Time From Symptoms to Carotid Endarterectomy or Stenting and Perioperative Risk

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Background and Purpose—Prior meta-analysis showed that carotid endarterectomy benefits decline with increasing surgical delay following symptoms. For symptomatic patients in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), we assessed if differences in time between symptoms and carotid endarterectomy or carotid artery stenting are associated with differences in risk of peri-procedural stroke or death.

Methods—We analyzed the 1180 symptomatic patients in CREST who received their assigned procedure and had clearly defined timing of symptoms. Patients were classified into 3 groups based on time from symptoms to procedure: <15, 15 to 60, and >60 days.

Results—For carotid endarterectomy, risk of peri-procedural stroke or death was not significantly different for the 2 later time periods relative to the earliest time period (hazard ratio, 0.74; 95% confidence interval, 0.22–2.49 for 15–60 days and hazard ratio, 0.91; 95% confidence interval, 0.25–3.33 for >60 days; P=0.89). For carotid artery stenting, risk of peri-procedural stroke or death was also not significantly different for later time periods relative to the earliest time period (hazard ratio, 1.12; 95% confidence interval, 0.53–2.40 for 15–60 days and hazard ratio, 1.15; 95% confidence interval, 0.48–2.75 for >60 days; P=0.93).

Conclusions—Time from symptoms to carotid endarterectomy or carotid artery stenting did not alter peri-procedural safety, supporting early revascularization regardless of modality.

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

Key Words: carotid stenosis • endarterectomy, carotid • humans • stents • stroke

A meta-analysis of 2 trials of carotid endarterectomy (CEA) versus medical management for symptomatic carotid stenosis showed that time from the last symptomatic event to randomization significantly modified efficacy of surgery.1 The benefits of endarterectomy were greatest for patients operated within 2 weeks after their last ischemic event. Emergent endarterectomy for stroke-in-evolution carries high operative risk, but for stable patients with minor stroke or transient ischemic attack (TIA), surgery in the first week after symptoms does not carry a substantially increased risk.2 Early endarterectomy is thus often encouraged.3 Some have suggested that stenting is safe even if done emergently in patients with symptomatic occlusion;4 however, small series suggest that early stenting carries greater risk than delayed stenting.5

This analysis describes the relationship between time from symptoms to revascularization and peri-procedural risk of stroke or death for both revascularization methods.

A trial of carotid artery stenting versus carotid endarterectomy (CREST) randomized 2502 symptomatic and asymptomatic patients to either CEA or carotid artery stenting (CAS). The primary results have been published.6 All governing review boards approved the protocol and every subject gave informed consent. This analysis focuses on 1180 symptomatic patients receiving the assigned procedure within thirty days of randomization and in whom the timing of qualifying symptoms was documented. Time from qualifying symptoms to revascularization was treated as a categorical variable, with categories of <15, 15 to 60, and >60 days. The current analysis used the outcome of peri-procedural stroke or death. The peri-procedural period was defined as 30 days after procedure for those receiving treatment within 30 days of randomization or 36 days after randomization for those not receiving treatment within 30 days.

Results

The qualifying ischemic event was a transient ischemic attack for 42% (499/1180) of individuals, an ischemic stroke for 4% (47/1180), and an asymptomatic carotid stenosis for 54% (634/1180) of individuals. This analysis is available from Stroke at http://stroke.ahajournals.org.

Methods

The periprocedural period was defined as 30 days after procedure for those receiving treatment within 30 days of randomization or 36 days after randomization for those not receiving treatment within 30 days.
41% (487/1180) of individuals, and amaurosis fugax for the remaining 16% (194/1180).

Median time from symptoms to randomization was 15 days (interquartile range, 5–49) for CEA and 14 days (interquartile range, 5–44) for CAS. Median time from symptoms to revascularization was 22 days (interquartile range, 8–58) for CEA (n=597) and 18 days (interquartile range, 8–51) for CAS (n=583). Fifty-nine percent of patients had endarterectomy within 30 days; 60%, stenting within 30 days. Thirty-nine percent of patients had endarterectomy within 14 days; 43%, stenting within 14 days. A total of 3.2% of endarterectomies were performed within 2 days, and 5.3% of stenting cases were performed within 2 days. Timing of revascularization did not differ significantly by revascularization method (Table 1).

Overall, the risk of a periprocedural stroke or death end point was 4.2% (50/1180). The risk of periprocedural stroke or death was not significantly different for the 2 later time periods relative to those who got the procedure <15 days of qualifying symptom (P=0.97; Table 2). Figure shows the risk of periprocedural stroke or death relative to time after revascularization for the 3 time groups. We also performed the same analysis stratified by treatment type. For CEA, risk of periprocedural stroke or death was not significantly different for the 2 later time periods relative to the earliest time period (HR, 0.74; 95% CI, 0.22–2.49 for 15 to 60 days and HR, 0.91; 95% CI, 0.25–3.33 for >60 days; P=0.89). For CAS, risk of periprocedural stroke or death was also not significantly different for later time periods for CAS relative to the earliest time period (HR, 1.12; 95% CI, 0.53–2.40 for 15 to 60 days and HR, 1.15; 95% CI, 0.48–2.75 for >60 days; P=0.93).

**Discussion**

Time from symptoms to treatment did not affect periprocedural safety of CEA or CAS or the risk of stroke after the periprocedural period. Early revascularization seems to be safe for both procedures.

Because patients were not randomized to early versus delayed surgery, it is not possible to conclude definitively that

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**Table 1. Timing of Revascularization Overall and by Subgroups of Treatment, Sex, and Degree of Qualifying Stenosis**

<table>
<thead>
<tr>
<th></th>
<th>Median Time to Revascularization</th>
<th>Percentage of Patients Undergoing Revascularization Within Specified Time Periods After Index Stroke, TIA, or Amaurosis Fugax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median Time IQR (Q1–Q3), d</td>
<td>&lt;15 d</td>
</tr>
<tr>
<td>Overall</td>
<td>20 (8–55)</td>
<td>484 (41.1%)</td>
</tr>
<tr>
<td>CAS (n=583)</td>
<td>18 (8–51)</td>
<td>251 (43.1%)</td>
</tr>
<tr>
<td>CEA (n=597)</td>
<td>22 (8–58)</td>
<td>233 (39.0%)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women (n=410)</td>
<td>20 (8–53)</td>
<td>176 (42.9%)</td>
</tr>
<tr>
<td>Men (n=770)</td>
<td>21 (8–56)</td>
<td>308 (40.0%)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤70 y (n=667)</td>
<td>20 (8–55)</td>
<td>268 (40.2%)</td>
</tr>
<tr>
<td>Age &gt;70 y (n=513)</td>
<td>20 (8–55)</td>
<td>216 (42.1%)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke (n=487)</td>
<td>20 (8–59)</td>
<td>198 (40.7%)</td>
</tr>
<tr>
<td>TIA (n=499)</td>
<td>19 (7–46)</td>
<td>226 (45.3%)</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>27.5 (10–65)</td>
<td>60 (30.9%)</td>
</tr>
</tbody>
</table>

**Table 2. Risk of Periprocedural Stroke or Death by Time From Qualifying Event to Procedure for Symptomatic Patients**

<table>
<thead>
<tr>
<th>Periprocedural Stroke or Death</th>
<th>Overall</th>
<th>CAS</th>
<th>CEA</th>
<th>Overall</th>
<th>CAS</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time From Qualifying Event to Procedure, d</td>
<td>&lt;15 d</td>
<td>15–60 d</td>
<td>&gt;60 d</td>
<td>P Value</td>
<td>&lt;15 days</td>
<td>15–60 d</td>
</tr>
<tr>
<td>Events/no. of subjects</td>
<td>20/484</td>
<td>18/432</td>
<td>12/264</td>
<td>...</td>
<td>14/251</td>
<td>13/213</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>Reference</td>
<td>0.98</td>
<td>1.07</td>
<td>0.97</td>
<td>Reference</td>
<td>1.12</td>
</tr>
</tbody>
</table>

**CAS** indicates carotid artery stenting; **CEA** indicates carotid endarterectomy; and **IQR** indicates interquartile range.

*Adjusted for age, sex, and type of revascularization (CAS vs CEA).
timing of revascularization had no effect on risk. Unknown or unmeasured differences between early and later revascularized patients may have confounded the comparison of risks. However, given the current recommendations to revascularize early, intentionally delaying treatment would not be ethical. Furthermore, by not having a treatment group managed purely medically, we cannot conclude that delayed surgery is appropriate simply because it seems to carry no greater risk of complications. Early treatment should be the goal because it ought to lead to less time at risk of artery-to-artery embolism.

Timing should not be used to influence the decision to perform stenting versus endarterectomy in patients with symptomatic carotid stenosis.

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**References**


**Figure.** Kaplan–Meier curve (periprocedural stroke or death).
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