1984; NASCET 1991 = North American Symptomatic Carotid Endarterectomy Trial; NASCET 1998; CAVATAS = Carotid and Vertebral Artery Transluminal Angioplasty Study; SPACE = Stent-protected Angioplasty versus Carotid Endarterectomy trial; EVA-3S = Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial; ICSS = International Carotid Stenting Study; CREST = Carotid Revascularization Endarterectomy versus Stenting Trial. B, Perioperative stroke and death rate for CAS in symptomatic patients. CINC 1980; CINC 1984; ACAS 1995; ACST 1995; ACST 2004; SPACE 2006; EVA-3S 2006; ICSS 2009; CREST 2010. C, Perioperative stroke and death rate for CEA in asymptomatic patients. WALLSTENT; CAVATAS; SPACE 2006; EVA-3S; ICSS; CREST. D, Perioperative stroke and death rate for CAS in asymptomatic patients. CREST.
CEA over the coming decade. By 2020, it may be reasonable to require stroke and death rates <3% 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 interventionalists, 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 periprocedural 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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Abstract

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

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

Frank L. Silver, MD; Ariane Mackey, MD; Wayne M. Clark, MD; William Brooks, MD; Carlos H. Timaran, MD; David Chiu, MD; Larry B. Goldstein, MD; James E. Meschia, MD; Robert D. Ferguson, MD; Wesley S. Moore, MD; George Howard, DrPH; Thomas G. Brott, MD; for the CREST Investigators

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脳卒中および目的：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る。本研究では CREST 試験（Carotid Revascularization Endarterectomy Versus Stenting Trial）のデータを分析し、症候性患者と無症候性患者における安全性を検討した。

方法：CREST 試験は、高脳梗塞群患者を対象に、CAS と CEA の安全性および有効性を比較した無作為試験で、無作為割り付けの180日以内に特定の症状が認められた患者を症候性患者とみなした。主な評価項目は、脳卒中の発症率、心臓強度、死亡、または4年間の脳関連死率であった。

結果：無症候性患者1,231例、症候性患者1,181例を伴せて症候性患者全体で、脳卒中の発症率、心臓強度、死亡の總発生率に関して CAS と CEA の間に差はみられなかった（5.2% vs. 4.5%，ハザード比=1.18, 95% CI: 0.82 – 1.68, p = 0.38）。脳卒中と死亡を併せて発生率は CAS の方が CEA よりも高かった（44% vs. 23%，ハザード比=1.98, 95% CI: 1.21 – 2.98, p = 0.002）。症候性患者における脳卒中の発症率については、CAS の方が 6.0 ± 0.9%、CEA の方が 3.2 ± 0.7%であった（ハザード比=1.89, 95% CI: 1.11 – 3.21, p = 0.02）。症候性患者における脳卒中の発生率は、CAS の方が 25 ± 0.6%、CEA の方が 14 ± 0.5%であった（ハザード比=1.86, 95% CI: 0.78 – 4.42, p = 0.15）。80歳以上の患者も含められた症候性患者の発生率は低かった。

結論：症候性患者で無症候性患者を伴せて、CREST 試験の主要評価項目において CAS と CEA の間に有意差はみられなかった。症候性患者では、無症候性患者の脳卒中の発生率は CAS の方が低かった。しかし、症候性患者でも CAS および CEA 施行における脳卒中の発症率および死亡率は過去の無作為試験で得られた値を下回ると同等であり、現行のガイドラインに示された合併症の関係下であった。

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