Morbidity/Mortality Abstract 202M2

CAROTID ENDARTERECTOMY IN SYMPTOMATIC CAROTID STENOSIS: NASCET COMPARATIVE RESULTS AT 30 MONTHS OF FOLLOW-UP

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References


5. Taylor DW. Department of Clinical Epidemiology and Biostatistics, McMaster University, Chedoque, Canada (Biostatistician and Chairman of the NASCET Writing Committee), personal communication.

Objectives of Abstract

1) To apply the life table reconstruction method of Singer\(^5\) to a clinical outcome study (NASCET),

2) To then compare the stroke and mortality results of the Medical and Surgical (endarterectomy) treatment groups of the NASCET Study, and

3) To relate study group event rates to Framingham, Group Life, and U.S. population expected.

Patients Studied

This was a multicenter, randomized clinical trial of carotid endarterectomy for high-grade (70-99\%) stenosis. Both the Surgical and the Medical group under study received appropriate medical treatment (e.g., anti-lipid, anti-hypertensive, anti-platelet, and, as warranted, anti-diabetic treatment), but the Surgical group also received endarterectomy. The 50 participating centers in the United States and Canada each had to have a qualifying level of expertise (low perioperative complication rate and a satisfactory volume of endarterectomy cases) in order to be eligible centers. The 328 Surgical and 331 Medical subjects participating in the high-grade stenosis arm of the study were assembled according to selection criteria requiring the following: a carotid-distribution TIA or non-disabling stroke within the previous 120 days; angiographic evidence of 70-99\% stenosis of an ipsilateral internal carotid artery that was suitable for endarterectomy; age less than 80; and informed consent. Excluded from the study were also those who had significant cardio-embolic risk; concurrent major organ-system failure or malignancy judged to have significant 5-year mortality risk; or an intracranial lesion more serious than the surgically accessible carotid one.

Patients with bilateral stenosis who were assigned to the Surgical group were permitted to undergo bilateral endarterectomy, providing that the "symptomatic side" was operated upon first. However, simultaneous coronary bypass/carotid endarterectomy and simultaneous bilateral endarterectomy were not permitted. Patients who crossed-over to the other treatment group were included in the original assignment group up to the date of crossover.

The mean age\(^6\) was 66 in the Medical group, 65 in the Surgical group, which groups were 69\% and 68\% male, respectively. Randomization created balanced treatment groups with respect to the qualifying cerebrovascular event, underlying vascular lesions, and important prognostic characteristic (such as smoking status, presence of hypertension, hyperlipidemia, diabetes, angina and claudication). Approximately two-thirds of each group had TIA as their qualifying condition. The severity of ipsilateral stenosis (verified by strong inter-observer agreement) was comparable between the two groups (roughly 42\%, 35\%, and 23\% of each group had stenoses of 70-79\%, 80-89\%, and 90-99\% severity respectively).

The NASCET high-grade stenosis results were reported in August 1991 because of evidence of significant endarterectomy treatment efficacy, according to pre-planned rules for terminating further randomization. A parallel study of medium-grade stenosis (30-69\%) is still ongoing. While no new subjects will be entered, the
original subjects of this high-grade stenosis study will continue to be followed and periodically reported on.

Follow-Up

Follow-up was 100% complete, and average duration of follow-up was 18 months. Enrollment of the 659 subjects occurred between January 1, 1988, and February 21, 1991. One crossover from Surgical to Medical occurred (due to refusal of endarterectomy), with the other 327 Surgical subjects receiving endarterectomy an average of two days after randomization. Of the 331 subjects randomly assigned to Medical treatment, 21 crossed over to Surgical (10 after TIA, 6 after a stroke, 2 prior to other required surgery, 2 after refusing the random assignment, and 1 on the advice of a nonparticipating physician).

All deaths were assessed for causation, and all stroke events were characterized according to a standardized classification scheme of the NINDS (National Institute of Neurological Disorders and Stroke). Strokes producing functional deficits persisting beyond 90 days were considered major. The perioperative period was considered to be the time from randomization to 30 days after surgery, or 32 days on the average. In the perioperative period, 19 Surgical subjects experienced study-events, namely 18 strokes (5 major, 1 fatal) and 1 non-stroke fatality, for a total of 2 deaths. In the comparable 32-day "perioperative" period, 11 Medical subjects experienced strokes (2 major, 1 fatal) with no other deaths occurring. Perioperative strokes and deaths were included in the NASCET event-rate and survival curves, and information was not available to segregate these from the life table results reported for the first interval of follow-up.

Expected Mortality and Stroke-Rate

The NASCET high-grade stenosis study groups were compared to each other, using the group with lower mortality and stroke incidence as the "expected." (Table 2) For all NASCET target outcomes, the lower incidence group was the Surgical group. Further comparison was made of each of these treatment groups versus selected population expected rates. (Table 3) Because certain data needed for proper derivation of expected rates was lacking, these comparisons are more illustrative than analytic.

For mortality, comparison to U.S. general population mortality rates was made using 1979-81 U.S. Decennial Life Tables. First-year mean q' was approximated from the reported median age by adding three years and entering U.S. Tables at the higher tabular age, weighting the group mean q' for sex composition. Aggregate annual mortality rates were then calculated for each group, after using 5% per year advancement of mean q'. Because of the high degree of selection in the NASCET enrollment process and the significant extent of exclusions, mortality comparison was also made to 1975-79 Group Life mortality rates, with similar weighting, advancement, and derivation of aggregate annual mortality rate.

For stroke incidence, comparison was made to Framingham Study Experience, 1950-1968 M and F combined, as reported by Singer in his Table 1C. Detailed information on age-sex composition of NASCET study subjects was not available, so matching to Framingham data could not be performed in the manner conducted by Singer. However, a reasonable estimate could be made. Since 60% of the NASCET subjects were identified as hypertensive, it was felt that the expected stroke rate should be weighted toward Singer's "definitely hypertensive" group. Since the NASCET study included more male subjects than the SHEP-adjusted Framingham numbers (68% versus 43%), it was felt that the 13.5/1000 stroke-incidence rate of the 65-74 mixed M-F age group would make a reasonable estimate for purposes of comparison to NASCET. Given the short duration of the study interval (2.5 years) and lack of detailed compositional-information at time zero and by duration, this incidence rate was used for the mean annual incidence rate of the entire (short) study period.

Additional Methodology

The NASCET results as published in the N Engl J Med, furnished an outcome table (author's Table 2) showing cumulative event rates at two years to three decimal places; a mortality summary (author's Table 3) showing cumulative mortality at 30 months of follow-up; and six Kaplan-Meier event-free survival curves, with \( \delta \), at start of each six-month interval shown at the bottom of each graph.

An examination of the \( \delta \) values (see "\( \mathcal{C} \)" column in Table 1) reveals that while no subjects were "lost to follow-up" (i.e., FU was "100% complete"), there are substantial numbers of study subjects in both the Medical and Surgical groups whose duration of FU is short (i.e., late enrollment, short duration of observation). These lives are "withdrawn" lives for life-table purposes, even though they did not "withdraw" from the study. Thus, if event rates were based exclusively on interval survival rates \( (r_i = 1-p_i) \), and if geometric mean annual event rate \( \bar{r} \) were the only available summary statistic, some information would be lost. If the number of withdrawn lives could be calculated, and exact exposure \( E \) deduced, then \( n/E \) interval and mean event-rates could
be calculated. The advantage of aggregate mean annual event rates ($\bar{r}$) is that they are exposure-weighted, and better preserve the effect of the pattern of morbidity. As a comparison of $\bar{r}$ and $\tilde{r}$ in Table 1 shows, even though the NASCET study was of short duration, the difference between geometric $\bar{r}$ and exposure-weighted $\tilde{r}$ is meaningful, and reflects the pattern of high early-interval event frequency.

Tables comparable to Table 1 were created for each of the outcome parameters listed in Table 2. Caliper measurements of each six-month cumulative survival were taken from the Kaplan-Meier curves. As a check, the exact (3 decimal place) measurement at two years (author's Table 2) corresponded within .003 to the numbers arrived at by caliper measurement, suggesting reasonable accuracy of the other 6-month measurements. Singer's method permitted reconstruction of a double-decrement life table with events (n), withdrawals (w), and exposure (NER) calculated in step-wise fashion. Because the intervals were six months, the exposure calculated directly by the reconstruction method in this case yielded a sum of person half-years. Multiplying by 0.5 converted NER to interval (and cumulative) exposures, E, measured in full person-years. For Table 2, $d/E$ and $n/E$ data, aggregate annual mortality rates ($\hat{q}$) and event rates ($\tilde{r}$) were thus calculated.

Dr. Taylor, the chairman of the NASCET Writing Committee, was unable to release information beyond that which was published, but he did indicate his belief that the median age reported in the study was close to the true mean age, and that his Table 3 mortality data was 30-month cumulative mortality.

Results

The various neurologic event-rates were consistently lower in the Surgically-treated group than the Medical group, even with perioperative events included. All-cause mortality showed an EDR of 19 favoring the Surgical group. When Surgical group mortality was compared to U.S. population expected, the stroke incidence rate proved substantially greater than population-expected (Framingham) for both Medical and Surgical groups.

At 30 months of follow-up, the Surgical group had significantly lower event rates for stroke and stroke-and-death combined than did the Medical group, as shown in Table 1 and in the author's six Kaplan-Meier survival curves (their figure 1). One outcome measure ("any major stroke or death") showed a statistically-significant difference in favor of the Surgical group with P<.01, and all five of the other outcome comparisons showed statistically-significant difference at the P<.001 level. These five others were: any ipsilateral stroke; any stroke; any stroke or death; any major or fatal ipsilateral stroke; and any major or fatal stroke.

Discussion

As described by the NASCET authors, carotid endarterectomy was introduced in 1954 as rational therapy for ischemic disease distal to documented obstruction of an internal carotid artery. However, the history of endarterectomy was colored by initially unfavorable results in randomized trials, and high but widely variable rates of serious complications. Secular trend toward declining rates of first and fatal strokes; the growing role of risk-factor management and anti-platelet agents in stroke prophylaxis; and the recognition and treatment of concurrent coronary and other vascular disease have greatly changed the environment in which endarterectomy competes as a treatment choice.

Results similar to the NASCET results have been reported from the recent European Carotid Surgery Trial where a 14% risk reduction over three years was shown in a group of 778 symptomatic patients with severe (70-99%) stenosis.

Benefit of endarterectomy has been shown to 30 months follow-up in a select group of individuals with symptomatic, arteriographically-documented, high-grade carotid stenosis, as compared to a concurrent comparison group of medically-treated controls. The neurologic complication rate and mortality rate perioperatively were 5.5% and 0.6% respectively (versus 3.3% and 0.3% in the unoperated group for the comparable time period). The surgical benefit emerged at about three
months post-op, at which point the Medical and Surgical survival curves crossed over, with the Surgical groups maintaining more favorable outcomes thereafter. At the 30-month point, stroke and fatal stroke rates for the Surgical group were significantly lower than for the Medical group, while all-cause mortality was not significantly different.

### Table 1

**Comparative Morbidity, Any Stroke, Patients with High-Grade Carotid Stenosis, 1988-1991, With or Without Carotid Endarterectomy**

<table>
<thead>
<tr>
<th>Interval Start-end (months)</th>
<th>Alive at Start</th>
<th>Event-Free Survival</th>
<th>Interval of Event Rate</th>
<th>No. of Withdrawn Events</th>
<th>No. Exposed to Risk</th>
<th>Exposure Pers-Yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>328</td>
<td>.925</td>
<td>.925</td>
<td>.075</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>6-12</td>
<td>257</td>
<td>.900</td>
<td>.973</td>
<td>.027</td>
<td>6</td>
<td>49</td>
</tr>
<tr>
<td>12-18</td>
<td>202</td>
<td>.880</td>
<td>.978</td>
<td>.022</td>
<td>4</td>
<td>43</td>
</tr>
<tr>
<td>18-24</td>
<td>155</td>
<td>.874</td>
<td>.993</td>
<td>.007</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>24-30</td>
<td>108</td>
<td>.874</td>
<td>1.000</td>
<td>&quot;0&quot;</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>30-</td>
<td>49</td>
<td>.874</td>
<td></td>
<td></td>
<td>34</td>
<td>245</td>
</tr>
</tbody>
</table>

**Endarterectomy (Surgical) Group**

0-6 = 52.4

**Unoperated (Medical) Group**

0-6 = 125.6

### Table 2

**Morbidity and Mortality of Target Outcomes, Medically Treated Group Compared with Endarterectomy (Surgical) Group, All Durations Combined**

<table>
<thead>
<tr>
<th>Target Outcome Event</th>
<th>No. of Events</th>
<th>Exposure</th>
<th>Event Rate/1000/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke</td>
<td>Med. 65</td>
<td>Surg. 34</td>
<td>401.8 449 162 76 86</td>
</tr>
<tr>
<td>Any major or fatal stroke</td>
<td>Med. 29</td>
<td>Surg. 10</td>
<td>418.8 486 69 21 48</td>
</tr>
<tr>
<td>Any major stroke or death</td>
<td>Med. 39</td>
<td>Surg. 20</td>
<td>426.3 488.5 92 41 51</td>
</tr>
<tr>
<td>Any stroke or death</td>
<td>Med. 76</td>
<td>Surg. 42</td>
<td>404.5 466.3 188 90 98</td>
</tr>
<tr>
<td>Deaths (all causes)</td>
<td>Med. 21</td>
<td>Surg. 15</td>
<td>426.3 488.5 49 31 18</td>
</tr>
</tbody>
</table>
### Table 3
**Comparative Mortality and Stroke Incidence, NASCET Groups, All Durations Combined, versus Estimated Expected Rates**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Expected</td>
<td>d</td>
<td>US</td>
<td>d'</td>
</tr>
<tr>
<td>Surg</td>
<td>328</td>
<td>488.5</td>
<td>15</td>
<td>15.4</td>
<td>12.7</td>
</tr>
<tr>
<td>Med</td>
<td>331</td>
<td>426.3</td>
<td>21</td>
<td>14.5</td>
<td>12.4</td>
</tr>
</tbody>
</table>

**Basis of Expected Mortality Rates:**
- * US = 1979-81 U.S. Life Tables, M and F.
- GRP = 1975-79 Group Life Tables, M and F.

### Any Stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>Alive at Start Pers-Yrs</th>
<th>Exposure Pers-Yrs</th>
<th>No. of Events</th>
<th>Morbidity Ratio vs. F'ham*</th>
<th>Mean Ann. Event Rate/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Expected</td>
<td>n</td>
<td>F'ham</td>
<td>n'</td>
</tr>
<tr>
<td>Surg</td>
<td>328</td>
<td>449</td>
<td>34</td>
<td>6.3</td>
<td>540%</td>
</tr>
<tr>
<td>Med</td>
<td>331</td>
<td>402</td>
<td>65</td>
<td>5.5</td>
<td>1180%</td>
</tr>
</tbody>
</table>

**Basis of Expected Morbidity Rates:**