Complication Rates After Left- Versus Right-Sided Carotid Endarterectomy

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Background—Studies suggest that the side of carotid endarterectomy (CE) may influence the rate of postoperative complications. We sought to clarify this by (1) analysis of individual-level data from 3 large studies and (2) systematic review and meta-analysis of additional published descriptions of outcomes by side.

Methods and Results—The Western Canada Carotid Endarterectomy (WCCE) study (n = 3164) was analyzed for outcomes by side along with data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET; n = 1415), and the ASA [Acetylsalicylic Acid] in Carotid Endarterectomy Trial (ACE; n = 2469). Pooled analysis of individual-level data from these three studies allowed calculation of rate ratios for stroke or death by side. Medline and EMBASE were searched to identify additional studies reporting CE outcomes by side, and an overall risk ratio for outcomes by side was determined with fixed-effects meta-analysis. The WCCE in-hospital stroke or death rates for left and right-sided CE were 3.72% and 3.07%, respectively (P = 0.27). A pooled analysis of the NASCET and ACE trials also revealed higher stroke or death rates for left-sided CE (5.39% versus 2.96%; P < 0.001). The corresponding risk-adjusted rate ratios for stroke or death for left- versus right-sided surgery were 1.22 (95% CI, 0.83 to 1.77) for WCCE and 1.82 (1.32 to 2.50) for the pooled NASCET and ACE trials. Systematic review of the literature identified 2 additional studies. Meta-analysis of all 5 available studies yielded a corresponding pooled rate ratio for stroke or death of 1.36 (1.18 to 1.56).

Conclusions—Left-sided CE is consistently associated with higher postoperative adverse event rates. Research into potential mechanisms is required to explain and address this finding. (Circ Cardiovasc Qual Outcomes. 2009;2:00-00.)

Key Words: endarterectomy, carotid ■ surgery ■ outcomes assessment

Since the introduction of carotid endarterectomy (CE), there has been an effort to determine the groups of patients to which the procedure can be most safely applied with the largest associated benefit. In assessing the balance of risks and benefits, one must consider both the situation where the benefits of carotid endarterectomy are greatest, and also the circumstances in which postoperative complication rates are highest, because the benefit of CE in trials such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET)2,6,7 and the European Carotid Surgery Trial8–10 is dependent on achieving a low short-term postoperative complication rate. Accordingly, the exploration of predictors of postoperative adverse events is important for determining appropriate patient populations for the procedure, or patient populations where special care considerations may be required to prevent complications of the procedure.5

The side on which CE is performed may be such a predictor, as recent randomized controlled trials and observational studies have suggested that outcomes may be poorer in left-sided procedures.2,11–14 However, this finding is statistically insignificant in most studies, and the magnitude of the difference varies across studies. We recently examined the outcomes of CE in Western Canada in an observational study.15 Along with this observational database, we also have access to individual patient level data from 2 large randomized controlled trials (NASCET and the ASA [Acetylsalicylic Acid] in Carotid Endarterectomy [ACE] trial).2,14

Here, we present a mixed methods study in which we explore the relationship between side of surgery and outcomes through (1) risk-adjusted analysis of individual-level data from 3 large studies where this was available (ie, the WCCE data,15–16 the NASCET trial,2 and the ACE trial14) and (2) a supplementary systematic review of the literature for published descriptions of CE complication rates by side and meta-analysis of additional published studies along with the above 3 studies to investigate the consistency of this finding in available published literature.

Methods

Individual-Level Pooled Analysis

Data Sources
The CE cases in the WCCE were identified by screening hospital discharge abstract data in the provinces of British Columbia, Alberta,
Saskatchewan, and Manitoba, Canada, during 2000 and 2001. Two trained chart reviewers then abstracted detailed information from hospital charts on demographics, preoperative characteristics, surgical variables, and outcomes. In total, 3167 cases were reviewed,15–16 and 3 cases were dropped because of missing side data.

We also analyzed individual-level patient data from 2 major randomized controlled trials of CE, NASCET,2 and ACE.14 NASCET randomized patients to best medical care or best medical care plus CE. A focal retinal or hemispheric TIA or nondisabling stroke occurring within 180 days of randomization was required for entry. Excluded were patients with potential cardioembolic abnormalities, organ failure, or cancer likely to cause death within 5 years. All subsequent strokes and deaths were recorded and submitted to blind external adjudication. We analyzed data from 1415 symptomatic surgical patients. The ACE trial, meanwhile, randomized patients undergoing CE to 4 dosages of aspirin. Both symptomatic and asymptomatic patients were included and followed for 3 months postoperatively. We analyzed 2469 surgical patients of which 1255 were symptomatic and 1214 were asymptomatic.

Outcomes

Our outcome of interest for each of these studies was the composite of postoperative stroke or death. Of note, however, the 2 randomized controlled trials (NASCET and ACE) reported rates of these events at 30 days, whereas the WCCE compiled information on in-hospital events only.12–16 We dealt with this discrepancy by limiting our subsequent analyses to permit the use of simpler statistical methods. Furthermore, most meta-analyses pool data from all trials for all outcomes. We instead performed a meta-analysis of the NASCET and ACE trials without pooling asymptomatic patients to determine homogeneity of the rate ratios. Multiple binomial regression analysis was performed with a log link to assess whether the relationship between side of surgery and outcome was confounded or modified (interaction) by other patient characteristics (specifically, patient age, sex, symptom presentation, degree of stenosis, history of diabetes, and history of myocardial infarction). The level of clustering of patients within study was quantified by calculating the design effect as 1+(M−1)r, where M is the mean cluster size and r is the estimated intraclass correlation coefficient.

Confirmatory Systematic Review and Meta-Analysis

Data Sources

We also searched Medline and EMBASE for published clinical trials or observational community-based studies that reported on outcomes of CE using the terms “side,” “outcomes,” and “carotid endarterectomy.” The search was initially conducted for the years 1965 through to the end of 2007. A verification search for potential new articles reporting outcomes by side was performed in June of 2009. The search was conducted by 2 of the authors (W.G. and L.G.) independently, and yielded the same results. We also consulted CE experts to supplement the literature search. We accepted only articles that reported outcome rates by side. The data on outcomes by side were also abstracted independently by the same 2 authors and found to be concordant.

Meta-Analysis of Left- Versus Right-Sided Complication Rates From the Literature

A meta-analysis of the suitable studies found in the systematic search was conducted for the years 1965 through to the end of 2007. A verification search for potential new articles reporting outcomes by side was performed in June of 2009. The search was conducted by 2 of the authors (W.G. and L.G.) independently, and yielded the same results. We also consulted CE experts to supplement the literature search. We accepted only articles that reported outcome rates by side. The data on outcomes by side were also abstracted independently by the same 2 authors and found to be concordant.

Results

Individual-Level Pooled Analysis

A total of 3164 patients were included from WCCE, of which 1912 presented with symptoms and 1252 were asymptomatic. Among the 3884 patients enrolled in the ACE and NASCET clinical trials, 2670 were symptomatic and 1214 were not. The mean cluster size was 52 patients among the 136 study centers represented by these 3 studies. The estimated intraclass correlation coefficient was 0.0029, resulting in a design effect of only 1.15. As the magnitude of the design effect was small, it was felt appropriate to not account for clustering in subsequent analyses to permit the use of simpler statistical analyses without the loss of information.

Table 1 presents the clinical characteristics of left- versus right-sided CE cases, with separate presentation of data for the clinical trials (NASCET and ACE, combined) and the observational community-based studies (WCCE and community-based studies).
observed in the observational WCCE study. In general, patients in the observational WCCE study were more likely to harbor risk factors for stroke than did patients in the clinical trials. The clinical characteristics of left- versus right-sided cases were generally quite similar, though there were statistically significant side differences in symptom presentation for both study designs, and in proportion of cases with more than 70% stenosis in the clinical trial patients.

Table 2 reveals that there was a higher rate of the combined stroke or death outcome when comparing left- to right-sided CE (3.72 versus 3.07%) in the observational WCCE study. This difference was not statistically significant, but yielded a corresponding pooled rate ratio of 1.22 (95% CI, 0.56, 3.72) for WCCE and 1.44 (0.56, 3.72) for the pooled clinical trials (NASCET and ACE; n = 3884).

We then determined the risk-adjusted pooled rate ratio using multiple binomial regression, with analysis controlling for age, sex, degree of stenosis, diabetes, history of myocardial infarction, and presentation (asymptomatic versus transient ischemic attack versus stroke). This analysis yielded an adjusted rate ratio for stroke or death of 1.22 (95% CI, 0.83 to 1.77) for WCCE and 1.82 (1.32 to 2.50) for the pooled NASCET and ACE clinical trials. The higher stroke or death rate seen in left-sided surgery is thus not explained by the potential confounding variables that we could adjust for from these studies.

In the NASCET trial, the finding of worse outcomes for patients with left-sided disease was confined to patients undergoing surgical CE. A parallel analysis by side of carotid disease in nonsurgically-treated NASCET control patients revealed a slightly higher event rate on the right side at 30 days (3.3% versus 1.7%; P = 0.05) and equivalent event rates by side at 90 days (5.4% right versus 5.0% left; P = 0.74).

The clinically rich data from NASCET and ACE also permitted us to investigate whether differences in common surgical factors (type of anesthesia, cerebral monitoring, heparin use, intraluminal shunting, and type of arteriotomy closure) existed based on the side of surgery. Table 3 demonstrates that these procedural factors were generally similar for left- versus right-sided surgery.

### Confirmatory Systematic Review and Meta-Analysis

Our literature search identified a total of 51 studies that provide information on CE adverse event rates by side (Table 4). These include the 3 studies (ACE, NASCET, and WCCE) reported in the individual-level analysis above, and 2 other studies. Together, these 5 studies represent a total of 15,015 patients, and consistently reveal a higher stroke or death rate for left-sided procedures.

We briefly highlight the 2 additional studies: Tu et al (2003) studied 6038 patients undergoing CE in Ontario, Canada, and showed a statistically significant poorer outcome in left-sided surgery compared to right-sided surgery (in-hospital stroke or death rate of 6.6% versus 5.3%; P = 0.036). Maxwell et al (2000), meanwhile, evaluated CE in 2305 patients in North Carolina via a chart review and reported an in-hospital stroke or death rate of 3.8% for left-sided surgery and 3.2% for right-sided surgery.

### Table 3. Surgical Factors According to Side of Carotid Endarterectomy From NASCET and ACE

<table>
<thead>
<tr>
<th>Percent of Group</th>
<th>Clinical Trials (NASCET and ACE; n = 3884)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left Side (n = 2024)</td>
</tr>
<tr>
<td>General anesthesia (vs local)</td>
<td>11.9</td>
</tr>
<tr>
<td>Cerebral monitoring (vs none)</td>
<td>46.1</td>
</tr>
<tr>
<td>Intraluminal shunting (vs none)</td>
<td>43.6</td>
</tr>
<tr>
<td>Heparin reversed (vs not reversed)</td>
<td>41.8</td>
</tr>
<tr>
<td>Simple arteriotomy closure (vs patch/other)</td>
<td>71.5</td>
</tr>
</tbody>
</table>
The Figure illustrates the results of our traditional meta-analysis that pooled the findings for left- versus right-sided adverse event rates for the 5 studies listed in Table 4. The point estimates for the rate ratios reported by each of the individual studies was higher than 1.0, indicating that the studies consistently indicate poorer outcomes for left-sided surgery. The formal test for heterogeneity across studies was not statistically significant \((P=0.19)\), and the ensuing fixed-effects meta-analysis yielded a pooled rate ratio of 1.36 (95% CI, 1.18 to 1.56), for left-sided versus right-sided procedures.

**Discussion**

Our study indicates that left-sided surgery is a risk factor for stroke and death in CE. This was established by performing an individual-level analysis of data from 3 large studies, with a multivariable analysis that controlled for several potential confounders. We then extended our investigation of the significant finding of worse outcomes associated with left-sided CE by performing a confirmatory systematic review and meta-analysis that solidifies our study finding.

Given the consistency of this finding, we now need to consider potential explanations. This question has been liberated in the literature with only speculative suggestions.\(^7\)\(^1\)\(^1\)\(^3\)\(^4\)\(^1\)\(^4\)\(^1\)\(^8\) Much of the discussion has centered on the notion that more events and subsequently more surgeries occur on the left, because the left cerebral hemisphere is most often dominant and therefore more eloquent, and is correspondingly more likely to register symptomatic events. Two of the previously mentioned observational studies had a preponderance of left-sided surgery: 52% \((P=0.014)\) in the Maxwell et al (2001) study\(^1\)\(^1\) and 53% in WCCE \((P<0.05)\). It is proposed that silent strokes would be more likely to occur in the less eloquent right hemisphere and be under-reported, because these would often only be detected by a skilled neurologist or systematic imaging.

NASCET data on medically treated patients, however, provide an argument against the theory that silent events on the right fully account for the side difference in outcomes. The fact that outcomes are not poorer in medically-treated patients with left-sided disease suggests that hemispheric dominance and silent events do not fully explain the differences by side. Rather, there may be an aspect of the surgery itself that could be influencing event rates. However, our exploration of potential surgical factors recorded in NASCET and ACE that may affect outcomes does not reveal any notable differences by side and thus does not seem to provide an explanation for the poorer outcomes of left-sided procedures (Table 3).

There is some speculation regarding the potential role of handedness of the surgeon performing the procedure, and some surgeons anecdotally report that for anatomic reasons, left-sided carotid endarterectomy is technically more difficult for a right-handed surgeon. Surgeon handedness has certainly been implicated in the outcomes of other surgeries including total knee arthroplasty (TKA), where recent literature sug-

### Table 4. Summary of Stroke or Death Rates and Rate Ratios in Relation to Side of Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Events Counted</th>
<th>Left Side (n/N)</th>
<th>Right Side (n/N)</th>
<th>Rate Ratio (95% CI)</th>
<th>(P) Value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCCE</td>
<td>Observational</td>
<td>In-hospital</td>
<td>3.72 (62/1667)</td>
<td>3.01 (45/1497)</td>
<td>1.24 (0.85, 1.80)</td>
<td>0.27</td>
<td>Chart review of all carotid endarterectomies performed in western Canada from 2000 to 2001</td>
</tr>
<tr>
<td>Maxwell et al (2000)</td>
<td>Observational</td>
<td>In-hospital</td>
<td>3.78 (45/1190)</td>
<td>3.23 (36/1115)</td>
<td>1.17 (0.76, 1.80)</td>
<td>0.47</td>
<td>Chart review of all carotid endarterectomies performed at New Hanover Regional Medical Center from 1979 to 1998</td>
</tr>
<tr>
<td>Tu et al (2003)</td>
<td>Observational</td>
<td>30 d</td>
<td>6.60 (203/3074)</td>
<td>5.30 (156/2946)</td>
<td>1.25 (1.02, 1.53)</td>
<td>0.04</td>
<td>Review of the Ontario Carotid Endarterectomy Registry from 1994 to 1997</td>
</tr>
<tr>
<td>NASCET</td>
<td>Clinical trial</td>
<td>30 d</td>
<td>8.72 (65/745)</td>
<td>4.03 (27/670)</td>
<td>2.17 (1.40, 3.35)</td>
<td>&lt;0.001</td>
<td>Multicenter randomized controlled trial of patients with symptomatic carotid artery stenosis</td>
</tr>
<tr>
<td>ACE</td>
<td>Clinical trial</td>
<td>30 d</td>
<td>6.18 (79/1279)</td>
<td>4.12 (49/1190)</td>
<td>1.50 (1.06, 2.12)</td>
<td>0.02</td>
<td>Multicenter randomized controlled trial of aspirin use with carotid endarterectomy</td>
</tr>
</tbody>
</table>

Figure. Fixed effects meta-analysis of the risk ratio for stroke or death for left-sided versus right-sided CE (test for heterogeneity, \(P=0.19\)).

The Figure illustrates the results of our traditional meta-analysis that pooled the findings for left- versus right-sided adverse event rates for the 5 studies listed in Table 4. The point estimates for the rate ratios reported by each of the individual studies was higher than 1.0, indicating that the studies consistently indicate poorer outcomes for left-sided surgery. The formal test for heterogeneity across studies was not statistically significant \((P=0.19)\), and the ensuing fixed-effects meta-analysis yielded a pooled rate ratio of 1.36 (95% CI, 1.18 to 1.56), for left-sided versus right-sided procedures.
gests that outcomes on left knees are worse when the procedure is performed by a right-handed surgeon. Also, there is active research in the area of laparoscopic surgery to help accommodate left-handed surgeons during cholecystectomy. The combined data from NASCET and ACE provide some intriguing supplementary data on the potential contribution of surgeon handedness to the poorer outcomes in left-sided CE. Information on surgeon handedness is available for 2243 CE procedures in the 2 trials. Among these, 1937 were performed by right-handed surgeons and 306 by left-handed or ambidextrous surgeons. The 30-day stroke or death rates for right-handed surgeons were 6.7% for left-sided CE and 3.1% for right-sided CE. The corresponding rates, meanwhile, for left-handed and ambidextrous surgeons were lower at 2.7% for left-sided CE and 0% for right-sided CE. We emphasize that the above points are merely speculation regarding a potential role of handedness as a factor underlying the outcome difference by side.

Further research is now needed to clarify the potential contribution of handedness to our study findings. If handedness is indeed found to be a contributing factor, there would be a need to develop modified surgical approaches that improve ergonomics for right-handed surgeon operating on left carotid arteries. Alternatively, if microemboli from surgery account for the phenomenon, then consideration could be given to the use and evaluation of embolic capture devices similar to those being considered in the context of coronary artery procedures and during carotid artery stenting. Stork et al reported that left sided CE was associated with an increased risk of microembolic events detected intraoperatively.

A strength of this study is our ability to analyze individual-level data from 3 large CE studies—the WCCE, NASCET, and ACE. The resulting analyses permit multivariable analysis controlling for potential confounding variables. A related strength is our combination of data from both clinical trials and observational data. Despite differences in study populations and settings, our finding of higher adverse event rates for left-sided surgery appears to be consistent.

Our study also has limitations. First, it is conceivable that there are unpublished studies demonstrating no difference between left- and right-sided surgeries. In this regard, individual patient-level data from other large carotid endarterectomy trials could be analyzed by the groups conducting these studies to determine whether our finding is consistent. A second limitation relates to the differential timing of study outcomes in the studies assessed in our review. As previously stated, some studies examined 30-day postoperative outcomes, whereas others were based on in-hospital outcomes. The relevance of this discrepancy is relatively minor in an analysis such as ours that pools within-study risk ratios. Nevertheless, uniform end point timing across studies would have been preferable. A third global limitation is that this study does not explain a mechanism to account for higher event rates on the left side. Some possible explanations are presented in preceding paragraphs, but these are purely speculative.

Despite these limitations, our mixed methods study demonstrates a consistent finding that left-sided surgery is an independent risk factor for increased rates of postoperative stroke or death after CE. Recognizing that the benefits of CE hinge on acceptable short-term risks of the procedure, research is now needed to clarify the mechanism(s) underlying this increased risk, to determine whether these can be modified.

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Disclosures

None.

References

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