The Risk and Benefit of Endarterectomy in Women With Symptomatic Internal Carotid Artery Disease

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Background and Purpose—Perioperative risk and long-term benefit of carotid endarterectomy (CE) are not detailed in women with symptomatic internal carotid artery (ICA) stenosis. Our aim was to compare the efficacy of CE versus medical therapy in women and men with symptomatic ICA stenosis.

Methods—Data were taken from the North American Symptomatic Carotid Endarterectomy Trial (873 women, 2012 men) and the ASA and Carotid Endarterectomy trial (335 women, 813 men).

Results—The 30-day perioperative risk of death was higher in women than in men (2.3% versus 0.8%, P=0.002). Higher perioperative risk of stroke and death was also observed (7.6% versus 5.9%) but not statistically significant. With ≥70% stenosis, the 5-year absolute risk reduction (ARR) in stroke from CE was similar between women (15.1%) and men (17.3%). With 50% to 69% stenosis, CE was not beneficial in women (ARR=3.0%, P=0.94), contrary to men (ARR=10.0%, P=0.02). Medically treated women had low risk for stroke. A stroke prognosis instrument (SPI-II) assigned points to 7 factors that identified higher risk for medically treated women: 3 points for hemispheric (not retinal) event, history of diabetes, previous stroke; 2 for age older than 70 years, stroke (not transient ischemic attack); 1 for severe hypertension, history of myocardial infarction. CE was beneficial only for 29.0% of women with 50% to 69% stenosis who had the highest total score of 8 to 15 (ARR=8.9%).

Conclusions—Women and men with ≥70% symptomatic stenosis had similar long-term benefit from CE, although the perioperative risks were higher for women. CE was not beneficial for women with 50% to 69% stenosis without other risk factors for stroke. (Stroke. 2005;36:27-31.)

Key Words: carotid endarterectomy ■ carotid stenosis ■ stroke, ischemic ■ women

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opulation-based studies have shown that women, at any age, have a lower risk of stroke than men.1,2 However, because women on average live 5 to 10 years longer than men and the risk of stroke increases with advancing age, the burden of stroke is greater in women than in men. Over an entire lifetime, strokes cause the death of 1 in 6 women and only 1 in 12 men.3 The importance of this public health issue has led to an increasing interest in the distinctive features of stroke in women with respect to risk factors, clinical outcomes, and response to treatments.4,5

The benefit of carotid endarterectomy (CE) to prevent stroke for patients with symptomatic severe (≥70%) internal carotid artery (ICA) stenosis has been shown in 2 large trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST).6,7 Patients with 50% to 69% symptomatic ICA stenosis benefitted less from CE.6,9 Although not assessed in detail, women were reported to have a reduced benefit from CE compared with men.

The aim of the present study was to examine the risk of ischemic stroke and the long-term benefit of CE, in women compared with men, using data from the NASCET. Also, the perioperative risk of CE in women was compared with men by combining data from the NASCET and the ASA and Carotid Endarterectomy (ACE) trial.

Subjects and Methods

The NASCET

The NASCET was designed to determine the efficacy of CE in patients with symptomatic ICA stenosis. Patients were enrolled if they had a transient ischemic attack or nondisabling ischemic stroke within 180 days of randomization and an angiographic stenosis in the ipsilateral ICA. Patients were ineligible if they had a probable cardiac source of embolism or had other serious disease likely to cause death within 5 years. Details of the final results have been published.8

From December 1987 through December 1996, 2885 patients were randomly assigned to either best medical care plus CE (N=1436) or best medical care alone (N=1449). Patients were examined by a neurologist at 30 days and every 4 months. The...
The ACE Trial

The ACE trial was designed to seek the optimum dose of aspirin to reduce the perioperative risk of stroke and death in patients scheduled for CE. The ACE trial was performed concurrent to NASCET, and most of the ACE trial centers (85.1%) participated in NASCET. From July 1994 through April 1998, 2804 patients (1292 symptomatic) undergoing CE were assigned to 4 different doses of aspirin. Patient entry criteria were similar to those of NASCET. Patients were assessed by a neurologist, at 30 days and at 3 months. All outcome events were centrally reviewed. In contrast to NASCET, angiography (91.4% of the symptomatic patients) was performed at the discretion of the investigator in the ACE trial and 2.9% of the symptomatic patients had a previous endarterectomy. The analyses in the present study were, thus, restricted to the 1148 symptomatic ACE patients who had angiography and no previous CE.

Study Outcomes

For the present study, the 30-day perioperative risk of stroke and death by gender was assessed by combining data from the 1415 NASCET patients in the surgical arm who proceeded to the operating room with the 1148 symptomatic ACE patients. Long-term benefit of CE was assessed only in NASCET patients. In the ACE trial, patients were followed-up for only 3 months; therefore, no long-term data were available.

In 1991 the Stroke Prognosis Instrument (SPI-I) was developed for identifying groups of patients with a recent transient ischemic attack or nondisabling ischemic stroke who are at increased risk for stroke or death. Further refinements were added by introducing new predictive variables, and the SPI-II was tested successfully for external validity and transportability. Seven predictive factors were identified and assigned a point value ranging from 1 to 3 determined by its predictive importance. One factor, congestive heart failure with a point value of 3, is not appropriate in the NASCET, because patients with serious cardiac disorders were excluded from the trial. To retain the 7-factor construct of the SPI-II, the present study substituted this factor by assigning a hemispheric index event (not retinal) a value of 3. This substitution was reasonable because recent studies have reported magnitudes of relative stroke risk for a hemispheric index event similar to that of congestive heart failure in SPI-II. The other 6 factors were the same as those validated in SPI-II. Each patient’s total risk score was determined as the sum of the points for 7 factors: hemispheric (not retinal) index event (3 points), history of diabetes mellitus (3 points), stroke before the index event (3 points), age older than 70 years (2 points), stroke (not transient ischemic attack) as the index event (2 points), severe hypertension with systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg (1 point), and history of myocardial infarction or evidence of myocardial infarction on electrocardiogram (1 point).

In the present study, patients with 50% to 69% ICA stenosis were stratified into risk categories according to their total SPI-II score: 0 to 3 points as low risk, 4 to 7 as middle risk, and 8 to 15 as high risk. Additional intermediate, overlapping categories of 2 to 5 points and 6 to 11 points were added to provide finer gradations of the outcome results.

Statistical Analysis

The baseline characteristics of women and men were compared using chi-squared tests. The 5-year risks of any ischemic stroke ipsilateral to the symptomatic ICA stenosis in the medical and surgical groups were estimated by gender and degree of stenosis from Kaplan–Meier event-free survival curves. The Kaplan–Meier analyses also counted all strokes (in any territory) and all deaths (from any cause) that occurred during the 30-day perioperative period in the surgical arm. All strokes and all deaths were counted during a comparable 32-day period after randomization in the patients in the medical arm, because the median time from randomization to CE in the surgical arm was 2 days. The present study was an on-treatment analysis. Patients who changed treatment group during follow-up were censored at the date of crossover.

Differences in event-free survival between groups were assessed for statistical significance by the log-rank test. The benefit of CE was reported in terms of the absolute reduction of the risk (ARR) of ipsilateral stroke. The number of patients who would need to be treated with CE to prevent 1 additional ipsilateral stroke within 5 years after the procedure was calculated and referred to as the number needed to treat. Cox proportional hazards regression was used to assess whether the relationship between the risk of stroke and gender was confounded by other risk factors. Adjusted hazard ratios (interpreted as relative risks) with corresponding 95% confidence intervals were used to report the results. Tests of heterogeneity using Cox regression were also performed to assess the statistical significance of treatment effects between genders and among total risk score categories.

Results

The baseline characteristics of the 1208 women and 2825 men are shown after aggregation of 335 women and 813 men in ACE with 873 women and 2012 men in the NASCET (Table 1).
Combining the data from the 2 trials, the mean age was 66.4 years in women and 66.5 years in men. The severity of ICA stenosis was virtually identical between women and men. Several significant differences were observed between women and men. Women were more likely than men to be obese, to be current smokers, to have a history of hypertension, and to have a history of hyperlipidemia. However, women had less widespread manifest atherosclerotic disease as evidenced by a lower frequency of previous stroke, previous myocardial infarction, intermittent claudication, ICA plaque ulceration, brain infarct on imaging, and contralateral ICA occlusion.

Perioperative Risk of Stroke and Death
The 30-day risk of death from the NASCET and ACE trials combined (Table 2) was higher for women than for men (2.3% versus 0.8%, \( P = 0.002 \)). This was primarily because of a higher risk of fatal stroke in women. The 30-day risk of any stroke and any death was also higher for women than for men (2.9% versus 1.9%, \( P = 0.10 \)). Disabling or fatal stroke had no benefit from CE because women had a lower risk of stroke than men when they were treated medically. The 5-year absolute risk reduction of ipsilateral stroke within 5 years was 7 for women and 6 for men. There was no difference in absolute risk reduction between genders (test of heterogeneity \( P = 0.78 \)). The reduction of disabling or fatal ipsilateral ischemic stroke by CE for patients with \( \geq 70\% \) ICA stenosis was less in women than in men with a number needed to treat of 20 and 9, respectively (Table 3).

Women with 50% to 69% ICA stenosis, contrary to men, had no benefit from CE because women had a lower risk of stroke than men when they were treated medically. The 5-year absolute risk reduction of ipsilateral stroke was only 3.0% (\( P = 0.94 \)) in women compared with 10.0% (\( P = 0.02 \)) in men, corresponding to a 5-year number needed to treat of 33 and 10, respectively (Table 3). However, the test of heterogeneity to assess the difference in absolute risk reduction between genders was not statistically significant (\( P = 0.26 \)). For patients with <50% ICA stenosis, no benefit from CE was observed in men (ARR = 4.6%, \( P = 0.13 \)) or in women (ARR = 2.7%, \( P = 0.38 \)).

Analysis by Risk Factor Profile in Women and Men With 50% to 69% ICA Stenosis
Table 4 and Figure 2 show the risk of stroke and ARR by CE according to SPI-II risk score. An increased 5-year risk of ipsilateral ischemic stroke was related to a higher SPI-II total risk score in medically treated women and men with 50% to 69% ICA stenosis. However, medically treated women with low SPI-II scores, 0 to 3 or 2 to 5, were at low risk for stroke (0.0% and 6.3%, respectively), whereas men with the same SPI-II scores had several times the risk of stroke (18.5% and 19.2%, respectively). Men generally had some benefit from CE regardless of the total risk score, with the benefit increasing with a higher risk score (\( P = 0.42 \) for the test of heterogeneity of absolute risk reductions among men’s risk score categories). Only 29.0% of the women with 50% to 69% stenosis were in the uppermost category (total score of

### Table 2. 30-Day Risks (%) of Perioperative Stroke and Death and of Cause of Death for the NASCET and ACE Trials Combined

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Women (n=753)</th>
<th>Men (n=1810)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke and any death</td>
<td>7.6</td>
<td>5.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Disabling or fatal stroke and any death</td>
<td>2.9</td>
<td>1.9</td>
<td>0.10</td>
</tr>
<tr>
<td>Disabling or fatal stroke</td>
<td>2.1</td>
<td>1.5</td>
<td>0.26</td>
</tr>
<tr>
<td>Any death</td>
<td>2.3</td>
<td>0.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Cause of Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.5</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Cardiac*</td>
<td>0.4</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Other vascular</td>
<td>0.4</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Nonvascular</td>
<td>0.0</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

*Causes of cardiac death included myocardial infarction, other ischemic heart disease, congestive heart failure, and sudden death.

Among medically treated patients with 50% to 69% ICA stenosis, women had a lower risk of ipsilateral stroke than men (16.1% versus 25.3%, \( P = 0.03 \)). After adjusting for all baseline characteristics listed in Table 1 in a Cox regression analysis, the hazard of ipsilateral stroke was 1.8 (95% CI, 1.0 to 3.4) times higher in men than in women with 50% to 69% ICA stenosis. Among patients with <50% ICA stenosis, the risk of ipsilateral stroke in women and men was similar (14.9% versus 18.7%, \( P = 0.46 \)).

Women with \( \geq 70\% \) ICA stenosis benefited from CE in preventing an ipsilateral ischemic stroke (Table 3). Women and men had similar benefits with an absolute risk reduction of 15.1% (\( P = 0.007 \)) and 17.3% (\( P < 0.001 \)), respectively. The number needed to treat by CE to prevent 1 additional ipsilateral stroke within 5 years was 7 for women and 6 for men. There was no difference in absolute risk reduction between genders (test of heterogeneity \( P = 0.78 \)). The reduction of disabling or fatal ipsilateral ischemic stroke by CE for patients with \( \geq 70\% \) ICA stenosis was less in women than in men with a number needed to treat of 20 and 9, respectively (Table 3).

Long-Term Benefit of Endarterectomy
The 5-year risks of ipsilateral ischemic stroke in medically treated women and men, according to degree of ICA stenosis, are shown in Figure 1 and Table 3. For medically treated patients with \( \geq 70\% \) stenosis, the risk of ipsilateral stroke was similar in women and men (28.9% versus 29.8%, \( P = 0.42 \)). Among medically treated patients with 50% to 69% ICA stenosis, women had a lower risk of ipsilateral stroke than men (16.1% versus 25.3%, \( P = 0.03 \)). After adjusting for all baseline characteristics listed in Table 1 in a Cox regression analysis, the hazard of ipsilateral stroke was 1.8 (95% CI, 1.0 to 3.4) times higher in men than in women with 50% to 69% ICA stenosis. Among patients with <50% ICA stenosis, the risk of ipsilateral stroke in women and men was similar (14.9% versus 18.7%, \( P = 0.46 \)).

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8 to 15) and had a reasonable amount of benefit from CE (ARR=8.9%), although not statistically significant. For the other 71.0% of the women with lower risk scores, CE was either of marginal or no benefit.

**Discussion**

The present study is the first report that specifically focused on assessing the benefit of CE in women with symptomatic ICA disease. All women and men with ≥70% ICA stenosis benefited from CE in preventing a stroke of any severity. Only 7 women or 6 men were needed to undergo CE to prevent 1 additional ipsilateral ischemic stroke within a 5-year period. Because the benefit of CE was less for patients with 50% to 69% ICA stenosis, a risk factor scale was used to stratify the efficacy of CE. The patients’ risk factor profile had a major role in determining the level of benefit for patients with 50% to 69% ICA stenosis, more so in women than in men. Patients of both genders with ≥50% ICA stenosis did not benefit from CE.

The perioperative risk of death was significantly twice as high in women than in men. The perioperative risk of stroke and death was also higher in women (7.6%) than in men.
In conclusion, women with $\geq 70\%$ symptomatic ICA stenosis had similar long-term benefit from CE to that of men, although the perioperative risks were higher for women. For the majority of women with $50\%$ to $69\%$ ICA stenosis, CE was of no benefit. The present study identified a small percentage of women with $50\%$ to $69\%$ stenosis and a high risk factor profile who were at a higher risk for stroke and had a greater chance of benefit.

Acknowledgments

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References

15. Hansen F, Mangell B, Sonesson B, Lanne T. Diameter and compliance in women with 50% to 69% internal carotid artery stenosis according to gender and total SPI-II risk score. The number of patients at risk is shown below each bar. The Kaplan–Meier risk estimates are shown above the bars.

Several important limitations need to be considered to interpret the present study. First, the findings resulted from a subgroup analysis. However, in accordance with published guidelines, the subgroups examined were defined by a baseline characteristic that could not be affected by the treatment.17,18 Furthermore, the outcomes were identified in the design of the trial and patients were prospectively followed-up. Second, the test for heterogeneity of CE profiles across risk-factor profiles did not reach statistical significance. Nonetheless, the results support the principle that patients with lower risk factor profiles were less likely to benefit from CE than those with higher risk factor profiles. Third, different randomized trials, NASCET and ACE, were combined to estimate the perioperative risk. However, most of the trial centers participated in both. Moreover, the same methods of selecting surgeons and patients were used in both trials, and the perioperative outcomes were identically assessed. Combining 2 cohorts of patients provided more statistical power to examine perioperative risks of CE. Finally, patients enrolled in the NASCET and ACE trials were operated on by surgeons expert in CE, chosen because they had a perioperative stroke and death rate of $<6\%$. The benefit of CE, contingent on a low perioperative stroke and death rate, can only be achieved by selecting patients who have no serious comorbid conditions.
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