Benefit of carotid endarterectomy for symptomatic and asymptomatic severe carotid artery stenosis: a Markov model based on data from randomized controlled trials

Clinical article

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Object. Several major randomized controlled trials of carotid endarterectomy (CEA) in patients with both symptomatic and asymptomatic carotid artery stenosis have addressed the net effects of CEA on the risk of stroke. However, because the risk of stroke among patients with asymptomatic carotid stenosis is relatively low, whether to treat their stenosis with CEA remains an important public health issue.

Methods. The authors constructed a Markov model to evaluate the effectiveness of CEA. In modeling 4 health states, the probability of transition to another state was estimated using data from major randomized controlled trials. Adopting 3 comorbidity index values for baseline analyses, the authors expressed outcomes in terms of the expected number of quality-adjusted life years (QALYs) for a hypothetical cohort undergoing CEA and another without treatment.

Results. In the authors’ baseline analysis, CEA for asymptomatic stenosis yielded a very small benefit (0.07 QALY) for 70-year-old, normal-risk CEA candidates. Benefits decreased further, often becoming negative, as patient age, surgical risk, or comorbidity index increased. In patients with symptomatic stenosis, CEA was always more effective than conservative management, even considering variables such as comorbidities limiting life expectancy, advanced age, and increased perioperative risk.

Conclusions. Carotid endarterectomy for severe carotid stenosis consistently and significantly benefits patients with recent symptoms. However, surgery for asymptomatic stenosis appears justified only in carefully selected conditions: low treatment risks in relatively young individuals without any comorbidities.

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KEY WORDS • carotid stenosis • carotid endarterectomy • Markov model

Several major RCTs of CEA in both symptomatic and asymptomatic patients have considered the net effects of CEA on the risk of a major stroke.13,14,18,29 Pooled analysis of data from these major trials have confirmed substantial benefit from CEA for severe CA stenosis in patients who manifested symptoms within a preceding 6-month period.31 Carotid endarterectomy could provide an absolute reduction of 11–17% in the risk of stroke within 2–3 years in patients with symptomatic severe stenosis.13,29

Publication of the ACAS14 in 1995 was followed by a large increase in the number of CEA procedures performed in the United States.11,21 The authors of several subsequently published guidelines have recommended clinical implementation of such prophylactic surgery.4,15,17 Additional information concerning the optimal management of asymptomatic stenosis was provided by a recent large study performed in Europe.18 The 2 randomized studies (the ACAS and the European study) revealed small but significant absolute reductions in the risk of stroke at 5 years (5.4–5.9%).14,18 However, because the risk of stroke in patients with asymptomatic carotid stenosis is relatively low, CEA may be only marginally effective for decreasing risk in these patients. Therefore, the question of whether to perform CEA in patients with asymptomatic severe CA stenosis remains an important public health issue. In the medical literature, prophylactic endarterectomy has been recommended only in limited circumstances.19,23,30

In the present study, we sought to determine the conditions in which CEA is beneficial for severe CA stenosis in patients with and without symptoms, construct a mathematical model of the natural history of CA stenosis...
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compatible with major RCT and the natural history data, and then use the model to quantify the benefit of prophylactic CEA.

Methods

Markov Model

We constructed a Markov model\textsuperscript{10,32} to evaluate the effectiveness of CEA in patients with carotid stenosis (Fig. 1). The hypothetical cohort of patients was asymptomatic or recently symptomatic, with the symptomatic episode being a transient ischemic attack or nondisabling stroke within the previous 6 months. Analysis was conducted using currently available data from several RCTs\textsuperscript{13,14,18,29} and their pooled analysis.\textsuperscript{31}

After diagnosis and initial treatment, the Markov model was used to track long-term prognosis in patients with carotid stenosis. Our Markov model involved a specified set of mutually exclusive and exhaustive health states among which existed transition probabilities of moving (or not moving) from 1 state to another. We modeled 4 health states: “well with stenosis,” “well without stenosis,” “poststroke,” and “dead.” The analysis was continued until all individuals in the hypothetical cohort died of stroke or another cause.

During a yearly cycle, healthy patients (“well with

![Diagram of the Markov model. Prophylactic treatment for severe CA stenosis (upper), and the model for patients with asymptomatic (middle) and symptomatic (lower) carotid stenosis are shown. s = surgical risk.](image-url)
stenosis” and “well without stenosis”) might survive with or without stroke, or die of causes other than stroke. The stroke ratio for conservatively treated patients with recently symptomatic stenosis has been shown to be high during the early period and then decline gradually.\textsuperscript{13,29} Based on a recent pooled analysis, we estimated the risk of stroke (q) in patients with symptomatic severe stenosis to be 16% in the first year, 8% in the second, 5% in the third, and then to remain at 1.7% for each subsequent year.\textsuperscript{31} The rate of stroke after surgery for symptomatic stenosis was assumed to be 2.3%.\textsuperscript{31} Based on recent RCT data in patients with asymptomatic carotid stenosis,\textsuperscript{18} we assumed that these patients incur stroke at a constant rate: 2.2% without surgery, and 1.0% after surgery per year. During a yearly cycle, patients in the poststroke state might survive or die. For simplicity, patients were assumed to retain the same death rate and to maintain the same level of functioning until they died. We also estimated that the mortality rate after stroke would be 20%, and that the survivors (80%) would sustain disability. Transient ischemic attacks or minor strokes without disability were not included in our analysis.

### Annual Death Rate in Patients With Carotid Stenosis

The hazard function \( P'(x) \), namely the annual death rate of the general population at age \( x \), closely approximates an exponential function.\textsuperscript{4} By regression analysis of death rates for each age group obtained from Japanese Life Statistics data, the following approximation was obtained:\textsuperscript{9,36,37}

\[
P'(x) = e^{-10.58 + 0.095x}
\]

However, patients with CA stenosis may experience an excess cardiovascular mortality rate compared to the general population, and results were expected to be influenced by the survival rate in each cohort. We therefore altered the formula so that the mortality rate in the general population was multiplied by a comorbidity index, \( c \):

\[
P(x) = c \times e^{-10.58+0.095x}
\]

We then assigned 3 different values to the comorbidity index in our baseline analyses: first analysis (\( c = 1 \); normal life expectancy in the general population), second analysis (\( c = 2 \); reduced life expectancy in a population with carotid stenosis corresponding to normal-risk CEA candidates) and third analysis (\( c = 3 \); excessively reduced life expectancy in a population with carotid stenosis representing high-risk CEA candidates). When the 3 corresponding survival curves were plotted (Fig. 2), the curve for the second analysis corresponded well with recently reported results of a population-based survival study in patients who underwent CEA.\textsuperscript{25} Annual death rates were assumed to be equal for both the surgical and medical arms of the study after the first month (accounting for the initial 30-day operative mortality rate) because CEA cannot be expected to influence the long-term risks of dying of causes other than stroke.

### Treatment for CA Stenosis

Individuals in the treatment cohort were considered to have undergone CEA at the beginning of the first cycle. They then might die perioperatively (dead), survive with neurological deficits (poststroke state), or survive with normal neurological function (well without stenosis). We also assumed that restenosis of the CA would never occur after treatment. We assumed in the baseline analysis that the treatment-related combined mortality and morbidity rate was 3.0%, with 20% of affected patients dying, and the remaining 80% surviving with disability.
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Quality-Adjusted Life Years Values

We expressed the outcome of each treatment strategy in terms of the expected number of QALYs gained. To establish this number, we assigned a QALY weight score ranging between 0.00 and 1.00 to each of the different health states in the model. By convention, death was assigned a value of 0. According to previous decision analysis, we assign a value of 0.60 to survival with a posttreatment or poststroke neurological deficit. Normal function with or without carotid stenosis was assigned a value of 1.00.

Both stroke and treatment complications have more impact on lifetime QALYs if they occur earlier. To incorporate this factor, age-sensitive values for QALY were calculated by discounting the original values at the rate of 3% per year in the baseline analysis. Lifetime QALY equaled the sum of the number of years spent in each health state after each had been multiplied by the QALY weight associated with that state. We then calculated the expected benefit associated with treatment as QALY gain: treatment benefit = (expected QALY with immediate CEA) – (expected QALY without CEA).

Sensitivity Analysis

A sensitivity analysis was performed by altering the input values for individual variables within a clinically reasonable range to assess the effects of uncertainties in the assumptions made in the baseline analyses. Ranges of variables tested included stroke ratio in asymptomatic patients who were well with stenosis, 1.5–2.9%; stroke ratio in asymptomatic patients who were well without stenosis, 0.7–1.3%; stroke ratio in symptomatic patients who were well with stenosis, 0.7 × q% to 1.3 × q%; stroke ratio in symptomatic patients who were well without stenosis, 1.6–2.9%; risk of CEA, 1–10%; patient age, 60–80 years; discount rate, 0–7% per year; and QALY value for a poststroke state, 0.3–0.9.

Results

Asymptomatic Carotid Stenosis

Using our assumptions, we obtained a mathematical model compatible with RCT data, and the benefits of CEA were quantified (Fig. 3). In general, benefits obtained from CEA in patients with asymptomatic stenosis were small and often negative. In our baseline analysis in 70-year-old patients (surgical risk of 3%), treatment for carotid stenosis obtained an additional 0.38, 0.31, and 0.26 QALYs in the first (c = 1), second (c = 2), and third (c = 3) analyses, respectively. The relationship between surgical risks and QALY gain in each year population is shown in Fig. 3. Younger age was related to a larger QALY gain. Even in elderly patients, QALY gains were relatively resistant to surgical risks. In symptomatic patients, QALY gains from CEA remained positive despite an increased comorbidity index (Fig. 4). In all situations, treatment for asymptomatic stenosis was more effective than a conservative management strategy, except when perioperative risk was excessively high.

In our sensitivity analysis, we examined additional factors that might make prophylactic treatment more or less beneficial (Table 1, lower portion). Treatment risk, risk of stroke without surgery, and assigned QALY values for poststroke patients were significant factors for QALY gain from surgery, while the benefit was stable when other variables were considered.

Discussion

Carotid endarterectomy for asymptomatic stenosis has been the focus of many reports and trials during the past decade. The authors of large RCTs have demonstrated a net benefit of CEA beyond that of the best medical treatment. In the ACAS, the absolute risk reduction for stroke or death after 5 years was estimated to be 5.9%. While in the Asymptomatic Carotid Surgery Trial the estimated reduction was 5.4%. Therefore, long-term survival after CEA for asymptomatic stenosis is an important consideration when deciding whether to perform this prophylactic procedure. Moreover, the clinical situation is more complicated than in a simple stroke-risk versus treatment-risk analysis. We used a Markov model to address this problem. Markov modeling permits an increase in the complexity of the model, such as incorporating stroke rate in patients with or without CEA, surgical risk, or the long-term survival rate of “CEA candidates.” Our findings indicated that decreased survival rates resulted in smaller benefits from CEA.

Several natural history studies in patients with asymptomatic carotid stenosis have demonstrated decreased 5- and 10-year survival rates compared with the general population (Table 2). Patients included in most of these patients who did not have surgery had large effects on the results, especially in the first analysis, while the influence of stroke rate after surgery was relatively small. The risks associated with prophylactic CEA had significant effects on the results in all analyses. Age and the discounting ratio also had some influence on QALY gain in the first analysis: older patients and a high discount ratio favored treatment less. Assigned QALY values for poststroke patients had little impact on the results in any analysis.

Symptomatic Carotid Stenosis

In the baseline analysis for symptomatic stenosis, surgery produced a relatively large QALY gain. Treatment for carotid stenosis obtained an additional 0.38, 0.31, and 0.26 QALYs in the first (c = 1), second (c = 2), and third (c = 3) analyses, respectively. In the second analysis, treatment proved to be less beneficial (Table 1, lower portion). Treatment risk, risk of stroke without surgery, and assigned QALY values for poststroke patients were significant factors for QALY gain from surgery, while the benefit was stable when other variables were considered.
studies had a mean age of 70 years or slightly less, demonstrating high 5- and 10-year mortality rates. In a recent population-based study from Sweden, half of patients (mean age 70 years) who underwent CEA for either symptomatic or asymptomatic carotid stenosis were dead after 10 years.25 On the other hand, the average life expectancy after 70 years in Sweden was 13.7 years for men and 16.5 years for women.25 These findings caused some concern about the long-term overall benefit from this increasingly performed prophylactic procedure. Similar longevity was reported in patients who underwent surgery for vascular diseases at other anatomical sites: the authors of a published series concerning revascularization for peripheral artery disease with claudication reported a
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10-year survival of 54%,24 and in another study concerning elective repair of an infrarenal aortic aneurysm, the overall survival was 75 and 45% at 5 and 10 years, respectively.20 Clearly, these patients represented a select group likely to have multifocal atherosclerotic complications capable of influencing long-term survival.

Sensitivity analyses of the asymptomatic cohort provided further insights into clinical applicability of CEA. Age had significant effects on the results, with younger age usually favoring treatment, and CEA in elderly patients producing a very limited or often negative benefit. The discount rate also was influential: at higher discount rates, a treatment strategy with early risks (CEA) and delayed benefits (stroke prevention) was less favored. On the other hand, CEA would be preferable at a lower discount rate. As expected, the assumed stroke risk in patients without CEA was a significant factor for benefit from treatment.

Surgical risks were also critical to the results. If surgical risk in patients with asymptomatic stenosis exceeded 5%, the treatment strategy resulted in harm to normal risk CEA candidates—reflecting the relatively low risk of stroke in patients without surgery. Thus far, perioperative stroke or death rates of 2.3 to 6.9%, respectively, have been reported in asymptomatic patients.8,14,28,34 Because these estimates closely approach the threshold for causing harm, ongoing audits of achieved results outside the trial setting is necessary in every center that offers surgery to asymptomatic patients.

In contrast, sensitivity analysis in symptomatic stenosis showed robustness of our results in the presence of parameter variation within clinically plausible ranges. Irrespective of comorbidities limiting life expectancy, as well as advanced age, patients with symptomatic stenosis were deemed to be operative candidates for CEA. Although increased perioperative risk was observed in patients with

TABLE 1: Input values and sensitivity analyses for selected variables in patients with severe carotid stenosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Input Value</th>
<th>Sensitivity Analysis (QALY gain)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (best ~ worst)</td>
<td>First Analysis (c = 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline (best ~ worst)</td>
</tr>
<tr>
<td>asymptomatic cohorts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stroke rate: “well w/ stenosis” (%)</td>
<td>2.2 (2.9 ~ 1.5)</td>
<td>0.16 (0.47 ~ −0.16)</td>
</tr>
<tr>
<td>stroke rate: “well w/o stenosis” (%)</td>
<td>1.0 (0.7 ~ 1.3)</td>
<td>0.16 (0.30 ~ 0.02)</td>
</tr>
<tr>
<td>tx risks of CEA (%)</td>
<td>3 (1 ~ 10)</td>
<td>0.16 (0.28 ~ −0.27)</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>70 (60 ~ 80)</td>
<td>0.16 (0.34 ~ 0.04)</td>
</tr>
<tr>
<td>discount rate (%)</td>
<td>3 (0 ~ 7)</td>
<td>0.16 (0.27 ~ 0.08)</td>
</tr>
<tr>
<td>poststroke QALY</td>
<td>0.6 (0.3 ~ 0.9)</td>
<td>0.16 (0.33 ~ −0.02)</td>
</tr>
<tr>
<td>symptomatic cohorts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stroke rate: “well w stenosis” (%)</td>
<td>2.3 (1.6 ~ 2.9)</td>
<td>0.38 (0.70 ~ 0.05)</td>
</tr>
<tr>
<td>stroke rate: “well w/o stenosis” (%)</td>
<td>1.0 (1.3 ~ 0.7) × q</td>
<td>0.38 (0.57 ~ 0.23)</td>
</tr>
<tr>
<td>tx risks of CEA (%)</td>
<td>2.3 (1 ~ 10)</td>
<td>0.38 (0.50 ~ −0.02)</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>70 (60 ~ 80)</td>
<td>0.38 (0.45 ~ 0.28)</td>
</tr>
<tr>
<td>discount rate (%)</td>
<td>3 (0 ~ 7)</td>
<td>0.38 (0.48 ~ 0.29)</td>
</tr>
<tr>
<td>poststroke QALY</td>
<td>0.6 (0.3 ~ 0.9)</td>
<td>0.38 (0.73 ~ 0.04)</td>
</tr>
</tbody>
</table>

* q = 16% in the first, 8% in the second, 5% in the third year, and 1.7% per year thereafter.

TABLE 2: Five- and 10-year survival rates after CEA in the literature

<table>
<thead>
<tr>
<th>Authors &amp; Yr</th>
<th>No. of Patients</th>
<th>Mean Age (yrs)</th>
<th>% 5-Yr Survival</th>
<th>% 10-Yr Survival</th>
<th>Stenosis (symptomatic or asymptomatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branchereau et al., 1998</td>
<td>312</td>
<td>70</td>
<td>75</td>
<td>59</td>
<td>asymptomatic</td>
</tr>
<tr>
<td>Cao et al., 1999</td>
<td>301</td>
<td>67</td>
<td>?</td>
<td>66</td>
<td>asymptomatic</td>
</tr>
<tr>
<td>Inzitari et al., 2000</td>
<td>1820</td>
<td>66</td>
<td>82</td>
<td>?</td>
<td>asymptomatic w/ contralateral symptoms</td>
</tr>
<tr>
<td>AbuRahma et al., 2003</td>
<td>82</td>
<td>66</td>
<td>83</td>
<td>67</td>
<td>asymptomatic w/ contralateral occlusion</td>
</tr>
<tr>
<td>LaMuraglia et al., 2004</td>
<td>1897</td>
<td>70</td>
<td>72</td>
<td>45</td>
<td>asymptomatic (64%) &amp; symptomatic (36%)</td>
</tr>
<tr>
<td>Kragsterman et al., 2006</td>
<td>631</td>
<td>70</td>
<td>78</td>
<td>46</td>
<td>asymptomatic</td>
</tr>
<tr>
<td></td>
<td>5177</td>
<td>70</td>
<td>81</td>
<td>54</td>
<td>symptomatic</td>
</tr>
</tbody>
</table>

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symptomatic stenosis, CEA may nonetheless be beneficial in the long term.  

Study limitations undoubtedly restrict applicability of our model. To construct the mathematical model, we made several simplifying assumptions that should be reviewed carefully regarding reliability and validity. First, we assumed that restenosis of a CA would never occur after treatment. Although restenosis after CEA has been reported to occur in 18% of patients over a 5-year period,1 long-term follow-up studies of the durability of CEA still are needed. We postulated that because effects caused by restenosis would be reflected by data from RCTs, independent consideration of this factor would have little influence on our results.

Second, we assumed for simplicity that patients in a poststroke state would retain the same death rate and level of functioning until they died. Although a disabled patient actually would have greater risk of premature death than the general population, data concerning the death rate in these patients are extremely limited. Therefore, any attempt to incorporate this factor would have been counterproductive because of relatively large errors in estimation.

The authors of multiple clinical series have reported less invasive interventional techniques such as CAS to be comparable alternatives to CEA. With technical refinements in CAS, several prospective RCTs have compared CAS with CEA, with varied results.27,33,35 Although the “Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis”27 and “Stent-Pro tected Angioplasty versus Carotid Endarterectomy”33 trials failed to show noninferiority of CAS to CEA in normal-risk symptomatic patients, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial,35 which specifically focused on patients, either symptomatic or asymptomatic, who were at a high risk because of comorbidities (severe coronary disease, chronic obstructive pulmonary disease, or renal disease) or advanced age, found CAS not to be inferior (and probably superior) to CEA in this population. Our study indeed indicated that CEA might not be effective in these patients. Because cholesterol-lowering drugs have been shown to reduce the incidence of stroke among patients at increased risk for cardiovascular disease,3 our results suggest a need for further RCTs in high-risk patients, comparing CAS with medical treatment rather than with CEA.

**Conclusions**

Under the assumptions of our mathematical model, prophylactic surgery for severe CA stenosis consistently yielded a benefit in patients with symptoms occurring within a 6-month period before the procedure. Surgery for asymptomatic stenosis, however, is not likely to have a large impact on the burden of stroke. The benefit of CEA for such patients is only marginal and is rapidly lost because of the increased rate of surgical complications, advanced age, and comorbidities. Nonetheless, our results suggest that there exist conditions under which CEA for asymptomatic severe stenosis might offer benefits, as low treatment risks in relatively young patients without comorbidities might justify intervention.

**Disclaimer**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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