Time From Symptoms to Carotid Endarterectomy or Stenting and Perioperative Risk

James F. Meschia, MD; L. Nelson Hopkins, MD; Irfan Altafullah, MD; Lawrence R. Wechsler, MD; Grant Stotts, MD; Nicole R. Gonzales, MD; Jenifer H. Voeks, PhD; George Howard, Dr PH; Thomas G. Brott, MD

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 were 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.3 Early endarterectomy is thus often encouraged.3 Some have suggested that stenting is safer if done emergently in patients with symptomatic occlusion;4 however, small series suggest that early stenting carries greater risk than delayed stenting.3

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

Methods

Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) randomized 2502 symptomatic and asymptomatic patients to either CEA or carotid artery stenting (CAS). The primary results have been published.5 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 42% (499/1180) of individuals, an ischemic stroke for...
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 the earliest time period (HR, 0.98; 95% CI, 0.52–1.87 for 15 to 60 days and HR, 1.07; 95% CI, 0.52–2.21 for >60 days; 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

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

<table>
<thead>
<tr>
<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>Overall</td>
</tr>
<tr>
<td>CAS (n=583)</td>
<td>20 (8–55)</td>
</tr>
<tr>
<td>CEA (n=597)</td>
<td>22 (8–58)</td>
</tr>
<tr>
<td>Women (n=410)</td>
<td>20 (8–53)</td>
</tr>
<tr>
<td>Men (n=770)</td>
<td>21 (8–56)</td>
</tr>
<tr>
<td>Age ≤70 y (n=667)</td>
<td>20 (8–55)</td>
</tr>
<tr>
<td>Age &gt;70 y (n=513)</td>
<td>20 (8–55)</td>
</tr>
<tr>
<td>Stroke (n=487)</td>
<td>20 (8–59)</td>
</tr>
<tr>
<td>TIA (n=499)</td>
<td>19 (7–46)</td>
</tr>
<tr>
<td>Amaurosis fugax (n=194)</td>
<td>27.5 (10–65)</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>Time From Qualifying Event to Procedure, d</th>
<th>CAS</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>&lt;15 d</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>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>Reference</td>
<td>0.98</td>
<td>1.07</td>
</tr>
</tbody>
</table>
| CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; and HR, hazard ratio.

*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.

Sources of Funding

The research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NIH)—R01 NS 038384 and U01NS038384. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Supplemental support was received from Abbott Vascular, Inc.

Disclosures

Dr Hopkins receives university grants/research support from Toshiba, consults for Boston Scientific, Cordis, Abbott, and Covidien; has $>10000 financial interests in Boston Scientific, Valor Medical, Claret Medical Inc., Augmenix, Silk Road, Ostial, Apama, StimSox, Photolitec, ValenTx, Ellipse, Axtria, NextPlain, MedinaMed, and Ocular, and <$10000 from Endomation; receives <$10000 honoraria from Cordis Memorial Healthcare System, Complete Conf. Management, and Covidien, holds a >$10000 Board, Trustee, or Officer Position at Claret Medical (>-$10000); and a <$10000 Speakers Bureau position at Abbott Vascular and Toshiba (<-$10000). Dr Wechsler consults for Biogen Idec and San Bio, holds stock in Silk Road Medical and is on the ACT-1 Steering Committee. Dr Brott is a paid consultant with 3D Communications and Edwards Lifesciences. The other authors report no conflicts.

References

Time From Symptoms to Carotid Endarterectomy or Stenting and Perioperative Risk
James F. Meschia, L. Nelson Hopkins, Irfan Altafullah, Lawrence R. Wechsler, Grant Stotts, Nicole R. Gonzales, Jenifer H. Voeks, George Howard and Thomas G. Brott

Stroke. 2015;46:3540-3542; originally published online October 22, 2015;
doi: 10.1161/STROKEAHA.115.011123
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/12/3540

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/