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Efficacy versus Effectiveness of Carotid Endarterectomy

CONTEXT. Several well-known clinical trials have demonstrated that the value of carotid endarterectomy depends on preoperative symptoms and the degree of carotid artery stenosis. The benefit of surgery also depends on how the results of these clinical trials (defining the *efficacy* of carotid endarterectomy) are applied to actual clinical practice (the *effectiveness* of the procedure), where surgical risks are greater.

COUNT. The number of carotid endarterectomies needed to prevent one major stroke or death—that is, the number needed to treat (NNT).

CALCULATION. Reciprocal of the difference between the 5-year cumulative incidence of major stroke or death with medical therapy and the 5-year cumulative incidence of major stroke or death with carotid endarterectomy.

DATA SOURCES. Efficacy was calculated with data from the North American Symptomatic Carotid Endarterectomy Trials and the Asymptomatic Carotid Atherosclerosis Study. In calculating effectiveness, we accounted for increased surgical mortality rates reported in population-based studies.

RESULTS. For symptomatic patients, the NNT predicted by the effectiveness model differed little from that estimated by the efficacy model (10 versus 9 for severe carotid stenosis and 29 versus 23 for moderate carotid stenosis). However, the NNT predicted by the effectiveness model was substantially higher than that predicted by the efficacy model for patients with asymptomatic severe stenosis (63 versus 38).

CONCLUSIONS. In symptomatic patients, carotid endarterectomy is both efficacious and effective for severe and (to a lesser extent) moderate carotid stenosis. However, in asymptomatic patients, the benefits observed in published trials may overestimate those likely to be achieved in clinical practice.

Accumulating evidence from randomized, controlled trials shows that carotid endarterectomy reduces the risk for stroke in many patients with carotid artery stenosis.[1–6] In 1991, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) was terminated early because it found substantially lower stroke rates in patients who received surgical treatment for severe carotid stenosis.[5] In 1995, the Asymptomatic Carotid Atherosclerosis Study (ACAS) demonstrated more modest reductions in rates of stroke in asymptomatic patients with carotid stenosis.[2] Similarly modest reductions in symptomatic patients with moderate carotid stenosis were published recently by the NASCET investigators.[6] In response to this accumulating evidence, rates of carotid endarterectomy have more than doubled since 1990.[7, 8]

Despite increasing information about the efficacy of carotid endarterectomy, decision making about this procedure remains difficult. First, the benefits of the procedure vary widely across subgroups of patients. Second, the benefits seen in carefully controlled trials (defining the *efficacy* of the procedure) may not reflect those achieved in clinical practice (the *effectiveness* of the procedure). Patients in the community who undergo carotid endarterectomy are substantially older and have more comorbid conditions than the trial participants.[9, 10] In addition, the trials included

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only surgeons and hospitals with high procedure volumes and low complication rates with carotid endarterectomy.[11, 12] Because of these differences in patient selection and provider performance, surgical risks in community settings are substantially higher than those in trials.[9, 13]

To help clinicians assess the relative benefits of carotid endarterectomy, we calculated the number of operations needed to prevent one major stroke or death (i.e., the number needed to treat [NNT][14]) in asymptomatic and symptomatic patients with varying degrees of carotid stenosis. To examine efficacy, we calculated the NNT by using data from ACAS and NASCET. To estimate effectiveness under real-world conditions, we used surgical mortality risks likely to be encountered in clinical practice.

Methods

Calculation of the Number Needed To Treat

To measure the efficacy and effectiveness of carotid endarterectomy in different settings, we estimated the number of procedures needed to prevent one major stroke or death. A major stroke was defined as any stroke with disabling or permanent sequelae. To keep the focus of our analysis on those outcomes that are most important to both patients and clinicians, we did not include minor or transient strokes. Because rates of contralateral stroke are unaffected by surgery, we included only ipsilateral strokes. In counting deaths, we included those from surgery or stroke but excluded those from other causes. As shown in **Figure 1**, the NNT was calculated by taking the reciprocal of the absolute difference between the 5-year cumulative incidence of these events with medical therapy and the 5-year cumulative incidence of these events with carotid endarterectomy.

$$\text{Number Needed To Treat (NNT)} = \frac{1}{\text{Event Incidence (No Surgery)} - \text{Event Incidence (Surgery)}}$$

Example:

5-yr cumulative incidence of major stroke or death in patients with symptomatic severe stenosis

No surgery ≈ 15.7%

Surgery ≈ 5.1%

$$NNT \approx \frac{1}{(0.157 - 0.051)} \approx \frac{1}{0.106} \approx 9$$

FIGURE 1. "Back-of-the-envelope" calculation of the number of carotid endarterectomies needed to prevent one major stroke or death.

Efficacy

To estimate efficacy, we used cumulative event rates reported by NASCET (symptomatic patients) and ACAS (asymptomatic patients). For symptomatic patients, efficacy was stratified according to the severity of carotid stenosis (moderate stenosis, 50% to 69%; severe stenosis, 70% to 99%), as defined in the published trials.[5, 6]

Both the ACAS and the NASCET study that involved patients with moderate carotid stenosis reported 5-year event probabilities. The NASCET study that involved symptomatic patients with severe carotid stenosis was terminated early because high rates of stroke were seen in the patients receiving medical treatment. To facilitate comparisons between NNTs for these patients and for other patient subgroups, we extrapolated 2-year stroke probabilities reported by NASCET to 5-year estimates. In making this extrapolation, we assumed that the major stroke rate was the same (0.8% per year) with medical and surgical treatment after 2 years, as seen in the recently published NASCET data.[6]

Effectiveness

Because patients and hospitals were highly selected, surgical mortality rates (death from surgery was defined as any death within 30 days of operation) in the trials were low. Participants in ACAS had a surgical mortality rate of only 0.4% (0.1% if deaths from angiography are excluded). Surgical mortality rates for NASCET participants were 1.2% and 0.6% in the studies of moderate and severe stenosis, respectively. For estimates of NNT produced by the effectiveness model, we assumed an additional surgical risk for death of 1%, based on a population-based study of Medicare patients that compared surgical mortality rates at trial hospitals with surgical mortality rates at nontrial hospitals.[13] Because analogous studies of procedure-related risks for stroke are lacking, it is not known whether nonfatal complication rates are higher in clinical practice than in the trials. Thus, for both efficacy and effectiveness estimates of NNT, we use surgical stroke rates (any major stroke within 30 days of surgery) reported in the trials.

A full accounting of the NNT with carotid endarterectomy under real-world conditions must consider competing risks for death. Many patients undergoing carotid endarterectomy have substantial comorbid illness and high baseline mortality rates. As patients die from other causes, fewer patients are at risk for stroke. For this reason, actual stroke incidence would be somewhat lower than the trials suggest. Accounting for competing mortality risks in estimates of the NNT cannot be done on the "back of the envelope." The **Appendix** describes an approach to this calculation that is based on a decision analysis model.

Results

Efficacy

Based on data from the trials, the number of carotid endarterectomies needed to prevent one major stroke or death depends on whether patients have symptoms and on the severity of carotid stenosis. For example, the top of the right-hand column of **Table 1** contains the data needed to calculate the NNT for symptomatic patients with severe carotid stenosis. The 5-year cumulative incidence of major stroke or death is 15.7% without surgery and 5.1% with surgery. The reciprocal of the difference in risk (10.6%) is the NNT for this patient subgroup: nine procedures. The NNTs were higher for symptomatic patients with moderate stenosis (23 procedures) and asymptomatic patients with severe stenosis (38 procedures).

Effectiveness

The NNTs from the efficacy and effectiveness models differed little for patients with symptomatic severe carotid stenosis (9 versus 10 procedures). For these patients, projected differences in the 5-year incidence of major stroke or death in patients receiving surgery and patients receiving medical treatment remained relatively large (and, thus, the NNT remained relatively low) after surgical mortality rates were increased by 1%. However, NNTs from the efficacy and effectiveness models differed markedly for asymptomatic patients

TABLE 1.
Summary Estimates of Stroke Incidence in Patients with Carotid Artery Stenosis Treated with and without Surgery and of the Number of Procedures Needed To Prevent One Major Stroke or Death*

	PATIENT CHARACTERISTICS		
	ASYMPTOMATIC SEVERE STENOSIS	SYMPTOMATIC MODERATE STENOSIS	SYMPTOMATIC SEVERE STENOSIS
Efficacy			
5-year cumulative incidence of major stoke or death, %†			
No surgery	6.0	7.2	15.7
Surgery	3.4	2.8	5.1
Absolute difference, %	2.6	4.4	10.6
Number of procedures needed to prevent one major stroke or death	38	23	9
Effectiveness			
5-year cumulative incidence of major stoke or death, %†			
No surgery	6.0	7.2	15.7
Surgery	4.4	3.8	6.1
Absolute difference, %	1.6	3.4	9.6
Number of procedures needed to prevent one major stroke or death	63	29	10

**Efficacy estimates were derived directly from data published in the clinical trials; effectiveness estimates accounted for increased surgical mortality seen outside of the trials.*
†Only surgery and stroke-related deaths are included.

with severe stenosis (38 versus 63 procedures). For these patients, trial data suggested relatively narrow differences (2.6%) in the 5-year incidence of major stroke or death in patients receiving surgery and patients receiving medical treatment (**Table 1**). Increasing surgical mortality rates narrowed this gap still further (to 1.6%), increasing the NNTs substantially.

Figure 2 summarizes the efficacy and effectiveness of carotid endarterectomy for patients according to disease characteristics.

Discussion

Our analysis has two main findings. First, as is widely known from the clinical trials, carotid endarterectomy is most efficacious in symptomatic patients and patients with severe carotid stenosis. Thus, the number of procedures needed to prevent one major stroke or death is substantially higher in asymptomatic patients than in symptomatic patients with severe stenosis (38 versus 9 procedures). Among symptomatic patients, NNTs were higher for patients with moderate stenosis than for those with severe stenosis (23 versus 9 procedures).

Second, it is important to distinguish between the efficacy and the effectiveness of carotid endarterectomy, particularly in settings in which the therapeutic margin of surgery is relatively small. For asymptomatic patients with carotid stenosis (who now represent more than half of patients undergoing carotid endarterectomy[9,10]), increasing the surgical mortality rate by only 1.0% (from 0.4% in ACAS to 1.4% in clinical practice) nearly doubles the number of procedures needed to prevent one major stroke or death (from 38 to 63). Accounting for death from other causes (competing risks) further widens the gap between efficacy and effectiveness (**Appendix**). These issues are less important when the underlying benefit of carotid endarterectomy is sufficiently large, as it is in patients with symptomatic severe stenosis.

In assessing the relative benefits of carotid endarterectomy, we focused on the number of procedures needed to prevent one major stroke or death (NNT). We chose the NNT because it represents the magnitude of risk reduction in a clinically intuitive way (indicating how much effort and how many resources are needed to prevent a stroke) and its calculation is straightforward.[14] However, unlike more complex measures of benefit (e.g., quality-adjusted life-years gained), NNTs cannot be easily compared across interventions or diseases with different main outcomes. Also, no benchmark for a "reasonable" NNT has been defined. Nonetheless, the NNT was well suited to our primary goals of assessing the relative value of carotid endarterectomy in different settings and of comparing efficacy and effectiveness.

It is important to acknowledge several limitations in our NNT calculations. First, in our main analysis that described differences between efficacy and effectiveness, we considered only surgical mortality. In the real world, patients with carotid stenosis probably differ from trial patients in other ways. For example, they may have different risks for stroke with and without surgery. Because this issue has not been carefully explored, the magnitude and direction of this potential bias in our NNT calculations is difficult to predict. Second, our analysis was based entirely on data from ACAS and NASCET, two of the largest, most widely cited trials of carotid endarterectomy. The Veterans Affairs Cooperative Studies[3, 4] and the European Carotid Surgery Trial[1] reported lower reductions in risk for stroke with surgical treatment of carotid stenosis. The NNTs based on data from these trials would have been higher than those presented in our analysis. Third, we may not have considered all important patient subgroups. For example, data recently reported by NASCET indicate that the NNT is substantially higher for women than for men with symptomatic carotid stenosis.[6]

Finally, our simple calculation ignores some of the subtleties of clinical decision making. The event rates used are averages, reflecting aggregate data from carotid endarterectomy trials and the surgical mortality rate seen in the Medicare population as a whole. In practice, however, few patients are "average." Specific characteristics of individual patients influence the risk for stroke without surgery, the risks of surgery itself,

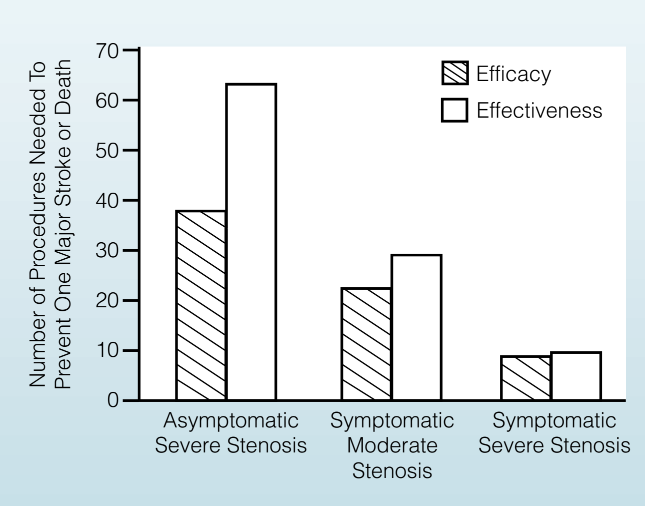

FIGURE 2. The number of carotid endarterectomy procedures needed to prevent one major stroke or death in patients with severe asymptomatic stenosis, moderate symptomatic stenosis, and severe symptomatic stenosis. Efficacy is calculated from trial data; effectiveness accounts for the higher surgical mortality rates likely to be encountered in clinical practice.

and the magnitude of competing risks. Unfortunately, the effect of each of these characteristics is not precisely known, and the net effect of these characteristics is not easily quantified. Our simple calculation, on the other hand, demonstrates the importance of one knowable variable: the surgical mortality rate. Clinicians should be aware of how local mortality rates after carotid endarterectomy compare with those reported in the trials. For asymptomatic patients in particular, even small increases can cause carotid endarterectomy to lose much of its value.

Take-Home Points

- **The efficacy of carotid endarterectomy in the prevention of stroke has been shown in large clinical trials.**
- **Surgical mortality rates are higher in clinical practice.**
- **We calculated the number of carotid endarterectomies needed to prevent one major stroke or death under trial conditions (*efficacy*) and real world conditions (*effectiveness*).**
- **For patients with asymptomatic carotid stenosis, the NNT was substantially higher under real world conditions than under trial conditions (63 versus 38).**
- **The difference between efficacy and effectiveness was less marked for patients with symptomatic stenosis.**
- **Decisions about carotid endarterectomy should be based on both patient characteristics and local rates of surgical mortality.**

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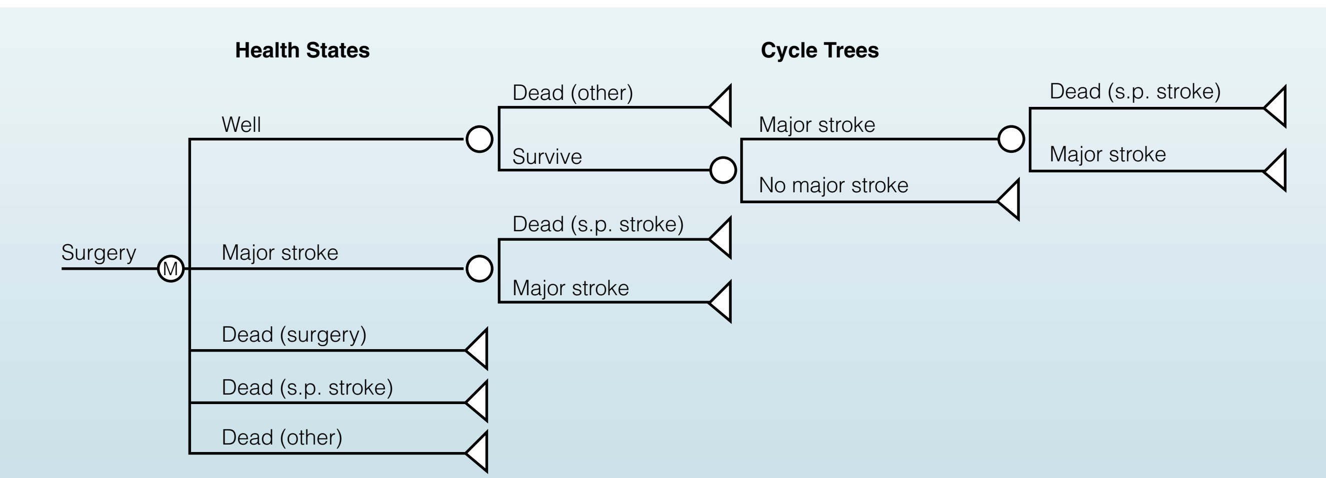
Appendix. Accounting for Death from Other Causes

A full accounting of the NNT with carotid endarterectomy under real-world conditions must include competing risks for death. In ACAS and NASCET, deaths not related to stroke or surgery were "censored" in the analysis of cumulative stroke incidence. Thus, the trials describe the probabilities of stroke that would be expected if patients could not die of other causes. However, real patients undergoing carotid endarterectomy have substantial comorbid illness and high baseline mortality rates. As patients die of other causes, fewer patients are at risk for stroke. For this reason, the actual stroke incidence would be somewhat lower than the trials suggest.

During calculation of the NNT with carotid endarterectomy, competing risks for death are also important because they do not affect medically treated patients and surgically treated patients equally. In medically treated patients, events occur gradually over time. As described above, the observed cumulative incidence of stroke will be reduced to the extent that patients die of other causes. With surgical treatment, however, most events occur immediately (at the time of surgery). Thus, the observed cumulative incidence of stroke will be relatively unaffected as patients subsequently die of other causes.

To account for competing risks for death, we used a Markov decision analysis model to simulate health outcomes experienced by large cohorts of identical, hypothetical patients with carotid stenosis receiving surgical or medical treatment.[15] In the surgical arm of the model (Appendix Figure), patients are initially distributed among the various health states according to estimated probabilities of perioperative stroke and death. With each subsequent "cycle" of the model, patients who are still alive are repeatedly exposed to risks for death and stroke, represented in the cycle trees. Patients experiencing these events make transitions to the appropriate health state. To calculate the 5-year cumulative incidence of major stroke or death, we let the model run for 60 one-month cycles and then added the proportion of patients in the health states "major stroke," "dead (surgery)," and "dead (s.p. [status post] stroke)." The medical arm of the model is similar but does not include the health state "dead (surgery)."

We increased the surgical mortality rates reported in the clinical trials by 1%. Risks for stroke were estimated directly from



APPENDIX FIGURE. Surgical arm of the Markov decision model used to account for competing risks for death in NNT calculations. s.p. = status post.

trial data. To calculate transition probabilities, we first converted the cumulative event probabilities (*P*Event at *t* years) reported in the trials to linearized annual rates (*r*) by using the logarithmic transformation

$$r = -\ln(1 - P\text{Event}) / t$$

We then converted annualized rates back to 1-month transition probabilities (*P*) by using the function

$$P = 1 - \exp(-r * 1/12)$$

Transition probabilities reflecting death from other causes were derived from age-specific mortality rates from U.S. Vital Statistics.[16] For this analysis, we assumed an average age of 73 years.[9, 10] Because patients undergoing carotid endarterectomy have higher baseline risks for death than the general population,[17, 18] an excess mortality rate of 0.5% per year was added to the baseline mortality rate.[19]

Accounting for death from other causes modestly increased the number of carotid endarterectomies needed to prevent one major stroke or death (Appendix Table). The NNT increased from 63 to 78 for patients with asymptomatic severe stenosis and from 29 to 36 for patients with symptomatic moderate stenosis. However, the NNT for patients with symptomatic severe stenosis increased negligibly (from 10 to 12).

APPENDIX TABLE

Summary Estimates of Stroke Incidence in Patients with Carotid Artery Stenosis Treated with and without Surgery and of the Number of Procedures Needed To Prevent One Major Stroke or Death*

	PATIENT CHARACTERISTICS		
	ASYMPTOMATIC SEVERE STENOSIS	SYMPTOMATIC MODERATE STENOSIS	SYMPTOMATIC SEVERE STENOSIS
Effectiveness			
5-year cumulative incidence of major stoke or death, %†			
No surgery	5.3	6.4	14.0
Surgery	4.1	3.7	5.6
Absolute difference, %	1.3	2.8	8.4
Number of procedures needed to prevent one major stroke or death	78	36	12

**Effectiveness estimates accounted for increased surgical mortality observed outside the trials and death from other causes. Death from other causes was accounted for.*
†Only surgery and stroke-related deaths were included.