Cost-effectiveness of screening for asymptomatic carotid stenosis

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Purpose: **The benefit of carotid endarterectomy for patients who are asymptomatic with >60% carotid stenosis has been established by the Asymptomatic Carotid Atherosclerosis Study (ACAS). Which screening strategy is most appropriate is still unclear. This study assessed the cost-effectiveness of ultrasound screening for asymptomatic carotid stenosis.**
Methods: **Cost-effectiveness analysis was performed with a Markov model and with data from ACAS and other studies.**
Results: **For 60-year-old patients with a 5% prevalence of 60% to 99% asymptomatic stenosis, duplex ultrasound screening increased average quality-adjusted life years (QALY; 11.485 vs 11.473) and lifetime cost of care ($5500 vs $5012) under base-case assumptions. The incremental cost per QALY gained (cost-effectiveness ratio) was $39,495. Screening was cost-effective with the following conditions: disease prevalence was 4.5% or more, the specificity of the screening test (ultrasound) was 91% or more, the stroke rate of patients who were medically treated was 3.3% or more, the relative risk reduction of surgery was 37% or more, the stroke rate associated with surgery was 160% or less than that of the North American Symptomatic Carotid Endarterectomy Trial or ACAS perioperative complication rates, and the cost of ultrasound screening was $300 or less. A one-time screening, compared with a screening every 5 years, had more QALY (11.485 vs 11.482) and lower cost ($5500 vs $5790). Screening without arteriography, compared with screening with arteriographic verification, provided few additional QALYs (11.486 vs 11.485) at additional cost ($6896 vs $5500). The cost-effectiveness ratio was sensitive to assumptions about the stroke rate of patients who were asymptomatic and other variables.**
Conclusions: **Screening for asymptomatic carotid stenosis can be cost-effective when both screening and carotid endarterectomy are performed in centers of excellence. (J Vasc Surg 1998;27:245-55.)**

The benefit of carotid endarterectomy (CEA) for patients who were asymptomatic with >60% stenosis has been established by a controlled clinical trial.[1] Detection of asymptomatic lesions requires screening of patients, usually by duplex ultrasound. Which screening strategy is most appropriate is unclear. The cost-effectiveness of screening for asymptomatic carotid stenosis has become a subject of debate.[1-4] We sought to determine the cost-effectiveness of screening for asymptomatic carotid stenosis by examining the effect of various variables on quality-adjusted life years (QALY) and lifetime cost of care.

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METHODS

A decision model was developed to examine the effect of screening or not screening on QALY and cost. The model combined published data of the accuracy and cost of duplex Doppler ultrasound and carotid arteriography and of the risks, benefits, and costs of endarterectomy to model survival, QALY, and cost for a hypothetical population. Predicted QALY and cost for the two choices (ultrasound screening or no screening, with or without preoperative arteriography) were compared to calculate the cost-effectiveness ratio (CE-ratio). All calculations were performed with Decision Maker software (Decision Maker 7.04, Pratt Medical Group, Inc., Massachusetts).

The model

Events in the first month after the decision to screen are described in Fig. 1. Patients who undergo

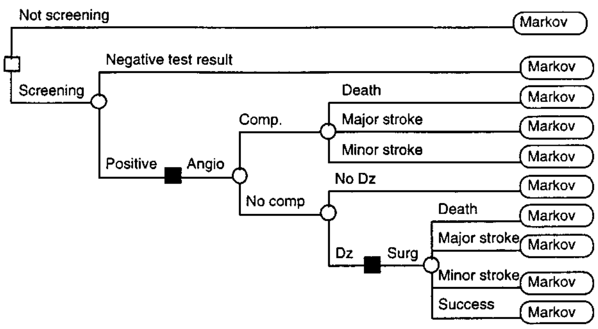

Fig. 1. Decision tree of events in month after decision to screen. *Square nodes* represent decisions, and *circular nodes* are chance nodes. Model accounts for complications of arteriography and fate of patients who had false-positive ultrasound scans. Patients enter Markov process after decision to screen (Fig. 2). *Angio,* carotid arteriography; *Comp,* complications; *Dz,* patient has 60% to 99% asymptomatic carotid stenosis; *Surg,* carotid endarterectomy.

Table I. Definition Of Markov States

State	*Definition*
Well	Patients with 0% to 59% asymptomatic stenosis as defined by ACAS
Asym	Patients with 60% to 99% asymptomatic carotid stenosis
Sym	Patients who have had a hemispheric transient ischemic attack or monocular blindness of <24 hours duration but with stenosis <60%
AsymSurg	Patients who have had uncomplicated carotid endarterectomy for asymptomatic stenosis >60%
SymSurg	Patients who have had uncomplicated carotid endarterectomy for symptomatic stenosis >60%
MinStk	Patients who have had minor strokes
MajStk	Patients who have had major stroke (e.g., causing a functional deficit persisting 90 or more days)
Death	Deceased

screening are found to have significant asymptomatic carotid stenosis >60% as defined by the Asymptomatic Carotid Atherosclerosis Study (ACAS),[1] or they are found not to have significant stenosis. Ultrasound scans classify patients into the following two groups: those with a positive test result (>60% stenosis) and those with a negative test result (<60% stenosis). Patients with positive tests undergo arteriography to confirm ultrasound findings. At present, patients with negative test results do not undergo further testing.

Patients who undergo arteriography may have periprocedure strokes, which can be minor, major, or fatal strokes. Patients undergo endarterectomy when >60% stenosis is verified arteriographically. The patients may have uncomplicated endarterectomies or complications that result in minor, major (causing functional deficits persisting >90 days), or fatal strokes. Presently, patients do not undergo further testing without >60% stenosis verified angiographically. Arteriography was assumed to be perfect in sensitivity and specificity.

Fig. 2 describes a Markov process in the months after screening. Patients who are aging may move from one of the eight Markov states to another (Table I). Patients who are Well may develop asymptomatic (Asym) or symptomatic (Sym) stenoses or die of unrelated causes. The transitional probability, the probability of changing from one state to another, may change monthly because of time-dependent effects, such as aging.

Testing and treatment of patients who were symptomatic. Because transient ischemic attack and other symptoms are easily recognized by clinicians, we assumed that patients underwent duplex ultrasound when symptoms occurred. Patients who were symptomatic with >60% stenosis underwent endarterectomy immediately.[5]

Follow-up testing. Patients who were symptomatic with <60% stenosis and patients who were postoperative underwent periodic testing. The interval between follow-up tests was assumed to be constant. The interval was every year for the base-case.

Frequency of screening. Different screening strategies were modeled. A one-time screening model tested patients who were asymptomatic once unless they became symptomatic (base-case). Other screening strategies tested patients periodically.

Death from other causes. The mortality rate increases with age in the general population. Patients with cerebrovascular disease have a higher risk of death than patients who are matched for age. An excess mortality rate was assessed to account for this higher risk.

Arteriography versus no arteriography. Because many clinicians perform endarterectomy without arteriography to avoid the attendant risk of complications,[6-9] we developed a separate model to study the cost-effectiveness of screening without arteriography. This model accounted for the implications of false-positive and false-negative ultrasound findings.

Transition among states. Patients in one state, excluding the state of Death, may progress to another state from month to month (Fig. 2). Patients in the Well state could progress to Asym or Sym, remain Well, or die. Patients in the Asym state could progress to Sym, have a minor or major stroke, or die. Patients who are Sym could not progress to the Well or Asym states.

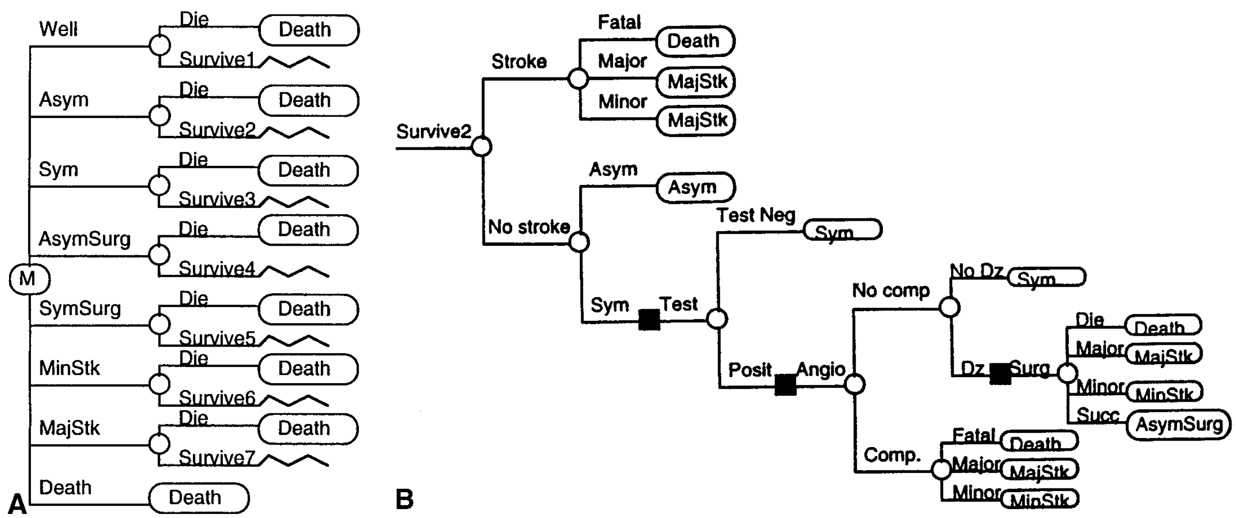

Fig. 2. A, Markov model for fate of patients after screening. *Well*, *Asym*, *Sym*, *AsymSurg*, *SymSurg*, *MinStk*, *MajStk*, and *Death* are Markov states (Table I). Patients who are aging may move from one of eight Markov states to another (i.e., from Well to Asym). **B,** Markov model for monthly transition for patients who develop asymptomatic stenosis after screening has been completed. Patients may have stroke, remain asymptomatic, or develop symptoms. Those developing symptoms (i.e., transient ischemic attack) are assumed to undergo ultrasound testing and then arteriographic verification and endarterectomy in patients with confirmed 60% to 99% stenosis. *Square nodes* represent decisions and *circular nodes* are chance nodes. *Angio,* carotid arteriography; *Comp,* complications; *Dz,* 60% to 99% stenosis; *Surg,* Carotid endarterectomy.

Table II. Accuracy of duplex ultrasound

Authors	*No. of cases*	*Sensitivity*	*Specificity*	*Notes*
Eliasziw et al.[10]	1011	0.68	0.67	Symptomatic patients with ≥70% stenosis
Moneta et al.[11]	353	0.84	0.94	60% to 99% asymptomatic carotid artery stenosis
Blakeley et al.[12]	3574	0.83-0.86	0.89-0.94	Meta-analysis, published articles; 70% to 99% stenosis
Kent et al.[13]	81	0.35-0.93	0.78-0.96	70% to 99% stenosis in symptomatic patients
Derdeyn et al.[2]	215	0.99	0.80	60% to 99% stenosis
Carpenter et al.[14]	110	0.97-1.0	0.52-1.0	60% to 99% stenosis

Data sources

Accuracy of duplex Doppler ultrasound. Reports of accuracy are highly variable (Table II).[10-14] A metaanalysis estimated that the sensitivity and specificity of ultrasound ranged from 83% to 86% and from 89% to 94%, respectively.[12] The sensitivity and specificity were assumed to be 85% and 92%, respectively, for the base-case analysis.

Disease prevalence. A summary of disease prevalence is found in Derdeyn et al.[2] Several additional studies merit discussion. In the Framingham Study, Fine-Edelstein et al.[15] found that the prevalence of >50% stenosis in patients aged 66 to 93 years was 7% in women and 9% in men. Salonen et al.[16] reported a 4.8% prevalence of >20% stenosis in Eastern Finnish men aged 60 years. Jungquist et al.[17] also reported a 3% rate of 60% to 99% stenosis in a Swedish population. In patients who were referred to the vascular laboratory at the University of Washington for carotid stenosis evaluation, 14% had mild cervical bruits, and 114 (8%) had >50% stenosis.[18] We therefore assumed a 5% disease prevalence for the base-case analysis (range, 3% to 20%).

Surgical risk. The risks of endarterectomy include minor and major perioperative (within 30 days) strokes and death during surgery. Base-case estimates were derived from ACAS results (Table III).[1] The risk of arteriography was excluded. Base-case estimates for patients who were symptomatic were taken from the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[5]

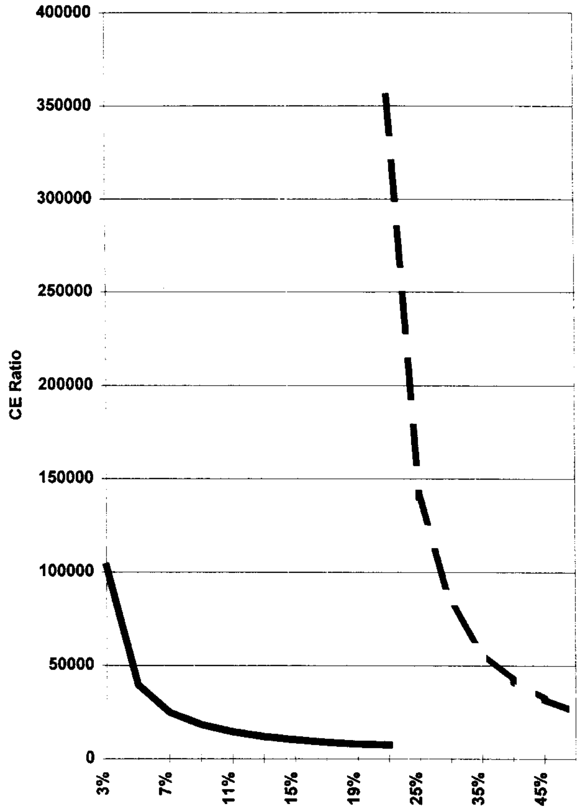

Fig. 3. *Solid line* shows prevalence of disease in screening population and cost-effectiveness of screening. Screening was cost-effective if prevalence of asymptomatic carotid stenosis was more than 4.5%. *Dashed line* shows surgical efficacy for patients who were asymptomatic and cost-effectiveness of screening. Screening was cost-effective if surgical efficacy was more than 37%. *Surgical efficacy,* (rate of stroke in medical patients - rate of stroke in surgical patients)/(rate of stroke in medical patients); *CE-Ratio,* Cost/QALY = (cost of screening - cost of not screening)/(QALY of screening - QALY of not screening).

Table III. Perioperative risks

Procedure (sources)	*Mortality rate*	*Nonfatal complication rate*
Angiography (ACAS)[1]	1/414 (0.24%)	4/414 (0.97%)
Carotid endarterectomy for asymptomatic patients (ACAS)[1]	2/825 (0.24%)	11/825 (1.33%)
Carotid endarterectomy for symptomatic patients (NASCET)[5]	2/328 (0.61%)	17/328 (5.18%)

ACAS, Asymptomatic Carotid Atherosclerosis Study[1]; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial.[5] The rate of surgical complications for asymptomatic patients does not include the risk of carotid arteriography related complications.

Table IV. Annual stroke rate after the perioperative period

Event type (source)	*Medical*	*Surgical*	*Relative risk reduction*
Any ipsilateral stroke in patients with asymptomatic 60% to 99% stenosis (ACAS)[1]	2.28%	0.72%	75%
Any stroke in patients with asymptomatic 60% to 99% stenosis (ACAS)[1]	3.96%	2.4%	41%
Any ipsilateral stroke in patients with symptomatic 70% to 99% stenosis (NASCET)[5]	12.84%	1.68%	87%
Any stroke in patients with symptomatic 70% to 99% stenosis (NASCET)[5]	16.8%	6.96%	59%

ACAS, Asymptomatic Carotid Atherosclerosis Study[1]; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial[5]; *Relative risk reduction,* (rate of stroke in medical patients - rate of stroke in surgical patients)/(rate of stroke in medical patients). The rate of stroke does not include perioperative (within 30 days) strokes.

Stroke risk. The estimated monthly rate of stroke in patients who were asymptomatic was derived from ACAS results.[1] The risk of perioperative strokes was excluded. In the ACAS study, the monthly rate of ipsilateral stroke, excluding perioperative stroke, was 0.05% (-LN(1-(0.051-0.023))/60 = 0.05%) for patients for surgical treatment and 0.19% (-LN(1-(0.11-0.004))/60 = 0.19%) for patients for medical treatment, with a relative risk reduction of 75%. The monthly rate of any stroke was 0.20% for patients for surgical treatment and 0.33% for patients for medical treatment, with a relative risk reduction of 41%. Because we did not separate ipsilateral stroke from other types of stroke, we used the rate of any stroke as our base-case estimate for stroke risk. We chose the more conservative, or less likely to be cost-effective, rate of any stroke, rather than ipsilateral stroke, because we were interested in determining overall benefit to patients and costs.

The stroke rate for patients who were symptomatic was taken from NASCET results (Table IV).[5] The monthly rate of any stroke, excluding perioperative stroke, was 0.58% for patients for surgical treatment and 1.4% for patients for medical treatment, with a relative risk reduction of 59%. The European Carotid Surgery Trial found no benefit from surgery in patients who were symptomatic with <30% stenosis.[19] NASCET and the European Carotid Surgery Trial have not reached definitive conclusions about patients who are symptomatic with stenosis between

30% and 69%, and both trials continue to randomize such patients. We assumed that patients who were symptomatic with 60% to 99% stenosis underwent endarterectomy immediately, and those patients with <60% symptomatic stenosis were medically managed. The risk of stroke in patients who were medically treated and symptomatic with <60% symptomatic stenosis was assumed to be 50% of those patients with 70% to 99% stenosis ($0.5 \times 1.4\% = 0.7\%$ from NASCET). In NASCET, 49% of postoperative strokes in patients for medical treatment were major, and 18% of the major strokes were fatal.

Patients with a stroke have a 5% to 9% annual rate of subsequent stroke and a monthly rate of 0.4% to 0.8%.[20] A monthly rate of 0.8% was used for the base-case analysis.

Excess mortality rate. An excess mortality rate was calculated as the difference between the NASCET's rate of nonstroke death in patients for medical treatment and the actuarial rate of death in the general population.[21] The excess mortality rate for patients who were surgical and asymptomatic (60% to 99% stenosis) was assumed to be the same for patients who were symptomatic. The excess mortality rate for patients with minor and major strokes was assumed to be 200% and 500%, respectively, of the rate in patients who were symptomatic.

Transitional probability. The monthly transitional probability from asymptomatic to symptomatic with >60% carotid stenosis was estimated from ACAS results. The monthly rate was 0.19% in patients for medical treatment and 0.08% in patients for surgical treatment. The transitional probability from Well to Asym (from asymptomatic <60% stenosis to asymptomatic >60% stenosis) was extrapolated from the literature. Salonen et al.[16] found that 4.8% of 60-year-old patients had >20% stenosis as compared with 2.3% in 54-year-old patients. This result implies a monthly transition rate of 0.4%. The rate was 0.45% for a similar method that was applied to the Framingham Study results.[15] The rate of transition from the Well to the Sym state (from <60% asymptomatic stenosis to symptomatic >60% stenosis) was assumed to be 50% of that from Well to Asym ($0.4\% \times 0.5 = 0.2\%$).

Quality of life adjustment and discounting. The degree to which major and minor strokes diminish the quality of life for a patient was adjusted with a factor that ranged from zero (Death) to one (Well). Our adjustment factors were derived from earlier studies.[22,23] Future expenditures and QALY were discounted at an annual discount rate of 5% but were tested at a range of 0% to 10%.

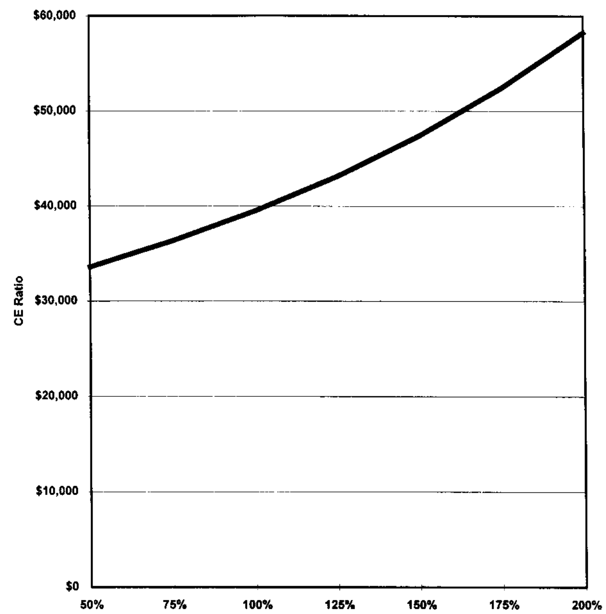

Fig. 4. Surgical complications and cost-effectiveness of screening. Screening was cost-effective if surgical complication rate was less than 160% of that in ACAS and NASCET. *Surgical complications,* rate of surgical complications compared with rates of complications in ACAS (for asymptomatic patients) and NASCET (for symptomatic patients); *CE-Ratio,* Cost/QALY = (cost of screening - cost of not screening)/(QALY of screening - QALY of not screening).

Costs. The cost of ultrasound was taken from the Medicare fee schedule. Costs of arteriography and endarterectomy were from Kent et al.[13] The following costs were derived: ultrasound, $206; arteriography, $2360; and endarterectomy, $10,850. We also followed Kent et al.[13] by adding a one-time cost of $13,000 for each minor or fatal stroke and $27,000 for each major stroke. These costs reflect estimated fees per patient who is hospitalized for stroke. In addition, we assumed that patients with minor and major strokes incurred $120 and $12,000 annually for chronic care, respectively. All costs are in 1994 United States dollars.

Table V summarizes these assumptions. Our base-case results apply to the decision to screen by ultrasound a population of 60-year-old patients who are asymptomatic and have a 5% prevalence of 60% to 99% asymptomatic stenosis.

RESULTS

Base-case analysis. Table VI reports costs and QALY of screening versus not screening under base-

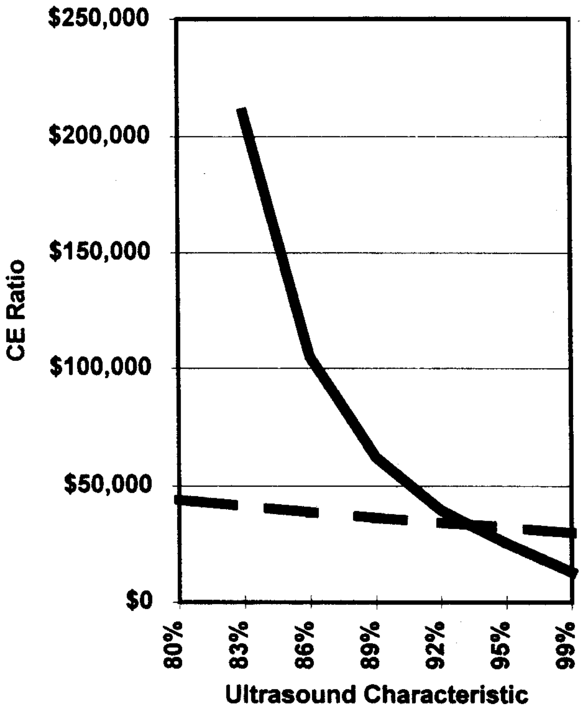

Fig. 5. Sensitivity and specificity of ultrasound and cost-effectiveness of screening. Cost-effectiveness of screening was independent of sensitivity of ultrasound (*dashed line*). Screening was cost-effective if specificity of ultrasound was more than 91% (*solid line*). *CE-Ratio,* Cost/QALY = (cost of screening - cost of not screening)/(QALY of screening - QALY of not screening).

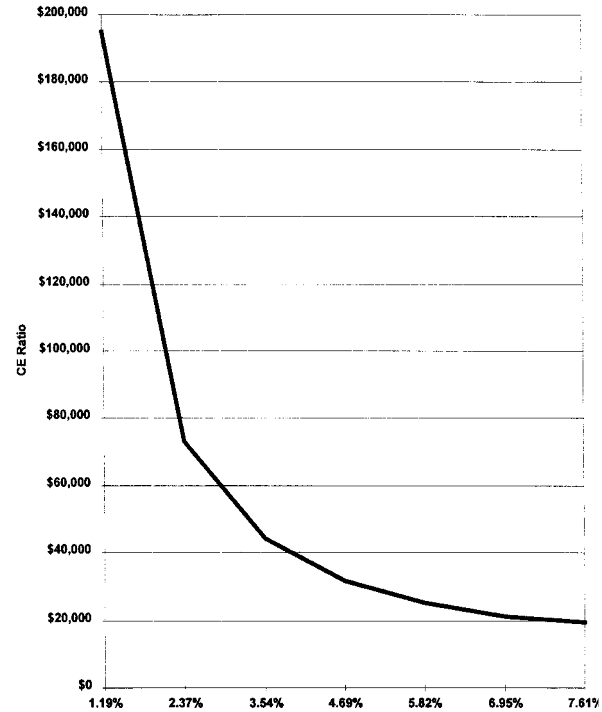

Fig. 6. Annual rate of strokes in patients with 60% to 99% asymptomatic stenosis and cost-effectiveness of screening. Screening was cost-effective if stroke rate of patients who were medically managed and asymptomatic was more than 3.3%. *CE-Ratio,* Cost/QALY = (cost of screening - cost of not screening)/(QALY of screening - QALY of not screening).

case assumptions. The screening of the hypothetical population increased average QALY (11.485 vs 11.473) and lifetime cost ($5500 vs $5013; Table VI, first three rows). The incremental cost was $39,495 per QALY gained.

If endarterectomy was performed on the basis of ultrasound results alone (Table VI, last three rows), screening as compared with not screening increased QALY (11.486 vs 11.473) and cost ($6896 vs $5589). The CE-ratio was $100,508. When the two screening strategies (with and without arteriography) were compared, screening without arteriography provided few QALYs (11.486 vs 11.485) at a cost of $1390 ($6896 vs $5500) resulting in a CE-ratio of $1,396,000.

Sensitivity analysis. Each variable in Table V was examined to determine the effect on the CE-ratio. Fig. 3 through Fig. 8 illustrate relationships between CE-ratio and selected parameters. The last column of Table V summarizes the effect of each variable on the cost-effectiveness of screening.

Disease prevalence. Screening was more cost-effective (CE-ratio was lower) in patients with greater disease prevalence (Fig. 3). As prevalence increased from 3% to 20%, the CE-ratio decreased from $102,160 to $7452. If we accept the current standard that a CE-ratio of $50,000 or less suggests an intervention is cost-effective, threshold prevalence was 4.5% for screening to be cost-effective (Table V, last column). Although no consensus on the exact limits of acceptable CE-ratios exists, interventions with CE-ratios of $50,000 or less are often considered cost-effective when compared with currently acceptable medical practices. Interventions with CE-ratios between $50,000 and $100,000 are considered borderline cost-effective, and those with higher ratios are not cost-effective.[24]

Surgical efficacy. The CE-ratio ranged from $357,869 to $6023 and surgical efficacy in patients who were asymptomatic varied from 20% to 80% relative risk reduction (Fig. 3). The threshold efficacy was 37%. Surgical efficacy for patients who were

Table V. Model parameters: base-case value, range, and effect on CE-ratio

Variable (sources)	*Base-case (Range)*	*CE-ratio <$50,000?*
Prevalence of 60-99% carotid stenosis[2,15-17]	5% (3% to 20%)	If >4.5%
Sensitivity of screening test[10-14]	0.85 (0.8-0.99)	Any*
Specificity of screening test[10-14]	0.92 (0.8-0.99)	If >0.91
Starting age of screening	60 (55-75)	If <63
Frequency of screening	Once (every 1-10 years)	If once
Interval between postoperative follow-up tests (months)[27]	12 (6-60)	Any*
Interval between follow-up tests for symptomatic patients (months)	12 (6-60)	Any*
Annual stroke rate in asymptomatic patients[1]	3.96 (0-7.92)	If >0.28%
Annual stroke rate in patients with <60% symptomatic stenosis[5]	8.4 (4.2-16.8)	Any*
Annual stroke rate in patients who have had minor strokes[20]	9.6 (0-28.8)	Any*
Annual stroke rate in patients who have had major strokes[20]	9.6 (0-28.8)	Any*
% of strokes that are major[1,5]	50% (25% to 75%)	If >42%
% of major strokes that are fatal[1,5]	18% (10% to 50%)	Any*
Rate of arteriography-related strokes[1]	1.2% (0% to 1.5%)	If <1.4%
% of arteriography-related strokes that are fatal	10% (0% to 30%)	Any*
% of arteriography-related strokes that are major strokes	30% (0% to 60%)	If <51%
Efficacy in patients with 60% to 99% asymptomatic stenosis[1]	41% (20% to 82%)	If >37%
Perioperative mortality rate in asymptomatic patients[1]	0.24% (0.12% to 0.48%)	If <160%†
Perioperative major stroke rate in asymptomatic patients[1]	0.38% (0.19% to 0.76%)	If <160%†
Perioperative minor stroke rate in asymptomatic patients[1]	0.92% (0.46% to 1.84%)	If <160%†
Efficacy of endarterectomy in asymptomatic patients[1]	59% (30% to 80%)	Any*
Perioperative mortality rate in symptomatic patients[5]	0.6% (0.3% to 1.2%)	If <160%†
Perioperative major stroke rate in symptomatic patients[1]	1.5% (0.75% to 3%)	If <160%†
Perioperative minor stroke rate in symptomatic patients[1]	3.7% (1.35% to 7.4%)	If <160%†
% of stenoses that are 70% or greater in patients with symptomatic stenosis	48% (24% to 96%)	Any*
Transition probability from Well to Asym[5,15,16]	0.04% (0% to 0.12%)	Any*
Transition probability from Well to Sym (see text)	0.02% (0% to 0.06%)	Any*
Transition probability from Asym to Sym[1]	0.19% (0% to 0.38%)	If >0.15%
Transition probability from AsymSurg/SymSurg to Sym[1]	0.08% (0% to 0.16%)	If <0.12%
Excess annual mortality rate[5]	2.28 (0-0.0456)	Any*
Excess annual mortality rate in patients with minor strokes	0.0456 (0-0.0912)	Any*
Excess annual mortality rate in patients with major strokes	0.114 (0-0.228)	Any*
Quality of life for minor stroke patients	0.8 (0.5-1.0)	Any*
Quality of life for major stroke patients	0.2 (0-0.5)	If <0.44
Annual discount rate	5% (0% to 10%)	If <7%
Cost of ultrasound	$206 (100-800)	If <$300
Cost of carotid endarterectomy[13]	$10,850 ($5,000-$20,000)	If <$18,000
Cost of carotid arteriography[13]	$2,360 ($1,000-$4,000)	If <$3,400
Cost of chronic care for major stroke (annual rate)	$12,000 ($6000-$24,000)	Any*
Duration of surgical efficacy (years)	10 (5-12)	If >8 years

Efficacy, (1-(rate of strokes in surgical patients)/(rate of strokes in medical patients)); *CE-ratio,* (cost of screening - cost of not screening)/(quality-adjusted life-year of screening - quality-adjusted life-year of not screening).
*The CE-ratio remained less than $50,000 when the corresponding parameter was varied within its range.
†The rate of surgical complications was compared with the rates in ACAS and NASCET (the base-case). A ratio of 100% implied that the rate of surgical complications in asymptomatic patients was the same as the ACAS rate and the rate in symptomatic patients was the same as the NASCET rate.

symptomatic did not affect the cost-effectiveness of screening.

Surgical complications. Both ACAS and NASCET selected surgeons by strict quality criteria to minimize the perioperative risks of endarterectomy (Fig. 4). We varied complication rates to examine the cost-effectiveness of screening when endarterectomy was performed in various clinical settings. If the complication rate was twice the ACAS and NASCET rates, the CE-ratio was $58,251. If the rate was reduced to half of the base-case rate, the CE-ratio was $33,575. Screening was cost-effective if the rate was less than 160% of that of ACAS and NASCET.

Accuracy of screening. The CE-ratio varied with the accuracy of screening (Fig. 5). As the specificity of ultrasound varied from 83% to 99%, the CE-ratio ranged from $208,470 to $13,050. The threshold specificity was 91%. The sensitivity of ultrasound had smaller effects on the CE-ratio, which ranged from $44,019 to $29,819 as sensitivity increased from 80% to 90%. Screening without

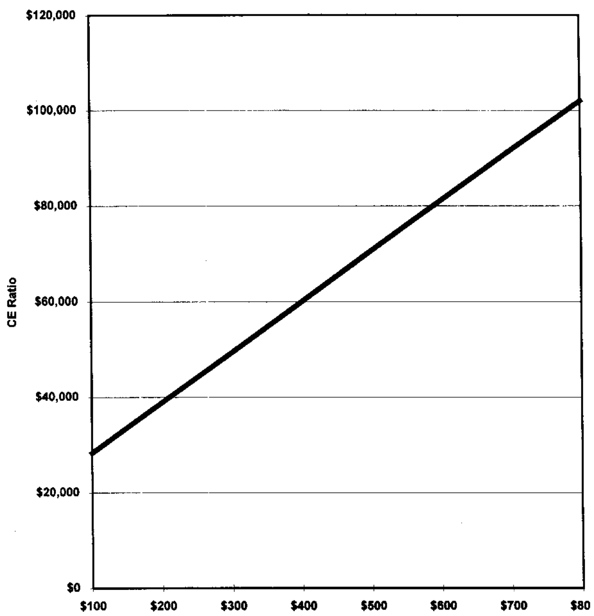

Fig. 7. Cost of ultrasound and cost-effectiveness of screening. Screening was cost-effective if cost of ultrasound was less than $300. *CE-Ratio,* Cost/QALY = (cost of screening - cost of not screening)/(QALY of screening - QALY of not screening).

arteriography was cost-effective when compared with screening with arteriography only if the specificity of ultrasound was 98% or greater.

Stroke rate. As the annual rate of stroke in patients who were asymptomatic increased from 1.2% to 7.6%, the CE-ratio decreased from $198,889 to $19,536 (Fig. 6). Screening was cost-effective if the annual stroke rate was more than 3.3%.

Cost of screening. The CE-ratio was also sensitive to the cost of ultrasound (Fig. 7). As the cost increased from $100 to $800, the CE-ratio increased from $28,291 to $102,277. The threshold cost was $300.

Arteriography-related complications. The relationship between the CE-ratio and the rate of arteriography-related complications is illustrated in Fig. 8. The CE-ratio was related inversely to the rate of complications and still remained below $50,000 if the complication rate was 1.4% or lower.

Other variables. The cost-effectiveness of screening (CE-ratio < $50,000; Table V, last column) was sensitive to frequency of screening, patient age, percentage of major strokes, rate of arteriography-related strokes, transitional probability from asymptomatic to symptomatic, rate of postoperative symptoms, length of surgical efficacy, discount rate, cost of surgery and arteriography, and quality of life in patients with major strokes. The cost-effectiveness of screening was not sensitive to sensitivity of ultrasound, interval between follow-up tests, stroke rate in patients who are symptomatic, stroke rate in patients with prior strokes, percentage of fatal major strokes, surgical efficacy in patients who are symptomatic, prevalence of 60% to 99% stenosis in patients who are symptomatic, transitional probability from Well to Asym or Sym, excess mortality rate, quality of life adjustment for patients with minor strokes, and cost of chronic care for patients with strokes. In addition, the use of ipsilateral stroke rate, as compared with any stroke, did not significantly change the cost-effectiveness of screening.

Table VI. Cost and QALY of screening versus not screening for patients with 5% prevalence of asymptomatic stenosis

Strategy	*QALY*	*Cost*	*CE-ratio*
Carotid arteriography was performed before endarterectomy			
No screening	11.473	$5,013	N.A.
Screening	11.485	$5,500	$39,495
Endarterectomy performed on the basis of ultrasound results			
No screening	11.473	$5,589	N.A.
Screening	11.486	$6,896	$100,538

QALY, quality-adjusted life year; N.A., not applicable; CE-ratio, (cost of screening - cost of not screening)/(quality-adjusted life year of screening - quality-adjusted life year of not screening).

DISCUSSION

Ultrasound screening for asymptomatic carotid stenosis in a general elderly population can increase QALY and be cost-effective if ultrasound is specific and endarterectomy is performed with low morbidity and mortality rates. However, this conclusion is contingent on the assumptions in the cost-effectiveness analysis.

First, base-case efficacy and risk of endarterectomy were derived from results of controlled clinical trials, which necessitates that surgery provide more than 37% relative risk reduction compared with medical management. The conclusions apply only when endarterectomy is performed by surgeons who have comparable results. CEA should be performed by surgeons with documented morbidity rates less than 160% of that reported in NASCET, for patients who were symptomatic, and ACAS, for patients who were asymptomatic, and at a cost less than $18,000. Surgeons therefore would be required to closely monitor their individual results for operations on patients who were symptomatic and asymptomatic.

Second, the cost-effectiveness of screening was sensitive to many variables. Screening was more cost-effective when performed once in high disease prevalence populations (>4.5% prevalence). Therefore a higher priority should be given to testing patients with cervical bruits, a history of smoking, diabetes, and high serum cholesterol levels.

Third, our base-case stroke rate was derived from ACAS, which applied extensive exclusion criteria in cohort selection. If the stroke rate of patients who were treated medically is lower than 3.3%, the CE-ratio would exceed $50,000. We followed Kent et al.[13] with respect to cost of stroke care, but by sensitivity analysis found that screening was cost-effective over a wide range of assumed costs. We used the rate of any stroke, rather than only ipsilateral stroke, in our analysis because we were interested in determining the overall benefit and cost. This conservative assumption would disfavor cost-effectiveness of screening, but screening proved to be cost-effective over a wide range of stroke rates for medical therapy.

In our model, we chose to vary age and disease prevalence independently. This artificial separation of two closely-linked variables was necessary because of the lack of data needed to accurately assign prevalence by age. The data seemed to vary greatly by author and geographic region. Linking age and prevalence would likely increase the cost-effectiveness of screening for asymptomatic stenosis because increasing values of each variable are associated with incremental increases in cost-effectiveness when treated independently.

ACAS noted a more modest relative risk reduction with surgical treatment of asymptomatic carotid stenosis for women than for men (17% vs 66%). We did not examine sex independent of other variables. However, we did perform sensitivity analysis of surgical relative risk reduction, which may be applied to the question. The threshold value of cost-effectiveness for relative risk reduction by surgery was 37%, which would imply that screening of female patients may be less likely to be cost-effective. However, because the model did not specifically address the issue of sex independently, no firm conclusions can be made.

The specificity of the screening test should exceed 91%, and the cost should be less than $300, which mandates strict quality assurance efforts by

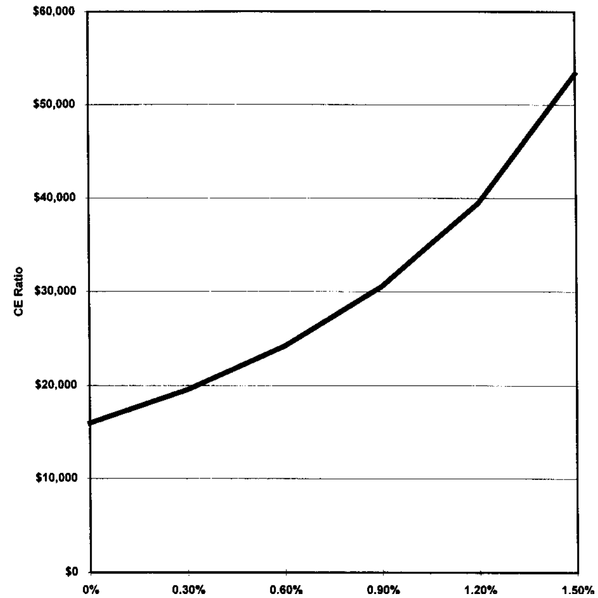

Fig. 8. Rate of carotid arteriography-related complications and cost-effectiveness of screening. Screening was cost-effective if rate of arteriographic complications was less than 1.4%. *CE-Ratio,* Cost/QALY = (cost of screening - cost of not screening)/(QALY of screening - QALY of not screening).

vascular laboratories to assure that such high specificities of testing can be achieved. The sensitivity of our model to specificity but not sensitivity of ultrasound implies that false-positive ultrasound study results are of chief importance in cost-effectiveness. The high cost of unnecessary patient morbidity incurred by arteriography and operations on patients without disease is of greater significance than missing patients with asymptomatic stenosis during screening.

Confirmatory arteriography should be performed with an attendant morbidity rate less than 1.4%, and the cost should be less than $3400. Requiring confirmatory arteriography shows the importance of avoiding unnecessary operations on patients with false-positive ultrasound results. The modeled strategy of surgery without preoperative arteriography was comparable in QALY with the strategy that required confirmatory arteriography, but the cost was much higher and exceeded the amount defined as cost-effective. Once again, the false-positive ultrasound scans with the attendant increase in cost because of unnecessary surgery were chiefly responsible for the effect. The potential benefit of surgery without confirmatory arteriography was erased by the cost of operations performed on patients who did not meet the criteria of the randomized trials. Our model suggests that results of CEA performed on the basis of duplex alone are equivalent medically to those obtained when confirmatory arteriography is required, with QALY nearly identical. The difference between the two strategies is confined to cost. Surgeons who perform CEA on the basis of duplex alone clearly need to rely on validated duplex criteria, which provide high specificity.[25] Perhaps the most sensible strategy would be one that combines confirmatory arteriography for stenoses in the low end of the >60% category, where duplex specificity is lowest. A duplex only strategy could be used for high grade lesions, which are likely to be nearly all >60%. Such an approach would be expected to decrease the morbidity rate because of operations prompted by false-positive duplex study results and because of arteriographic complications, while increasing overall cost-effectiveness.

Three recent studies have examined the cost-effectiveness of screening in patients who are asymptomatic. Derdeyn et al.[2] found that screening of a high-prevalence asymptomatic population (20% prevalence) led to reduced incidence of stroke. Matchar et al.[4] and Lee et al.[26] found that screening was not cost-effective in patients who are asymptomatic. Derdeyn et al.[2] did not explicitly model the process of aging and disease progression. Therefore a comparison of those results with our results is difficult. The latter studies used similar methods but arrived at different conclusions. We therefore sought to determine the causes.

Discrepancies could result from differences in base-case or model structures. We first modified our assumptions to resemble those used in Matchar et al.[4] These changes made screening more costly ($4147 vs $3227) and less effective (10.2469 vs 10.2552) than not screening. This change did not result from any single variable but to simultaneous changes of the following variables: rate of perioperative mortality and complications, cost of ultrasound, patient age, and interval of follow-up tests. Our base-case estimates of perioperative mortality rate and complications in patients who were asymptomatic derived from ACAS were much lower than those used in Matchar et al.[4] (0.24% vs 1.5% and 1.33% vs 5%, respectively).

Our model also differed from Matchar et al.[4] in structure. First, our patients underwent tests and treatment when symptoms occurred. Second, patients who were symptomatic were given ultrasound scans. Third, our Markov model had more states (eight vs three) so that the process of aging and disease progression were represented more accurately.

Lee et al.[26] also used different assumptions from those used in our model. They did not account for effects of aging, as we did. They also assumed that CEA conferred no benefit to patients beyond 5 years whereas we assumed lifelong benefit from CEA.

Like many other cost-effectiveness analyses, however, we relied on published data from the literature, which has inherent biases. Published data on accuracy of ultrasound are subject to verification biases. The data are often derived from results in academic medical centers, which are different from community practices.

Our model also made simplifying assumptions. Carotid arteriography was assumed to have perfect sensitivity and specificity, which could have created a bias in favor of screening. We also assumed that the interval between follow-up tests was constant (every year). The effect on the cost-effectiveness of screening is difficult to assess. We did not account for the cost of preoperative cardiac or medical evaluation, which may influence the cost-effectiveness of screening. We assumed no benefit of CEA performed in patients with <60% carotid stenosis (false-positives). This oversimplification could bias against cost-effectiveness of screening. Although the authors are unaware of documented benefit of CEA for asymptomatic stenosis <60%, presumably carotid endarterectomy produces a continuum of benefit rather than none at all.

Finally, our screening strategies were derived from duplex ultrasound with and without arteriography. We did not study magnetic resonance angiography as a supplement to ultrasound. The combination of ultrasound and magnetic resonance angiography supplemented by arteriography was found by Kent et al.[13] to provide the most favorable CE-ratio in evaluating patients who were symptomatic during hospitalization.

CONCLUSION

Screening of asymptomatic patients for more than 60% critical stenosis by duplex ultrasound can increase QALY and can be cost-effective. Both the screening test and subsequent procedures must be performed in centers of excellence to achieve these results.

REFERENCES

1. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421-8.
2. Derdeyn CP, Powers WJ, Moran CJ, Cross DTr, Allen BT.

Role of Doppler US in screening for carotid atherosclerotic disease. Radiology 1995;197:635-43.
3. Polak JF. Role of duplex US as a screening test for carotid atherosclerotic disease: benefit without cost? Radiology 1995;197:581-2.
4. Matchar D, Pauk J, Lipscomb J. Cost-effectiveness of carotid endarterectomy: a decision model analysis of three clinical scenarios. 10th International Joint Conference on Stroke and Cerebral Circulation 1995;249.
5. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445-53.
6. Ranger WR, Glover JL, Bendick PJ. Carotid endarterectomy based on preoperative duplex ultrasound. Am Surg 1995;61: 548-54.
7. Moore WS, Ziomek S, Quinones-Baldrich WJ, Machleder HI, Busuttil RW, Baker JD. Can clinical evaluation and noninvasive testing substitute for arteriography in the evaluation of carotid artery disease? Ann Surg 1988;208:91-4.
8. Wagner WH, Treiman RL, Cossman DV, Foran RF, Levin PM, Cohen JL. The diminishing role of diagnostic arteriography in carotid artery disease: duplex scanning as definitive preoperative study. Ann Vasc Surg 1991;5:105-10.
9. Gelabert HA, Moore WS. Carotid endarterectomy without angiography. Surg Clin North Am 1990;70:213-23.
10. Eliasziw M, Rankin RN, Fox AJ, Haynes RB, Barnett HJ. Accuracy and prognostic consequences of ultrasonography in identifying severe carotid artery stenosis. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Stroke 1995;26:1747-52.
11. Moneta GL, Edwards JM, Papanicolaou G, Hatsukami T, Taylor LM Jr., Strandness DE Jr., et al. Screening for asymptomatic internal carotid artery stenosis: duplex criteria for discriminating 60% to 99% stenosis. J Vasc Surg 1995;21: 989-94.
12. Blakeley DD, Oddone EZ, Hasselblad V, Simel DL, Matchar DB. Noninvasive carotid artery testing. A meta-analytic review. Ann Intern Med 1995;122:360-7.
13. Kent KC, Kuntz KM, Patel MR, et al. Perioperative imaging strategies for carotid endarterectomy. An analysis of morbidity and cost-effectiveness in symptomatic patients. JAMA 1995;274:888-93.
14. Carpenter JP, Lexa FJ, Davis JT. Determination of sixty percent or greater carotid artery stenosis by duplex Doppler ultrasonography. J Vasc Surg 1995;22:697-703.
15. Fine-Edelstein JS, Wolf PA, O'Leary DH, et al. Precursors of extracranial carotid atherosclerosis in the Framingham Study. Neurology 1994;44:1046-50.
16. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: a population-based ultrasonography study. Atherosclerosis 1990;81:33-40.
17. Jungquist G, Hanson BS, Isacsson SO, Janzon L, Steen B, Lindell SE. Risk factors for carotid artery stenosis: an epidemiological study of men aged 69 years. J Clin Epidemiol 1991;44:347-53.
18. Roederer GO, Langlois YE, Jager KA, et al. The natural history of carotid arterial disease in asymptomatic patients with cervical bruits. Stroke 1984;15:605-13.
19. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337:1235-43.
20. Moore WS, Mohr JP, Najafi H, Robertson JT, Stoney RJ, Toole JF. Carotid endarterectomy: practice guidelines. Report of the Ad Hoc Committee to the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery. J Vasc Surg 1992;15:469-79.
21. National Center for Health Statistics. Vital statistics of the United States, 1988 Vol II. Mortality, Part A, Section 6. Washington: Public Health Service; 1991.
22. Matchar DB, Pauker SG. Transient ischemic attacks in a man with coronary artery disease: two strategies neck and neck. Med Decis Making 1986;6:239-49.
23. Matchar DB, Pauker SG. Endarterectomy in carotid artery disease. A decision analysis. JAMA 1987;258:793-8.
24. Laupacis A, Feeny D, Desky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluation. Can Med Assoc J 1992;146:473-81.
25. Carpenter JP, Lexa FJ, Davis JT. Determination of greater than 60% carotid stenosis by duplex Doppler ultrasound. J Vasc Surg 1995;22:697-705.
26. Lee TL, Solomon NA, Heidenrech PA, et al. Cost-effectiveness of screening for carotid stenosis in asymptomatic persons. Ann Intern Med 1997;126:337-46.
27. Ouriel K, Green RM. Appropriate frequency of carotid duplex testing following carotid endarterectomy. Am J Surg 1995;170:144-7.

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