Effect of Patching on Reducing Restenosis in the Carotid Revascularization Endarterectomy Versus Stenting Trial

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Background and Purpose—The purpose is to determine whether patching during carotid endarterectomy (CEA) affects the perioperative and long-term risks of restenosis, stroke, death, and myocardial infarction as compared with primary closure.

Methods—We identified all patients who were randomized and underwent CEA in Carotid Revascularization Endarterectomy versus Stenting Trial. CEA patients who received a patch were compared with patients who underwent CEA with primary closure without a patch. We compared periprocedural and 4-year event rates, 2-year restenosis rates, and rates of reoperation between the 2 groups. We further analyzed results by surgeon specialty.

Results—There were 1151 patients who underwent CEA (753 [65%] with patch and 329 [29%] with primary closure). We excluded 44 patients who underwent eversion CEA and 25 patients missing CEA data (5%). Patch use differed by surgeon specialty: 89% of vascular surgeons, 6% of neurosurgeons, and 76% of thoracic surgeons patched. Comparing patients who received a patch versus those who did not, there was a significant reduction in the 2-year risk of restenosis, and this persisted after adjustment by surgeon specialty (hazard ratio, 0.35; 95% confidence interval, 0.16–0.74; \( P = 0.006 \)). There were no significant differences in the rates of periprocedural stroke and death (hazard ratio, 1.58; 95% confidence interval, 0.33–7.58; \( P = 0.57 \)), in immediate reoperation (hazard ratio, 0.6; 95% confidence interval, 0.16–2.27; \( P = 0.45 \)), or in the 4-year risk of ipsilateral stroke (hazard ratio, 1.23; 95% confidence interval, 0.42–3.63; \( P = 0.71 \)).

Conclusions—Patch closure in CEA is associated with reduction in restenosis although it is not associated with improved clinical outcomes. Thus, more widespread use of patching should be considered to improve long-term durability.

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

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Key Words: carotid artery narrowing • carotid artery stenosis • carotid endarterectomy • vascular closure patches

Carotid endarterectomy (CEA) is a well-established intervention for the prevention of stroke in patients with symptomatic and asymptomatic significant carotid artery stenosis.1–5 This operation is durable and has low rates of morbidity and mortality.6,7 It is, however, associated with a low but significant rate of restenosis of 5% to 15% because of intimal hyperplasia or progression of atherosclerotic disease, with the attendant significant treatment challenges.8–10 One of the factors potentially involved in the pathogenesis of recurrent carotid stenosis after CEA has been postulated to be the type of closure after endarterectomy.

Several retrospective studies have examined the role of primary closure of the carotid artery versus patch angioplasty in the development of carotid restenosis. These analyses have suggested that patch angioplasty is associated with a lower risk of restenosis and postoperative stroke.11–15 However, other investigators have shown no difference in the rate of restenosis after CEA with primary closure or angioplasty.16 Small prospective randomized trials by AbuRahma et al17–19 have indicated that patch angioplasty closure is associated with a lower risk of postoperative stroke and restenosis. One trial randomized patients who underwent bilateral CEAs to receive patch angioplasty on one side and primary closure on the other side. This study showed that patch endarterectomy was associated with significantly less postoperative neurological complications, stroke, and recurrent stenosis.17

However, overall evidence in support of the superiority of patch angioplasty versus primary closure after CEA is limited. A recent meta-analysis of trials comparing the 2 methods concluded that patch angioplasty may reduce the rate of

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restenosis, and potentially reduce the risk of postoperative ipsilateral stroke, with a nonsignificant trend toward reduction in mortality.20

Thus, we sought to perform a secondary analysis of a rigorous prospective, randomized controlled trial comparing CEA versus stenting (Carotid Revascularization Endarterectomy Versus Stenting Trial [CREST]).21 The close-long term follow-up of patients enrolled in this trial allowed us to analyze the rates of restenosis, periprocedural stroke, death, major adverse events, and reoperation in patients who underwent primary closure versus patch angioplasty after CEA.

Materials and Methods

The study design and primary results of CREST have been reported previously.21 Briefly, 2502 patients were enrolled in 117 clinical centers in the USA and Canada between December 21, 2000, and July 18, 2008. The protocol was approved by the ethics and institutional review committees of all study institutions, and informed consent was obtained from all participants. Eligible symptomatic patients had a transient ischemic attack, amaurosis fugax, or a minor nondisabling stroke within 180 days of enrollment, and an ipsilateral carotid stenosis of ≥50% by angiography, ≥70% by ultrasound criteria, or ≥70% by computed tomography, magnetic resonance angiography, or digital subtraction angiography when stenosis by ultrasound was ≥50% to 69%. Asymptomatic patients were eligible if they had a stenosis of ≥60% by angiography, ≥70% by ultrasound criteria, or ≥80% by computed tomography, magnetic resonance angiography, or digital subtraction angiography when stenosis by ultrasound was 50% to 69%.

Patients were randomly assigned to CEA or carotid artery stenting within 2 weeks of planned procedure. Stroke and myocardial infarction were adjudicated by specialty committees masked to treatment assignment. All other outcomes were assessed by investigators unmasked to treatment allocation.

We included patients who were randomized and underwent CEA in CREST. CEA was performed according to standard techniques on the basis of individual preferences of 477 surgeons. We individually reviewed all operative notes of primary closure CEA and excluded the basis of individual preferences of 477 surgeons. We individually reviewed all operative notes of primary closure CEA and excluded patients who underwent eversion CEA and 25 (48%) were asymptomatic at baseline; in 50% to 69%.

Patients had a stroke after identification of CREST-certified clinical center vascular laboratories with a standardized protocol that stipulated 16 doppler waveform samples at every examination.21 All ultrasound images and doppler waveforms were analyzed at a central facility, the Ultrasound Core Laboratory at the University of Washington Ultrasound Reading Center.

We compared periprocedural and 4-year event rates and 2-year restenosis rates, in addition to rates of reoperation between the 2 groups. The end points in this analysis were the primary end point of any stroke, death, or myocardial infarction within 30 days of procedure and ipsilateral stroke within 4 years of randomization. Periprocedural (within 30 days of procedure) and 4-year event rates, postoperative (≤30 days) return to the operating room, and restenosis rate at 2 years were assessed. Restenosis was defined as ≥70% diameter-reducing stenosis based on elevated peak systolic velocity of ≥3.0 m/s on duplex ultrasound. Analysis of the frequency of high-grade restenosis and occlusion was a prespecified secondary analysis of the CREST protocol. The decision to use 3.0 m/s as the definition for restenosis was also made before unblinding of the restenosis data.

Event rates were calculated by Kaplan–Meier survival estimates. Treatment differences were assessed using logistic regression and proportional hazard models adjusting first for symptomatic status and then also for board specialty of operator. In the full CREST cohort, including both carotid artery stenting and CEA patients, it was determined that age and symptomatic status were the most important factors to adjust in the analysis. Because this analysis only included CEA patients, we tested to see if both age and symptomatic status were associated with the outcomes. We determined that symptomatic status, but not age, was associated with the outcome and that inclusion or exclusion of age had almost no effect on the magnitude of the hazard ratio (HR). Because the number of events was somewhat small, and because age had little effect when included, we chose to adjust only for symptomatic status. Analyses were done with SAS (version 9.2).

Results

A total of 1151 patients underwent CEA in CREST. We excluded 44 patients who underwent eversion CEA and 25 patients missing CEA data. We analyzed the outcomes in 1082 patients, of whom 753 (70%) patients underwent CEA with patch angioplasty and 329 (30%) had CEA with primary closure. There were no significant differences between the 2 groups with respect to age, sex, comorbidities, and operative time (Table 1). Patients in the primary closure group were more likely to be white (96% versus 93%; P=0.04), symptomatic (66% versus 49%; P<0.0001), and receive general as opposed to regional anesthesia (97% versus 89%; P<0.0001). Surgeons were more likely to shunt patients in the patch group (65% versus 47%; P<0.0001; Table 1). There was a strong association between surgeon specialty and the use of patch: 89% of vascular surgeons and 76% of thoracic surgeons patched, whereas only 6% of neurosurgeons did so (Table 2). The type of patch used included 466 (62%) synthetic Hemashield Dacron patch, 217 (29%) bovine pericardial patch, 42 (6%) saphenous vein graft, 24 (3%) neck vein graft, and 4 (0.5%) unspecified.

Fifty-two patients had restenosis, of whom 27 (52%) were symptomatic and 25 (48%) were asymptomatic at baseline; in follow-up, 5 of these patients had a stroke after identification of

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
<th>Patch (n=753)</th>
<th>No Patch (n=329)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y (mean±SD)</strong></td>
<td>69.2±8.4</td>
<td>68.6±9.3</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>378 (47.3)</td>
<td>155 (47.3)</td>
<td>0.88</td>
</tr>
<tr>
<td>Female</td>
<td>375 (49.7)</td>
<td>174 (52.7)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Presentation:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>369 (49.0)</td>
<td>216 (65.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Comorbidity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>653 (86.7)</td>
<td>275 (83.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>232 (30.8)</td>
<td>107 (32.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>637 (84.9)</td>
<td>285 (87.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>Current tobacco smoker</td>
<td>198 (26.8)</td>
<td>84 (25.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td>346 (47.3)</td>
<td>131 (42.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>or CABG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided carotid lesion</td>
<td>403 (53.5)</td>
<td>164 (49.9)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Procedural factors:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General (vs block) anesthesia</td>
<td>671 (89.2)</td>
<td>319 (97.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Shunt used</td>
<td>471 (64.7)</td>
<td>148 (47.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Procedure time*, min</td>
<td>173.3±62.9</td>
<td>171.9±51.5</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*Procedure time is missing on all patients who received block anesthesia.
Table 2. CEA Technique by Surgeon Board Specialty*

<table>
<thead>
<tr>
<th>Specialty</th>
<th>CEA, n (%)</th>
<th>Patch, n (%)</th>
<th>Primary, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular surgeons</td>
<td>702 (65)</td>
<td>628 (89)</td>
<td>74 (11)</td>
</tr>
<tr>
<td>Neurosurgeons</td>
<td>233 (22)</td>
<td>14 (6)</td>
<td>219 (94)</td>
</tr>
<tr>
<td>Thoracic surgeons</td>
<td>142 (13)</td>
<td>108 (76)</td>
<td>34 (24)</td>
</tr>
</tbody>
</table>

CEA indicates carotid endarterectomy.
*Board specialty of surgeon was unavailable for 5 patients (3 patch and 2 no patch).

Significantly different after adjustment for surgeon specialty, a 65% reduction in the 2-year risk of restenosis with the use of patch (HR, 0.35; 95% CI, 0.16–0.74; P<0.01; Table 3).

Discussion

Restenosis after CEA occurs in 5% to 15% of patients and presents challenges for treatment by either open surgical or endovascular approaches.8–10 If left untreated, significant restenosis may become symptomatic.23 Technical aspects of CEA have been examined as potential risk factors for the development of restenosis. Specifically, controversy exists about the optimal type of carotid artery closure after endarterectomy. Some studies have indicated superiority of patch angioplasty over primary closure in reducing restenosis, but data have been limited because of small study sizes.20

Arguments against the routine use of patching in CEA raise the risks of introducing a foreign body and thus creating the possibility for infection. If an autologous vein patch is used, the argument against it focuses on the possibility of development of degenerative pseudoaneurysms secondary to the presence of arterial pressure in a thin-walled vein. Potential disadvantages of using a patch is longer carotid occlusion time, longer time to achieving hemostasis and thus prolonged operative times potentially raising the risk of perioperative complications, such as stroke.24

We performed a secondary analysis of CREST, the largest prospective randomized trial with rigorous follow-up comparing CEA versus carotid artery stenting in symptomatic and asymptomatic patients with significant carotid artery stenosis.21 Previous analysis of restenosis after CEA versus carotid artery stenting in CREST showed a similar restenosis rate of 6% for both the procedures.22 However, patients with restenosis had a 4-fold increase in the risk of ipsilateral stroke.22 We show that, when compared with primary closure, patch angioplasty is associated with a significantly lower risk of 2-year restenosis. The risks of periprocedural stroke and death, immediate reoperation, and stroke at 4 years postoperatively were lower with patch angioplasty when analysis was adjusted for age and symptomatic status. However, when adjusted for surgeon board specialty, these differences became no longer significant. Notably, the use of patch varied widely with surgeon specialty: most vascular and thoracic surgeons patched, whereas most neurosurgeons did not. CREST did not track infection or pseudoaneurysm formation, but the operative times were not longer when patch was used.

Another argument against patching concerns the fact that existing evidence in favor of patching is based on dated studies.20

Table 3. Two-Year Restenosis Rates After CEA With Patch Versus No Patch

<table>
<thead>
<tr>
<th></th>
<th>Patch</th>
<th>No Patch</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis</td>
<td>20 (3.1±0.7)</td>
<td>32 (10.7±1.8)</td>
<td>0.27 (0.15–0.48)</td>
<td>&lt;0.0001</td>
<td>0.35 (0.16–0.74)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Forty-six patients (13 no patch and 33 patch) are not included in the restenosis end point because they did not have ultrasounds read by the ultrasound core laboratory. Four patients with restenosis information (2 patch and 2 no patch) did not have information on board specialty. CEA indicates carotid endarterectomy; and CI, confidence interval.

*Adjusted for symptomatic status.
†Adjusted for symptomatic status and surgeon board specialty.
optimal medical management, perhaps patching would not be necessary for prevention of restenosis. Modern medical management of atherosclerosis was implemented in all CREST patients, including the use of statins, as well as control of diabetes mellitus and hypertension. All patients undergoing CEA were on aspirin for ≥5 days before the procedure, and continued on the medication indefinitely postoperatively. The use of statins was not mandatory in CREST. With the best currently available medical management in both the groups, the use of patching during CEA is still associated with a decreased risk of restenosis.

Several prospective randomized trials have addressed the question of whether patching is superior to primary closure in CEA, with the limitation of low patient numbers. A Cochrane review of prospective randomized trials comparing patching versus primary closure in CEA has shown that patching was associated with a statistically significant reduction in the risk of ipsilateral stroke at 30 days and 1 year, perioperative arterial occlusion, return to the operating room, any stroke at 1 year, and occlusion or restenosis >50% at 1 year. Patching was also associated with a nonsignificant reduction in overall stroke, and in combined stroke and death. There were no statistically significant differences in arterial rupture or hemorrhage, rate of local infection, or cranial nerve palsy between the 2 groups; as well as no pseudoaneurysm formation at 1 year in 1141 arteries. Although the authors note that the quality of the studies reviewed was not uniformly exceptional, the statistically significant differences found in the reviewed studies agree with our data.20

Other systematic reviews of randomized clinical trials comparing the effects of carotid patch angioplasty to primary closure in CEA have noted superiority of patching to primary closure in reducing the risks of perioperative and long-term stroke and death, perioperative arterial occlusion, and restenosis in long-term follow-up; ipsilateral stroke during the perioperative period and on long-term follow-up; and acute arterial occlusion, long-term restenosis, and death.26 Another comprehensive review identified 1281 operations and concluded that patch angioplasty was associated with a reduction in the risk of perioperative stroke, stroke on long-term follow-up, and restenosis.27 All these studies emphasized limitations to their recommendations for patching over primary closure because of the small number of events, significant losses to follow-up, and poor trial methodology and quality of the data.

Our work is in agreement with previous trials comparing patching versus primary closure in CEA in the reduced risk of restenosis with the use of a patch.28 Most restenoses occur in the first 2 years after CEA,28 and our follow-up thus captures most restenoses. Known risk factors for restenosis include diabetes mellitus, hyperlipidemia, cigarette smoking, and female sex.23 The clinical significance of reduced restenosis is historically not entirely clear. The rate of symptomatic restenosis is known to be lower than the overall rate of restenosis.28 Notably,

### Table 4. Periprocedural and 4-Year Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Periprocedural End Points</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patch</td>
<td>No. of Events (Rate±SEM)</td>
<td>No Patch</td>
</tr>
<tr>
<td>MI</td>
<td>19 (2.5±0.6)</td>
<td>6 (1.8±0.7)</td>
<td>1.46 (0.58–3.68)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9 (1.2±0.4)</td>
<td>13 (4.0±1.1)</td>
<td>0.35 (0.15–0.82)</td>
</tr>
<tr>
<td>Stroke and death</td>
<td>9 (1.2±0.4)</td>
<td>13 (4.0±1.1)</td>
<td>0.35 (0.15–0.82)</td>
</tr>
<tr>
<td>Primary end point</td>
<td>28 (3.7±0.7)</td>
<td>18 (5.5±1.3)</td>
<td>0.74 (0.41–1.35)</td>
</tr>
</tbody>
</table>

### Table 5. Return to the Operating Room in 30-Day Postoperative Period

<table>
<thead>
<tr>
<th></th>
<th>Patch (n=752) n (%)</th>
<th>No Patch (n=327) n (%)</th>
<th>Odds Ratio for Patch vs No Patch (95% CI)*</th>
<th>PValue</th>
<th>Odds Ratio for Patch vs No Patch (95% CI)†</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to operating room</td>
<td>9 (1.2%)</td>
<td>12 (3.7%)</td>
<td>0.29 (0.12–0.71)</td>
<td>0.007</td>
<td>0.51 (0.13–1.95)</td>
<td>0.32</td>
</tr>
<tr>
<td>Reason for return</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke and thrombosis</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>8</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and MI, myocardial infarction.
*Adjusted for symptomatic status.
†Adjusted for symptomatic status and surgeon board specialty.
in a recent CREST analysis, patients with restenosis had significantly higher risk of stroke. The results of this study suggest that restenosis is clinically significant in that it places the patient at a higher risk for stroke. In our study, the lower rates of restenosis with patching did not directly correlate to a reduction in perioperative and 4-year stroke, as the decrease in stroke rates lost significance when analyses was adjusted for surgeon specialty.

This study does have limitations in that it is not a randomized prospective trial designed to compare patching versus primary closure a priori, and there was no secondary randomization to the type of closure after CEA. We also cannot comment on the closure a priori, and there was no secondary randomization to prospective trial designed to compare patching versus primary closure after CEA. We also cannot comment on the significance when analyses was adjusted for surgeon specialty.

Conclusions

In conclusion, our secondary analysis of CREST data supports the use of patch angioplasty for closure of arteriotomy in CEA. More widespread use of patching should be considered because of the clear association of patch closure with reduction in the risk of restenosis, and thus with superior long-term durability.

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Disclosures

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