Systematic Review of the Risks of Carotid Endarterectomy in Relation to the Clinical Indication for and Timing of Surgery

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Background and Purpose—Reliable data on the risk of carotid endarterectomy (CEA) in relation to clinical indication and timing of surgery are necessary to target CEA more effectively, to inform patients, to adjust risks for case mix, and to understand the mechanisms of operative stroke.

Methods—We performed a systematic review of all studies published from 1980 to 2000 inclusive that reported the risk of stroke and death resulting from CEA. Pooled estimates of risk by type of presenting ischemic event and time since the last event were obtained by Mantel-Haenszel meta-analysis.

Results—Of 383 published studies, only 103 stratified risk by indication. Although the operative risk for symptomatic stenosis overall was higher than for asymptomatic stenosis (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.45 to 1.81; \( P < 0.00001 \); 59 studies), risk in patients with ocular events only tended to be lower than for asymptomatic stenosis (OR, 0.75; 95% CI, 0.50 to 1.14; 15 studies). Operative risk was the same for stroke and cerebral transient ischemic attack (OR, 1.16; 95% CI, 0.99 to 1.35; \( P = 0.08 \); 23 studies) but higher for cerebral transient ischemic attack than for ocular events only (OR, 2.31; 95% CI, 1.72 to 3.12; \( P < 0.00001 \); 19 studies) and for CEA for restenosis than primary surgery (OR, 1.95; 95% CI, 1.21 to 3.16; \( P = 0.018 \); 6 studies). Urgent CEA for evolving symptoms had a much higher risk (19.2%, 95% CI, 10.7 to 27.8) than CEA for stable symptoms (OR, 3.9; 95% CI, 2.7 to 5.7; \( P < 0.001 \); 13 studies), but there was no difference between early (<3 to 6 weeks) and late (>3 to 6 weeks) CEA for stroke in stable patients (OR, 1.13; 95% CI, 0.79 to 1.62; \( P = 0.62 \); 11 studies). All observations were highly consistent across studies.

Conclusions—Risk of stroke and death resulting from CEA is highly dependent on the clinical indication. Audits of risk should be stratified accordingly, and patients should be informed of the risk that relates to their presenting event.

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Key Words: carotid endarterectomy ■ complications ■ risk factors

Large randomized controlled trials have shown that carotid endarterectomy (CEA) is beneficial for recently symptomatic severe carotid stenosis1,2 and, to a lesser extent, for asymptomatic stenosis.3 However, the benefit is highly dependent on the operative risk. The risk of stroke and death resulting from CEA has been shown to be related to a number of patient characteristics, particularly the presence and nature of recent cerebrovascular events.4,5 There is little doubt that asymptomatic patients have a lower operative risk than patients with symptomatic stenosis,6 but there is uncertainty about the relative risks of surgery in patients with different types of symptomatic ischemic events such as ocular transient ischemic attack (TIA), cerebral TIA, “nonhemispheric” events, stroke, or symptomatic restenosis after previous CEA. The American Heart Association guidelines on CEA give target operative risks for TIA, stroke, and asymptomatic stenosis but do not subdivide the indications further.6—9

There are also no reliable data on the risks of CEA for stroke in evolution or crescendo TIA versus stable symptoms or for early versus late surgery in stable patients, and the

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AHA guidelines do not comment on the management of these acute evolving syndromes. Some studies have reported very high operative risks for urgent CEA for evolving symptoms10,11 whereas others have suggested that the risk is similar to that for stable symptoms.12 However, the numbers of patients within individual studies are far too small to draw reliable conclusions. The optimal timing of CEA in stable patients is also uncertain, particularly after stroke. The large randomized controlled trials initially recommended that surgery be delayed for 4 to 6 weeks after stroke,1,2 but this recommendation has subsequently been questioned.13,14 The AHA guidelines simply suggest that surgery should be performed within 6 months of symptoms and do not make any statement about the need for urgency or delay during this period.6—8

Reliable data on the effect of the type of presenting event and the timing of surgery on the risks of CEA are necessary so that surgery can be targeted more effectively, patients can
be properly informed of the risks, the operative risks of individual surgeons or institutions can be corrected for case mix, and we can better understand the mechanisms of operative stroke. However, the risk of stroke and death resulting from CEA is relatively low, and very large sample sizes (several thousand) are required to determine differences reliably and precisely. Meta-analysis allows the results of smaller studies to be combined in a way that achieves this. A systematic review ensures that all available data are included and minimizes any selection bias. Consistency between studies of any findings can then be tested, and the causes of heterogeneity can be determined.

We previously reported a systematic review and meta-analysis of all studies published before 1995 that reported the risk of stroke and death resulting from CEA. However, this review did not consider the timing of surgery, did not fully differentiate between all of the clinical indications for surgery, and was not sufficiently powered to determine certain comparisons reliably because data were reported in only a small proportion of studies. Moreover, much of the data included in the analyses were derived from studies of operations performed in the 1970s and reported in the 1980s and may not be clinically relevant today. To determine whether our previous observations are still valid and to determine the predictors of operative risk in more detail and with greater precision, we have expanded the review and updated the analyses to include all studies published up to and including 2000.

Subjects and Methods

We updated our previous review by performing a new systematic review of all published articles reporting outcome of CEA between 1994 and 2000 (inclusive). We researched 1994 to 1995 because, although our previous review covered the period up to and including 1995, there is a delay between publication of articles and inclusion in bibliographic databases, so some articles published toward the end of our previous review period could have been missed.

Search Strategy

All searches were performed independently by 2 researchers (R.B. and K.R.). First, studies were identified from MEDLINE and EMBASE using the search terms “carotid endarterectomy” and “carotid surgery.” Studies reporting the results of carotid surgery for nonatherosclerotic disease were excluded, as were animal studies and review articles that did not include original data. Both reviewers then screened the resulting list of references individually to identify any reports that might contain relevant information. These were then pooled, and the process was repeated using the abstracts, or the full report when necessary, as a guide to relevance (Figure 1). Second, the reference lists of all articles identified electronically were searched. Finally, the 6 journals that contained the largest number of relevant articles were searched by hand for the period 1994 to 2000 inclusive (Figure 1).

Inclusion Criteria

Papers published in any language were included if they fulfilled the following criteria: (1) the numbers of combined strokes and deaths occurring within 30 days of CEA (or similar time period) were reported; (2) the risks of stroke and/or death were defined or calculable per operation; (3) operative risks were reported according to the clinical indication; (4) patients undergoing bilateral simultaneous endarterectomy were excluded, or data were reported separately so that they could be excluded from the analysis; and (5) patients undergoing synchronous endarterectomy and coronary artery bypass grafting were excluded, or data were reported separately so that they could be excluded from the analysis.

Extraction of Data

Both researchers independently studied each article and recorded data on the number of operations performed, number of patients operated on, and number of strokes and deaths during the operative and postoperative periods. When the data were reported, they were recorded separately for each different clinical indication (the Table). Data recorded by the 2 independent observers were then compared; all disagreements were reexamined jointly, and appropriate corrections made.

To identify duplicate reporting of the same cohort of patients, the authorship of all papers was cross-referenced. When duplication was considered likely, only 1 article was included. After exclusion of duplicates or articles with inadequate data, a final database of articles was created for analysis.

Statistical Analysis

Interobserver agreement for search results and data extraction was calculated by simple proportions and the \( \kappa \) statistic. The absolute risk of stroke and death was calculated for each of the indications listed in the Table. Pooled estimates were calculated by Mantel-Haenszel meta-analysis. The 95% confidence intervals (CIs) of the pooled risk estimates were calculated, allowing for extrabinomial variation, because standard methods of calculating CIs produce artificially narrow intervals when there is heterogeneity of risk between different studies. For studies that reported data stratified according to \( \geq 1 \) clinical indication, differences in operative risks within studies were compared by odds ratios (ORs). Pooled estimates of these within-study comparisons were calculated with the Mantel-Haenszel method.

Results

Results of the search are shown in Figure 1. We identified 5268 references through the electronic search. By excluding animal studies, reports of nonendarterectomy carotid surgery, and other reports that were clearly not relevant on the basis of the title, the 2 independent reviewers identified 971 potentially relevant reports (96.1% agreement; \( \kappa = 0.86; 95\% \) CI, 0.85 to 0.87; \( P < 0.0001 \)). Further exclusions were possible after review of the abstracts (95.3% agreement; \( \kappa = 0.89; 95\% \) CI, 0.86 to 0.92; \( P < 0.0001 \)), leaving 309 articles to review in full. A further 27 articles were identified from the reference lists of these articles, and another 47 articles were found by hand searching of the 6 most productive journals for the period 1994 to 2000 inclusive (Figure 1), giving 383 potentially eligible articles. Five articles were identified that were published in 1994 but were not identified and included in our previous review.

After detailed review of the 383 potentially eligible articles and exclusion of duplicate publications or reports of overlapping case series, articles with inadequate data, and series reporting synchronous bilateral CEA or synchronous CEA and coronary artery bypass graft surgery, a final set of 213 articles reporting the risk of stroke and death after CEA published during 1994 to 2000 inclusive was identified. Of these, 39 reported the outcome of surgery but gave no information about the indication, and 118 reported the proportion of symptomatic versus asymptomatic patients operated on but did not report the operative risk separately. The remaining 56 studies reported results separately for symptomatic and/or asymptomatic patients, and 34 of these studies also stratified their results according to at least 2 different
types of presenting symptomatic events. A further 47 studies from 1980 to 1994 were included from our previous review, giving a total of 103 studies reporting data on 38,338 operations.

Of the 103 studies, 6 were randomized trials, and the others were surgical case series or studies of routinely collected data. Follow-up was performed by independent clinicians (usually neurologists) in 11 studies. In the remainder, follow-up was performed by the operating surgeon, or no indication was given as to who performed follow-up. Given the small numbers of studies that reported data from randomized trials or from studies with independent follow-up, it was not possible to perform separate analyses in these specific subgroups of studies. Analyses were therefore performed on all studies combined.

Agreement between reviewers for data extraction was good, with agreement on the number of operations in 91.6% of studies and on operative mortality and the risk of stroke.
and death in 96.5% and 86.1% of studies, respectively. All disagreements were resolved by joint review of the articles.

**Absolute Risks of Surgery**

Data from individual studies are given for each indication in Figures 2 through 8. The Table shows results of the meta-analyses of absolute risks of stroke and death resulting from CEA by indication and the number of studies and operations on which the estimates were based. Overall, meta-analysis of data from the 60 studies that reported the results of CEA (14,399 operations) for asymptomatic stenosis revealed an overall operative risk of stroke and death of 2.8% (95% CI, 2.4 to 3.2) compared with 5.1% (95% CI, 4.6 to 5.6) for the 95 studies reporting the risks of CEA (36,482) for symptomatic stenosis. The absolute risk of stroke and death ranged from 2.8% (95% CI, 2.2 to 3.4; 18 studies) for CEA for ocular events only to 19.2% (95% CI, 10.7 to 27.8; 12 studies) for surgery for ongoing cerebral symptoms. For each indication, the operative risks in the Table are also stratified according to whether the study was published before 1995. The risks during these 2 time periods were highly consistent, and there were no statistically significant differences for any indication.

**Comparisons of Risk by Indication Within Studies**

Although the overall meta-analyzed estimates of operative risk appear to have been stable over recent years, there was statistically significant heterogeneity between studies in the absolute risks reported for each indication (the Table). In other words, there were significant differences between studies in operative risks for the same indications. This is probably due to differences between studies in case mix, methodological quality, and surgical or anesthetic technique. It is therefore more appropriate to determine differences in operative risk by indication within studies and then use meta-analysis to combine the within-study ORs. This method of analysis is still not perfect because there may be differences in the abilities of and techniques used by different surgeons within the same unit. However factors such as case mix and perioperative care have been shown to influence surgical stroke and death rate to at least as great an extent as surgical techniques, and they are likely to be consistent within such studies. These analyses are presented in Figures 2 through 8.

**Figure 2 shows relative odds of stroke and death resulting from CEA for all symptomatic patients versus all asymptomatic patients in 59 studies. Fifty-two studies (88%) found that surgery for symptomatic stenosis had a higher operative risk than surgery for asymptomatic stenosis, and no study yielded a statistically significant trend in the opposite direction. The combined estimate of the relative odds of stroke and death for CEA for symptomatic versus asymptomatic stenosis was 1.62 (95% CI, 1.45 to 1.81; P<0.0001) and was remarkably

<table>
<thead>
<tr>
<th>Presenting Event</th>
<th>Time Period</th>
<th>Studies, n</th>
<th>Operations, n</th>
<th>Absolute Risk, % (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>&lt;1995</td>
<td>57</td>
<td>17,597</td>
<td>5.0 (4.4–5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥1995</td>
<td>38</td>
<td>18,885</td>
<td>5.1 (4.7–5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>95</td>
<td>36,482</td>
<td>5.1 (4.6–5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent</td>
<td>&lt;1995</td>
<td>9</td>
<td>143</td>
<td>16.8 (8.0–25.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥1995</td>
<td>4</td>
<td>65</td>
<td>24.6 (17.6–31.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>13</td>
<td>208</td>
<td>19.2 (10.7–27.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>&lt;1995</td>
<td>27</td>
<td>3071</td>
<td>7.3 (6.1–8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥1995</td>
<td>23</td>
<td>4563</td>
<td>7.0 (6.2–7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>50</td>
<td>7634</td>
<td>7.1 (6.1–8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral TIA</td>
<td>&lt;1995</td>
<td>11</td>
<td>4279</td>
<td>4.6 (3.9–5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥1995</td>
<td>13</td>
<td>3648</td>
<td>6.9 (6.2–7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>24</td>
<td>7927</td>
<td>5.5 (4.7–6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ocular event</td>
<td>&lt;1995</td>
<td>9</td>
<td>1050</td>
<td>3.0 (2.5–3.4)</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>≥1995</td>
<td>9</td>
<td>734</td>
<td>2.7 (1.9–3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>18</td>
<td>1784</td>
<td>2.8 (2.2–3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonhemispheric</td>
<td>&lt;1995</td>
<td>16</td>
<td>1275</td>
<td>4.2 (3.2–5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥1995</td>
<td>8</td>
<td>476</td>
<td>4.3 (3.4–5.2)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Total</td>
<td>24</td>
<td>1751</td>
<td>4.2 (3.2–5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;1995</td>
<td>29</td>
<td>3197</td>
<td>3.4 (2.5–4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥1995</td>
<td>28</td>
<td>10,088</td>
<td>3.0 (2.5–3.5)</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>57</td>
<td>13,285</td>
<td>2.8 (2.4–3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>&lt;1995</td>
<td>3</td>
<td>215</td>
<td>3.8 (2.7–4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥1995</td>
<td>9</td>
<td>699</td>
<td>4.4 (3.1–5.8)</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>12</td>
<td>914</td>
<td>4.4 (2.4–6.4)</td>
<td>&lt;0.001</td>
</tr>
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</table>
statistically consistent (heterogeneity, $P=0.94$). There was no difference between studies published before or after 1995.

Figure 3 shows only a minimal difference in the odds of stroke and death resulting from CEA for stroke versus cerebral TIA in 23 studies (OR, 1.16; 95% CI, 0.99 to 1.35; $P=0.08$). There was no significant heterogeneity between studies and no difference between studies published before or after 1995. Surgery for carotid territory cerebral events (TIA or stroke) was not significantly more risky than surgery for nonhemispheric events (OR, 1.33; 95% CI, 0.94 to 1.89; $P=0.15$; 14 studies; Figure 4). Often, no definition of what was meant by nonhemispheric events was given, but it generally appeared to include vertebrobasilar territory events and nonspecific symptoms such as dizziness and was usually reported as a category separate from ocular events.

**Figure 2.** Odds of combined stroke and death after CEA in patients operated on for symptomatic vs asymptomatic stenosis.
Surgery for cerebral TIA was associated with a higher risk than surgery for ocular events only (OR, 2.31; 95% CI, 1.72 to 3.13; P<0.001; Figure 5). This trend was present in all 19 studies from which data were available, and there was no heterogeneity between studies (P=0.996). The same trend was present for surgery for stable cerebral stroke versus ocular events only (OR, 2.80; 95% CI, 2.06 to 3.82; P<0.001; 19 studies). In the 15 studies in which the comparison was possible, even surgery for asymptomatic stenosis had a slightly higher operative risk than surgery for ocular events only (OR, 1.33; 95% CI, 0.88 to 2.00; P=0.22), and again there was no heterogeneity between studies. For none of these comparisons was there any difference between studies published before or after 1995.

The highest operative risks were reported in studies of surgery for stroke in evolution, crescendo TIA, and cases that were simply termed urgent (the Table and Figure 6). Thirteen studies reported data on these groups, and although the number of cases in each individual study was small, the results were consistent with a trend toward a higher operative risk in the urgent cases in all 13 studies. The combined relative odds of operative stroke and death resulting from

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study</th>
<th>Cerebral Stroke+TIA Events / Patients</th>
<th>Non Hemispheric Events / Patients</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>Boc et al (1983)</td>
<td>22 / 167</td>
<td>3 / 40</td>
<td>2.3</td>
<td>0.7-8.1</td>
</tr>
<tr>
<td>41</td>
<td>White et al (1983)</td>
<td>8 / 129</td>
<td>1 / 50</td>
<td>2.4</td>
<td>0.3-10</td>
</tr>
<tr>
<td>42</td>
<td>Bernstein et al (1983)</td>
<td>23 / 200</td>
<td>3 / 35</td>
<td>1.4</td>
<td>0.4-4.9</td>
</tr>
<tr>
<td>43</td>
<td>Rosenthal et al (1983)</td>
<td>25 / 528</td>
<td>9 / 174</td>
<td>0.9</td>
<td>0.4-2</td>
</tr>
<tr>
<td>44</td>
<td>Fode et al (1986)</td>
<td>99 / 1722</td>
<td>17 / 335</td>
<td>1.1</td>
<td>0.6-1.9</td>
</tr>
<tr>
<td>45</td>
<td>Fode et al (1982)</td>
<td>5 / 74</td>
<td>2 / 40</td>
<td>1.4</td>
<td>0.3-7.4</td>
</tr>
<tr>
<td>46</td>
<td>Moros et al (1983)</td>
<td>4 / 49</td>
<td>1 / 57</td>
<td>5.0</td>
<td>0.5-10</td>
</tr>
<tr>
<td>47</td>
<td>Perler et al (1994)</td>
<td>3 / 41</td>
<td>0 / 7</td>
<td>5.6</td>
<td>0-10</td>
</tr>
<tr>
<td>48</td>
<td>Poullas et al (1994)</td>
<td>9 / 600</td>
<td>0 / 45</td>
<td>6.9</td>
<td>0-10</td>
</tr>
<tr>
<td>49</td>
<td>Perler et al (1995)</td>
<td>2 / 59</td>
<td>0 / 9</td>
<td>3.3</td>
<td>0-10</td>
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<td>50</td>
<td>Perler et al (1996)</td>
<td>3 / 81</td>
<td>1 / 17</td>
<td>6.6</td>
<td>0.1-6.3</td>
</tr>
<tr>
<td>51</td>
<td>Pleitas et al (1997)</td>
<td>12 / 559</td>
<td>1 / 72</td>
<td>1.6</td>
<td>0.2-10</td>
</tr>
<tr>
<td>52</td>
<td>Syrek et al (1990)</td>
<td>1 / 19</td>
<td>0 / 5</td>
<td>3.0</td>
<td>0-10</td>
</tr>
<tr>
<td>53</td>
<td>Tretler et al (1999)</td>
<td>14 / 193</td>
<td>0 / 12</td>
<td>9.4</td>
<td>0-10</td>
</tr>
<tr>
<td>TOTAL</td>
<td>224 / 4421</td>
<td>38 / 908</td>
<td>1.33</td>
<td>0.94-1.89</td>
<td></td>
</tr>
</tbody>
</table>

Significance p=0.15
Heterogeneity p=0.98

Figure 3. Odds of stroke and death after CEA in patients presenting with cerebral TIA (ie, excluding ocular events) vs patients with established stroke.

Figure 4. Odds of stroke and death after CEA in patients presenting with established carotid territory stroke or TIA vs patients with presenting with nonhemispheric events only. Patients with ocular events were not included in either group.
Figure 5. Odds of stroke and death after CEA for asymptomatic stenosis, for patients presenting carotid territory TIA, and for patients presenting with carotid territory stroke each vs patients presenting with ocular events only.
surgery for these urgent indications versus nonurgent surgery was 4.9 (95% CI 3.4 to 7.1; \( P < 0.001 \)).

In contrast to surgery for evolving symptoms, there was no excess risk associated with early versus late CEA in patients with stable symptoms (Figure 7). The definitions of early and late differed between studies, but the findings were highly consistent across studies, and no individual study reported a statistically significantly increased risk for early surgery. Results were also very similar for surgery for TIA and surgery for stroke (data available from authors).

Only 6 studies reported data on the risk of CEA for restenosis versus primary surgery. Reoperation was associated with a significantly higher risk (OR, 1.95; 95% CI, 1.21 to 3.16; \( P < 0.018 \); Figure 8).

### Discussion

It is well recognized that the risk of stroke and death resulting from CEA is dependent on the symptom status of the patient.\(^5\),\(^8\),\(^16\) Yet, three quarters of all studies published between 1994 and 2000 inclusive failed to stratify their results even according to whether the patients were symptomatic or asymptomatic, despite the fact that the operative risk of CEA was the primary topic of the research in most studies. The data reported in these articles are consequently of very limited use. Our analyses were based on the 103 studies published between 1980 and 2000 (inclusive) that did stratify operative risk according to at least 1 aspect of symptom status.

The ad hoc committees of the AHA Stroke Council have produced guidelines on the acceptable operative risk of
CEA.6-9 They recommend that the combined risk of stroke and death resulting from CEA should be no more than 3% for asymptomatic patients, 5% for patients with TIA, 7% for patients with stroke, and 10% for patients with recurrent stenosis. The overall estimates of the absolute risk of stroke and death in our review (the Table) correspond reasonably well with these recommendations. However, there are a number of difficulties in interpreting these overall estimates of absolute operative risks. First, the estimates of risk for each of the indications were derived from a different (albeit overlapping) sample of studies, so risks for the different indications cannot be directly compared. Second, for each of the indications that we studied, there was statistically significant heterogeneity in operative risk between studies (ie, there were significant differences between studies in the operative risks for the same indications), so that interpretation of the overall absolute risks was not straightforward. This is likely to be due to differences between studies in case mix, methodological quality, and surgical or anesthetic technique. We have shown previously that published absolute risks of CEA differ, depending on whether the study was prospective or retrospective and whether postoperative assessment was performed by a surgeon or neurologist.23,24 There are also likely to be other biases such as publication bias.

Unlike the overall estimates of the absolute risks of surgery, the within-study relative odds of stroke and death resulting from CEA for 1 indication versus another can be interpreted reliably. In individual studies, patients with different clinical indications are likely to have been operated on by the same surgeon(s), and the quality of the postoperative clinical assessment and other aspects of study methodology will have been similar. This method of analysis is still not perfect because there may be differences in the ability and techniques used by different surgeons within the same unit. However, the reliability of the meta-analyses of the within-study comparisons is supported by the remarkably consistent results, with very little statistical heterogeneity between studies. It was therefore appropriate to use meta-analysis to derive precise estimates of the effects of the indication for surgery on the operative risk. These analyses have produced several original and clinically useful observations.

The AHA guidelines recommend maximum operative risks of 5% for TIA and 7% for stroke4 but do not differentiate between ocular events and cerebral events. Our analysis shows that when surgery for ocular events is considered separately, there is no difference between the operative risks of CEA for cerebral TIA and for cerebral stroke and makes a case for revision of the current AHA guidelines.

Patients with only ocular ischemic events have a consistently lower surgical risk than patients with cerebral TIA or stroke. Indeed, the operative risk in patients with ocular events was nonsignificantly lower than that in patients with asymptomatic stenosis. The strict distinction between surgery for symptomatic and asymptomatic stenosis is clearly an oversimplification. Future studies reporting the operative risk of CEA should consider patients with ocular ischemia and cerebral ischemia separately. The low operative risk of stroke in patients with ocular ischemic events is consistent with the similarly low risk of stroke in those on medical treatment.10-25 The explanation for this good prognosis in patients with ocular ischemic events is uncertain, and evidence of particularly good collateral circulation toward the ipsilateral cerebral hemisphere is conflicting.27-29

Many reports of the operative risk of CEA include a category of symptomatic indications that are generally called nonhemispheric. The clinical indications for surgery that are included in this category are usually undefined but appear to include posterior circulation events and nonspecific symptoms such as dizziness. By definition, these cases presumably have not had definite carotid territory events ipsilateral to the operated carotid artery. Although they might therefore be considered to have asymptomatic stenosis, the operative risk in this group was not significantly less than surgery for carotid territory cerebral TIA or stroke, and they should not be considered low risk for CEA.

The reported incidence of recurrent carotid stenosis after CEA varies from 1.2% to 35% but is dependent on the definition of restenosis and the length and methods of follow-up.30,31 A recent systematic review suggested that the incidence of >50% restenosis is about 10% in the first year after surgery but then falls to a stable level of 1% per year by the third year.32 It is uncertain how many patients with recurrent stenosis go on to develop symptoms, but several studies have suggested that restenosis has a more benign course than primary disease.32 Our review shows that CEA for recurrent stenosis has a 2-fold-higher risk of stroke and death than primary surgery. Unfortunately, there were insufficient data to stratify the analysis according to symptom status of either the primary or redo patients. However, the low absolute risk of surgery for restenosis (the Table) suggests that many
patients were asymptomatic. Therefore, our findings are probably not inconsistent with the AHA recommendation of a maximum operative risk of CEA for symptomatic restenosis of 10%. The decision to perform surgery on patients with symptomatic or asymptomatic restenosis should be performed with the knowledge that there is an increased risk of stroke and death, as well as an increased risk of local complications such as cranial nerve injury and wound hematoma. The increased operative risk may be due to differences in pathology between primary atherosclerotic stenosis and early restenosis, which is commonly due to smooth myointimal hyperplasia, rather than atherosclerotic plaque.

The issue of risk of CEA in relation to the timing of surgery can be separated into the question of the risk of surgery in the acute phase (ie, in patients with stroke in evolution and crescendo TIAs) and whether the risk of surgery differs between the subacute phase (first few weeks) and the nonacute phase in those patients who are neurologically stable. In relation to the acute phase, although the definitions of stroke in evolution and crescendo TIAs are somewhat subjective, they are widely recognized clinical syndromes. They have a relatively poor prognosis on medical treatment alone, so some surgeons feel that urgent CEA is indicated in those patients with severe stenosis. However, our analysis suggests that the operative risk of stroke and death in patients operated on in the acute phase is in the region of 20% and is 4 times greater than in patients with stable disease. The number of studies was relatively small, and the definitions of urgent surgery varied, but the finding of a very high risk in this situation was consistent. This risk must be balanced against the likely outcome if surgery had not been performed, but in the absence of randomized controlled trials of CEA for this indication, the data do not support a policy of CEA in the acute phase.

Although it has long been considered that CEA in the subacute phase (first few weeks) after established stroke has a high operative risk, perhaps because the brain is more susceptible to infarction if exposed to a further ischemic insult at this stage, there was no evidence in our analysis of any increased risk resulting from surgery in the subacute phase. Moreover, any increased operative risk would have to be balanced against the significant risk of stroke on medical treatment alone if surgery is delayed. Both the European Carotid Surgery Trial and North American Symptomatic Carotid Endarterectomy Trial found that this risk was highest in the first few weeks after randomization, with a 30-day stroke risk on medical treatment of 4.9%. Therefore, if there is no significant increase in surgical risk in patients who are neurologically stable, surgery should not be delayed. The AHA guidelines recommend performing surgery within 6 months of surgery but give no recommendation about the urgency of surgery during this period.

Conclusions

Although established guidelines on the use of CEA clearly state that the risk of the procedure is dependent on the clinical indication, most published reports of the risks of CEA do not stratify their results by indication. Our analyses show that the risk of stroke and death resulting from CEA is highly dependent on the clinical indication, and reports of surgical risk should be stratified accordingly. Categorization of patients as asymptomatic or asymptomatic is an oversimplification and is of limited use in predicting operative risk. There are clinically important differences in risk between the different symptomatic indications, and patients with only ocular ischemic events are closer in risk to patients with asymptomatic stenosis. In relation to the timing of surgery, the operative risk of CEA in the acute phase of ongoing cerebral ischemia is probably too high to be justified in routine clinical practice, but surgery in the subacute phase in patients with a stable neurological syndrome is not associated with a higher operative risk than later surgery.

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Editorial Comment

Risk Stratification by Clinical Symptoms and Timing of Carotid Endarterectomy: How Could It Optimize Our Decision Making and Benefit Patients With Carotid Stenosis?

Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveller, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;
Then took the other, as just as fair,
And having perhaps the better claim . . .

The prevention of stroke by surgical means originated half a century ago. In the early years, anecdotal criteria were used for the selection of patients with internal carotid artery stenosis for surgery. Within the last decade, the appropriateness of carotid endarterectomy (CEA) for the reduction of stroke risk has been demonstrated in a selected group of patients with symptomatic carotid artery stenosis. Analysis of pooled data from randomized control trials has confirmed the unequivocal results of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST), and Veterans Affairs Affairs Trial (VA 309). CEA is highly beneficial in patients with transient ischemic attack (TIA) and nondisabling stroke (modified Rankin score <3) with high-grade stenosis (≥70% diameter reduction). Within this group, CEA is most beneficial for the following patients: healthy elderly patients with hemispheric TIA, those with tandem extracranial and intracranial lesions, and those without evidence of collateral vessels. A moderate benefit has been reported in certain individuals with carotid stenosis caused by 50% to 69% diameter reduction. In the largest trial of asymptomatic subjects, the perioperative risk of stroke and death reported was very low, but results indicated that 83 subjects needed to be operated on to prevent 1 stroke in 2 years.

Because the rate of CEA is increasing in both Europe and the United States, the selection process of candidates for CEA needs to be according to the recommended guidelines to maintain the best results reported in the first publications. The benefit of CEA has been highly dependent on the operative risk. However, this benefit may not be solely dependent on the latter. The risk of stroke and death resulting from CEA has been shown to depend on a number of patient characteristics, particularly the presence and nature of recent cerebrovascular event. Yet, reliable data on parameters such as timing of surgery since the last event and benefit from CEA are still lacking. Asymptomatic patients with carotid stenosis are known to have a lower operative risk compared with symptomatic patients. For symptomatic patients, there is still uncertainty about the type of ischemic event and clinical decision making compared with the risk of operative stroke.

Therefore, classification of ischemic events into different categories such as ocular TIA, cerebral TIA, nonhemispheric events, cerebral infarction, or symptomatic restenosis after previous stroke may show differences in surgical operative risk and benefit. Furthermore, validated data on the risk of CEA for unstable patients with stroke in evolution or crescendo TIA or for early versus late surgery in stable patients are scarce. The risk of stroke is also dependent on whether the postoperative assessment was performed by a surgeon or a neurologist. Concomitant vascular risk factors such as diabetes mellitus are reported to worsen the outcome.

In this issue of Stroke, Bond et al10 present a systematic review of data from 383 potential reports on CEA. Pooled estimates of risk by type of clinical indication and timing of surgery since the last event are the focus of this review. The data reviewed from 60 studies (14 399 CEA cases) demonstrated an operative risk of stroke and death for asymptomatic stenosis of 2.8% (2.4% to 3.4%) versus 5.1% (4.6% to 5.6%) for symptomatic stenosis reported from 95 studies. Interestingly, the absolute risk of stroke and death for CEA was as low as 2.8% for ocular events and as high as 19.2% for patients with ongoing cerebral symptoms. This meta-analysis corroborated previous findings on the combined estimate of the relative odds of stroke and death for CEA in symptomatic patients versus asymptomatic patients. CEA for cerebral TIA was associated with a higher risk than surgery for ocular events only. This trend appeared to be consistent for patients with stable cerebral stroke versus ocular events only.

The indications for urgent CEA in a patient with acute ipsilateral ischemic stroke are controversial. A comparison of the risk of stroke and death in unstable and stable patients was performed. Unstable patients, defined as those with stroke in evolution and crescendo TIA, presented with the highest operative risk. Although only 13 studies, each with a low number of cases, reported outcome of CEA in unstable patients (all referred to as urgent), the results were consistent in all studies. However, no excess risk was associated with early versus late surgery in stable patients.

Optimization of management of stroke patients during recent years has resulted in an immense difference in outcome and survival for patients. CEA is a preventive measure for reduction of stroke risk. The ad hoc committees of the American Heart Association Stroke Council have established guidelines on the acceptable operative risk of CEA. These guidelines recommend that the combined risk of stroke and death resulting from CEA should not exceed 3% in asymptomatic patients, 5% in symptomatic patients with TIA, and 7% for those with stroke. Progress in therapeutic decision making for CEA is essential for minimizing the risk of stroke and death resulting from CEA.
The road we choose, ie, the decision we make when we refer subjects to CEA, has great implications for individual patients. As Robert Frost points out, taking the road less traveled has made all the difference. Clinical decision making for patient referral for CEA needs to follow the major guidelines, and audits of risk should be stratified accordingly.

Two roads diverged in a wood, and I—took the one
less travelled by,
And that has made all the difference.

Robert Frost

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