Evidence-based Practice

Erik Buskens, MD, PhD
Paul J. Nederkoorn, MD
Tineke Buijs-van der Woude, MSc
Willem P. T. M. Mali, MD, PhD
L. Jaap Kappelle, MD, PhD
Bert C. Eikelboom, MD, PhD
Yolanda van der Graaf, MD, PhD
M. G. Myriam Hunink, MD, PhD

Index terms:
Carotid arteries, MR, 172.12142, 904.12942
Carotid arteries, stenosis or obstruction, 172.721, 904.721
Carotid arteries, US, 172.12981, 172.12984, 904.12981, 904.12984
Cost-effectiveness
Economics, medical

Published online before print
10.1148/radiol.2331030863
Radiology 2004; 233:101–112

Abbreviations:
CEA = carotid endarterectomy
DSA = digital subtraction angiography
NASCET = North American Symptomatic Carotid Endarterectomy Trial
QALY = quality-adjusted life-year
TIA = transient ischemic attack

[1] From the Julius Center for Health Sciences and Primary Care (E.B., P.J.N., T.B.v.d.W., Y.v.d.G.) and Depts of Radiology (W.P.T.M.M.), Neurology (L.J.K.), and Vascular Surgery (B.C.E.), Univ Medical Center Utrecht, Heidelberglaan 100, Rm D01.335, 3584 CX Utrecht, the Netherlands; Program for Assessment of Radiologic Technology, Dept of Epidemiology and Biostatistics, and Dept of Radiology, Erasmus MC, Rotterdam, the Netherlands (M.G.M.H.); and Dept of Health Policy and Management, Harvard School of Public Health, Boston, Mass (M.G.M.H.). Received Jun 10, 2003; revision requested Aug 25; revision received Jan 6, 2004; accepted Feb 2. Supported by grant OG/030 from the Dutch Health Insurance Council, mandated by the Ministry of Health, Welfare and Sports. **Address correspondence to** E.B. (e-mail: *e.buskens@umcutrecht.nl*).

Authors stated no financial relationship to disclose.

Author contributions:
Guarantors of integrity of entire study, E.B., W.P.T.M.M., L.J.K., B.C.E., Y.v.d.G., M.G.M.H.; study concepts and design, E.B., W.P.T.M.M., L.J.K., B.C.E., Y.v.d.G., M.G.M.H.; literature research, E.B.; clinical studies, P.J.N.; data acquisition, P.J.N., E.B., T.B.v.d.W.; data analysis/interpretation, E.B., P.J.N.; statistical analysis, E.B.; manuscript preparation and editing, E.B.; manuscript definition of intellectual content, E.B., P.J.N., Y.v.d.G., M.G.M.H.; manuscript revision/review, E.B., W.P.T.M.M., L.J.K., B.C.E., Y.v.d.G., M.G.M.H.; manuscript final version approval, all authors

Imaging of Carotid Arteries in Symptomatic Patients: Cost-effectiveness of Diagnostic Strategies[1]

PURPOSE: To assess the cost-effectiveness of noninvasive imaging strategies in patients who have had a transient ischemic attack (TIA) or minor stroke and are suspected of having significant carotid artery stenosis.

MATERIALS AND METHODS: From 1997 through 2000, 350 patients were included in a multicenter blinded consecutive cohort study. The sensitivities and specificities of duplex ultrasonography (US), magnetic resonance (MR) angiography, and these two examinations combined were estimated by using digital subtraction angiography (DSA) as the reference standard. The actual costs (from a societal perspective) of performing imaging and endarterectomy were estimated. The survival, quality of life, and costs associated with stroke were based on data reported in the literature. Markov modeling was used to predict long-term outcomes. Subsequently, a decision model was used to calculate costs, quality-adjusted life-years (QALYs), and incremental costs per QALY gained for 62 examination-treatment strategies. Extensive sensitivity analyses were performed.

RESULTS: Duplex US had 88% sensitivity and 76% specificity with use of conventional cutoff criteria. MR angiography had comparable values: 92% sensitivity and 76% specificity. Combined concordant duplex US and MR angiography had superior diagnostic performance: 96% sensitivity and 80% specificity. Duplex US alone was the most efficient strategy. Adding MR angiography led to a marginal increase in QALYs gained but at prohibitive costs (cost-effectiveness ratio > €1 500 000 per QALY gained). Performing DSA owing to discordant duplex US and MR angiographic findings and to confirm duplex US and MR angiographic findings led to extra costs and QALY loss owing to complications. Sensitivity analyses revealed that duplex US as a stand-alone examination remained the preferred strategy while estimates and assumptions were varied across plausible ranges.

CONCLUSION: Duplex US performed without additional imaging is cost-effective in the selection of symptomatic patients suitable for endarterectomy. Adding MR angiography increases effectiveness slightly at disproportionately high costs, whereas DSA is inferior because of associated complications.

The results of several large randomized trials, such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial, have shown that patients with symptomatic carotid artery stenosis—specifically, those who have amaurosis fugax or have had a transient ischemic attack (TIA) or a minor stroke—may benefit from carotid endarterectomy (CEA). Patients with proved severe (ie, 70%–99%) stenosis of the internal carotid artery in particular can expect beneficial effects of this procedure (1,2). Relatively recent study results show that patients with moderate (ie, 50%–69%) stenosis may also benefit from surgery (3). Complications from preoperative angiography and from the endarterectomy procedure itself, however, limit the margin of benefit compared with the benefit of nonsurgical treatment. Finally, patients with low-grade (ie, <50%) stenosis are better off being treated with aspirin. Accordingly, a safe and reliable examination to estimate the degree of stenosis and determine the indication for surgery is necessary.

In the NASCET and the European Carotid Surgery Trial, the degree of stenosis was confirmed by performing digital subtraction angiography (DSA), which has since become the standard of reference. DSA, however, is associated with a 4% risk of TIA or minor stroke, a 1% risk of major stroke, and even a small (<1%) risk of death (4). Also, nonapparent infarctions have been identified in patients who did not show a clear neurologic deficit at DSA (5). Exposing all patients to a potentially harmful diagnostic examination to lower the future risk of stroke or death in only a subgroup of patients has questionable benefit. Overall, the potential benefit to symptomatic patients is diminished by the invasive nature of DSA. This diminished benefit has increasingly been recognized during the past decade. At present, noninvasive diagnostic examinations rather than DSA are recommended. In fact, noninvasive examinations are frequently used to select patients for surgery.

Studies of diagnostic duplex ultrasonographic (US) and magnetic resonance (MR) angiographic examinations have been performed, and promising results have been reported (6–12). However, critical comments regarding the substandard results of the noninvasive examination alternatives also have been reported (13). Furthermore, despite the seemingly obvious advantages of performing noninvasive examinations, the actual outcomes after these procedures in terms of strokes prevented, quality-adjusted life-years (QALYs) gained, and cost-effectiveness remain to be determined.

Adding further to the discussion, combination strategies such as duplex US combined with MR angiography are conceivable. The combination of an initial duplex US examination with results indicating severe (70%–99%) stenosis and a subsequent MR angiographic examination with results confirming this finding might be considered sufficient for deciding to perform surgery. In cases of discordant results of duplex US and MR angiography, however, clinicians may feel compelled to perform DSA. Also, in accordance with current standard practice, routine confirmation of severe stenosis by means of DSA is an option. Finally, numerous other examination strategies that take into account variable cutoff points for duplex US and MR angiography are conceivable—that is, they involve the use of alternative flow velocities or degrees of stenosis to define a positive examination result.

The purpose of the current study was to assess the cost-effectiveness of various noninvasive diagnostic imaging strategies in patients who had had a TIA or a minor stroke and were suspected of having significant carotid artery stenosis.

MATERIALS AND METHODS

Published Data on Diagnostic Performance

As described elsewhere (14), a blinded multicenter prospective consecutive cohort study was previously performed to assess the diagnostic accuracy of duplex US, MR angiography, and combinations of these examinations in the diagnosis of carotid artery stenosis in symptomatic patients, as compared with the diagnostic accuracy of DSA as the reference standard for estimation of examination performance values. Briefly, 350 patients with cerebrovascular symptoms—that is, those with amaurosis fugax or who had had a TIA or a minor stroke—who gave integral informed consent for both the clinical (previously described [14]) and the cost-effectiveness (current investigation) parts of the study were enrolled. Before the start of the study, integral institutional review board approval was also obtained from each participating center. Of all patients considered eligible for the study (n = 412), 15.0% could or would not participate: 3.4% had claustrophobia, 3.0% had a metal implant, and 8.8% refused, ultimately yielding 350 participating patients. Patients underwent duplex US, and if severe stenosis was suspected and they were considered potential candidates for CEA, MR angiography and DSA were subsequently performed.

In accordance with the results obtained in the NASCET and the European Carotid Surgery Trial, patients with 70%–99% stenosis (according to NASCET criteria) were treated with CEA (3,15). On the basis of data pertaining to the carotid arteries ipsilateral to the symptoms, the sensitivities and specificities of variable duplex US and MR angiographic criteria positive for severe stenosis were calculated. We also calculated the performance values for combinations of these examinations.

Current Cost Analysis Study

Parallel to the clinical study (14), the current investigation was focused on our estimation of the costs of the diagnostic examinations—including hospitalization, if applicable—and of CEA from a societal perspective, originally in terms of 1998 euros (in 1998, €1.00 equaled 2.20371 Dutch florins, which equaled approximately $1.11). Actual costs, which included the expenditures for personnel, equipment, materials, maintenance, housing, cleaning, administration, and overhead, were estimated (16). Cost data were recorded at one university hospital (University Medical Center Utrecht) and one general hospital (Enschede Medical Center, Enschede, the Netherlands). On the basis of the distribution of patients across various types of hospitals in the Netherlands, weighted average costs were calculated. Additional estimates of costs associated with hospitalization and stroke in the Dutch setting were derived from data published in the literature (17).

The actual short- and long-term costs associated with minor and major strokes, including those for diagnostic work-up, medication, hospitalization, rehabilitation, and nursing home admission, have been previously reported (18–21). The costs associated with a TIA and with death were estimated by using input from experts in the field and taking into account the costs of consultations with a general practitioner and/or a specialist, diagnostic testing, therapeutic procedures, and hospitalization.

Cost-effectiveness Analysis

In this study, we considered patients who had had a TIA or a minor stroke and at initially performed duplex US with use of a low peak systolic velocity threshold were suspected of having carotid artery stenosis. The cost-effectiveness of various examination-treatment strategies was compared by using a decision model created with a computer software program (Data 3.5; TreeAge Software, Williamstown, Mass). Short-term outcomes were based on the clinical study results (14). Long-term outcomes were estimated by combining published clinical trial data with age- and sex-specific Dutch survival statistics (1–3,22,23).

The major strategies evaluated were defined according to the diagnostic examinations or combinations of examinations performed. Sometimes MR angiography was not feasible: For example, in our clinical study (14), 11.5% of the eligible patients had contraindications to MR angiography or claustrophobia and thus underwent another imaging examination. For most strategies involving the use of MR angiography, we assumed that these patients would undergo DSA instead. We also assessed a strategy in which the duplex US results alone determined the indication for surgery in patients who were unable to undergo MR angiography and did not undergo DSA.

When the combination strategies yielded discordant results—that is, the duplex US and MR angiographic findings were not the same—MR angiography was considered the decisive examination or DSA was performed, depending on the strategy definition. All single-examination and combination strategies were also considered in combination with DSA to either rule in or rule out severe (ie, 70%–99%) stenosis.

Substrategies were defined according to variable threshold criteria for positive duplex US and MR angiographic results and two criteria for endarterectomy. For the individual noninvasive examinations, we considered two thresholds for positive results—a strict positivity criterion and a lenient positivity criterion—and two criteria for the indication for surgery—70%–99% stenosis and 50%–99% stenosis. Thus, four possible strategies per noninvasive examination strategy were considered. For combinations of duplex US and MR angiography, we considered either a lenient positivity criterion for duplex US followed by a lenient or strict positivity criterion for MR angiography, or strict criteria for both duplex US and MR angiography (three combinations), and again the two described criteria as indications for surgery. Thus, six strategies per combination of noninvasive examinations were considered. Finally, for DSA, we considered the two criteria for the indication for surgery. Thus, a total of 62 diagnostic strategies were analyzed.

The degree of carotid artery stenosis was categorized as 0%–49%, 50%–69%, or 70%–99% stenosis or as occlusion. Also, the initial conditions (TIA or minor stroke) and complications that occurred as a result of DSA or surgery were modeled. Next, a Markov process model with a 1-year cycle length was developed to extrapolate and evaluate the long-term outcomes of the diagnostic work-ups and subsequent treatments offered. The initial Markov health state reflected the outcome after the diagnostic work-up and treatment and was determined on the basis of survival length, stenosis degree, treatment given (nonsurgical vs endarterectomy), and neurologic disease (TIA, minor stroke, or major stroke as complication or finding at presentation) severity. Disease progression and death were modeled by allowing the health condition of patients to advance to more severe states during follow-up in the Markov model.

For each year (ie, one cycle) spent in a given health state, the associated quality-adjusted equivalent of 1 year and the associated costs during 1 year were accumulated. In accordance with current Dutch guidelines, the time preference was accounted for by using a 4% discount rate for costs and effects (24).

In symptomatic patients, besides optimal medical care, including aspirin therapy, surgery is generally considered to be indicated for treatment of 70%–99% stenosis. According to relatively recent study results (3), however, patients with 50%–69% stenosis—particularly men who have had a TIA or a minor stroke—may also expect limited benefits from surgery. For lower grade (<50%) stenoses, optimal nonsurgical care alone is recommended.

In the Markov model, optimal nonsurgical care was always assumed to have been given, whereas we considered two criteria as indications for endarterectomy: 70%–99% stenosis and 50%–99% stenosis. In addition, patients who had had a minor stroke were assumed to incur costs and to have ongoing limited disability as a result of the initial event. Therefore, the initial event—that is, TIA or minor stroke—was also distinguished in the model. Moreover, prognosis depends on the extent of the underlying vascular disorder. In symptomatic patients with low-grade stenosis, the risk of future events is lowest, whereas in patients with high-grade stenosis, the risk is highest, particularly during the period early after the initial event.

The associated risk estimates used in the model were derived from data published in the literature (3), and if these data were not reported in detail, they were refined with the help of experienced clinicians and scientists. In the Appendix (Tables A1 and A2), we present details about the risks of stroke over time and about the risk differences used to update survival probabilities.

Analyses

With respect to future cerebrovascular events, CEA will predominantly affect the prognosis related to the symptomatic carotid artery. Accordingly, only ipsilateral cerebrovascular events were modeled. Fatal contralateral cerebrovascular events and other cardiovascular mortalities, however, were accounted for by adjusting age- and sex-specific mortality rates for the Dutch population by using a disease-specific rate ratio (23). Utility weights for the health states of well, minor stroke, major stroke, and death—1.0, 0.8, 0.2, and 0.0, respectively—were derived from data published in the literature (25,26). We assumed that the disutility for TIA was equivalent to 2 days with major stroke.

The Markov model was used to estimate long-term outcomes in terms of life-years, QALYs, and costs associated with all possible health states, with the assumption that these outcomes would pertain to a symptomatic 55-year-old male patient. The results obtained by using the prognostic Markov model were used as input for the diagnosis and treatment decision model to perform a comprehensive long-term comparison of the diagnostic strategies (Fig 1). The expected lifetime costs and QALYs related to the various health states that occurred after the diagnostic strategies were compared by using the decision model. Similarly, incremental cost-effectiveness ratios for the successive strategies were calculated.

For strategies resulting in increased costs and worse outcomes, in terms of QALYs, as compared with the costs and outcomes associated with alternative strategies, reporting an incremental cost-effectiveness ratio is irrelevant: Inferior strategies are so-called dominated. Sensitivity analyses were performed to evaluate the effect of varying the estimates and assumptions used in the models.

RESULTS

Diagnostic Performance

The major diagnostic strategies that we compared, the point estimates of sensitivity and specificity, and the ranges of values obtained by using various cutoff criteria are presented in Table 1. With use of various peak systolic velocity cutoff criteria (27), the sensitivity of duplex US alone for the diagnosis of 70%–99% carotid artery stenosis varied between 87.5% and 98.6% and the specificity varied between 59.2% and 75.7% (14). Similar calculations for MR angiography alone yielded comparable values: sensitivities between 92.2% and 96.9% and specificities between 57.9% and 75.7% (14).

As expected, varying the positivity criterion caused a shift in the diagnostic characteristics of the examinations: With lower thresholds, sensitivity increased while specificity decreased, and vice versa. The combination of duplex US as a low-threshold initial examination with MR angiography as a definitive diagnostic examination, however, was superior, with an overall sensitivity of 92.1% and an overall specificity of 78.4%. Considering the results of the combination examination positive when either the duplex US findings or the MR angiographic findings indicated 70%–99% stenosis led to further improved overall sensitivity, 98.4%, but a decrease in overall specificity, to only 54.0%.

Additionally performing DSA in cases of discordant examination results—that is, when the results of one of the noninvasive examinations indicated the presence of a greater degree of stenosis than the degree threshold indication for surgery and the results of the other examination indicated the presence of a degree of stenosis below this threshold—also led to improved sensitivity: to 98.4%. However, in the scenario in which DSA was performed after duplex US and MR angiography yielded discordant results, in addition to the 11.5% of patients who were unable to undergo MR angiography, an additional 16.0% of patients had to undergo DSA because of discordant results. With other strategies, varying proportions of patients—up to 75% or 100% of the patients considered for surgery in the reference strategy—had to undergo DSA (Table 1).

Corresponding calculations of the diagnostic performance of individual examinations performed with the assumption of a 50% stenosis threshold for the indication for surgery resulted in small (ie, up to about 5%) decreases in sensitivity but substantial (ie, approximately 25%) increases in specificity. The effects on the diagnostic characteristics of the combination strategies were smaller: a 1% decrease in sensitivity and a 10% increase in specificity.

A final finding was that with all of the noninvasive examinations (ie, duplex US, MR angiography, and combination examinations), there tended to be a slight overestimation of the stenosis degree compared with the stenosis degree determined by using DSA. This finding implies that when DSA is not used to confirm noninvasive examination results, some patients—in the worst case, up to about 26%—might be considered "overtreated" (Table 1). Additional details on the probabilistic data used in the diagnostic decision model are presented in the Appendix (Tables A3 and A4).

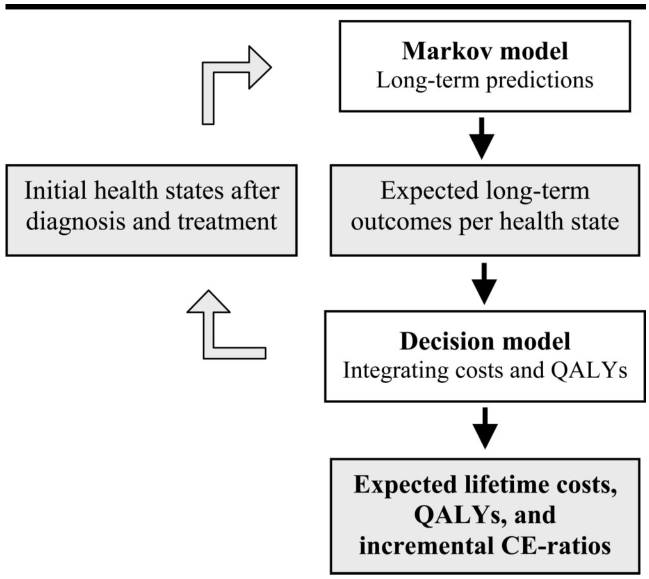

Figure 1. Two-step modeling structure. A Markov model was used to predict and evaluate long-term outcomes, and a decision model was used to integrate costs and QALYs. The initial health states evaluated in the Markov model are identical to the outcomes following diagnosis and treatment. Long-term outcomes, as predicted by using the Markov model, are used as input for the decision model. Expected costs and QALYs per health state are subsequently integrated into the decision model, yielding expected lifetime costs and QALYs, as well as incremental cost-effectiveness *(CE)* ratios for all diagnostic strategies.

Cost Analysis

The costs for duplex US, MR angiography, DSA, and CEA estimated in 1998 at the university hospital and the general hospital did not differ substantially (Table 2). The actual costs associated with stroke and subsequent rehabilitation were retrieved from the literature (17–21). The costs incurred after TIA or death were estimated with the help of experts in the field (Table 2).

Cost-effectiveness Analysis

First, the remaining life expectancy of a 55-year-old symptomatic male patient with carotid artery stenosis (various degrees modeled) who had had a TIA, minor stroke, or major stroke was estimated by using the Markov model (Table 3). Similarly, by taking into account the utility weights and the costs incurred owing to the various health states, expected QALYs and overall costs were estimated (Table 3).

Subsequently, various diagnostic strategies were compared in terms of costs, effects (ie, QALYs), and incremental cost-effectiveness ratios (ie, costs per QALY gained) (Figs 2–4). With use of the low-stenosis-degree threshold as the indication for surgery, duplex US as a single-examination strategy would, on average, yield 11.33 QALYs at $30 400 (Fig 2). Duplex US was both less expensive and more effective—that is, it was dominant—than nearly all other strategies, including DSA, the reference strategy. Performing duplex US in combination with MR angiography as a definitive examination or relying on the initial duplex US results if MR angiography appeared to be impossible would result in a marginal gain in QALYs. However, having all patients undergo MR angiography in addition to duplex US would yield considerable additional costs and thus result in a prohibitive incremental cost-effectiveness ratio for the combination strategy (>$1 665 000 per QALY gained).

All other strategies were less effective and more expensive—in other words, they were dominated. Notably, performing DSA in patients who could not undergo MR angiography or when duplex US and MR angiography yielded discordant results would result in QALY losses and increased costs. The strategy of performing duplex US as an initial examination and subsequently performing DSA if severe stenosis was suspected was also clearly dominated: This strategy, as compared with that of performing duplex US

TABLE 1
Sensitivities, Specificities, Proportions of Patients Requiring DSA, and Proportions of Patients Undergoing Nonindicated CEA according to Various Strategies

Examination Strategy	Sensitivity (%)*	Specificity (%)*	Patients Requiring DSA (%)†	Patients in Whom CEA Not Indicated (%)†
Only duplex US performed. If results positive, perform CEA.				
CEA indicated for ≥70% stenosis	87.5–98.6	59.2–75.7	0	13.1–22.0
CEA indicated for ≥50% stenosis	76.1–94.6	84.3–89.8	0	3.5–5.4
Only duplex US performed. If results positive, perform CEA. If results negative, perform DSA to exclude serious stenosis.				
CEA indicated for ≥70% stenosis	100	59.2–75.7	32.6–46.6	13.1–22.0
CEA indicated for ≥50% stenosis	100	84.4–89.8	32.6–46.6	3.5–5.4
Duplex US plus MR angiography performed. If either examination has positive results, perform CEA. If MR angiography impossible, rely on duplex US results.				
CEA indicated for ≥70% stenosis	96.8–98.4	51.4–65.5	0	18.6–26.3
CEA indicated for ≥50% stenosis	89.0–98.3	78.5–87.1	0	4.4–7.3
Only MR angiography performed. If results positive, perform CEA. If MR angiography impossible, perform DSA.				
CEA indicated for ≥70% stenosis	92.2–96.9	57.9–75.7	11.5	11.8–20.4
CEA indicated for ≥50% stenosis	80.4–94.6	84.5–91.8	11.5	2.6–4.8
Only MR angiography performed. If results positive, perform CEA. If results negative or MR angiography impossible, perform DSA to exclude serious stenosis.				
CEA indicated for ≥70% stenosis	100	57.9–75.7	40.8–51.4	11.8–20.4
CEA indicated for ≥50% stenosis	100	84.5–91.8	40.8–51.4	2.6–4.8
Duplex US (strict cutoff) plus DSA performed. If results positive, confirm them by performing DSA.				
CEA indicated for ≥70% stenosis	87.5–98.6	100	53.4–67.4	0
CEA indicated for ≥50% stenosis	76.1–94.6	100	53.4–67.4	0
MR angiography plus DSA performed. If combined examination impossible or has positive results, confirm results by performing DSA.				
CEA indicated for ≥70% stenosis	92.2–96.9	100	61.3–71.8	0
CEA indicated for ≥50% stenosis	80.4–94.6	100	61.3–71.8	0
Duplex US plus MR angiography performed. If both examinations have positive results, perform CEA. If MR angiography impossible, rely on duplex US results. If examinations have discordant results, rely on MR angiography results.‡				
CEA indicated for ≥70% stenosis	82.5–96.8	62.8–83.8	0	7.7–17.7
CEA indicated for ≥50% stenosis	64.9–91.7	88.2–93.5	0	1.9–3.5
Duplex US plus MR angiography performed. If both examinations have positive results, perform CEA. If MR angiography impossible, perform DSA. If examinations have discordant results, rely on MR angiography results.§				
CEA indicated for ≥70% stenosis	82.5–96.8	62.8–83.8	11.5	7.7–17.6
CEA indicated for ≥50% stenosis	64.9–91.7	88.2–93.5	11.5	1.9–3.5
Duplex US plus MR angiography performed. If both examinations have positive results, perform CEA. If MR angiography impossible or has discordant results, perform DSA.				
CEA indicated for ≥70% stenosis	96.3–98.4	58.0–80.2	18.4–27.9	7.7–17.6
CEA indicated for ≥50% stenosis	85.9–97.1	86.9–93.1	17.5–25.8	1.9–3.5
Duplex US plus MR angiography performed. If either examination has positive results or MR angiography impossible, confirm results by performing DSA.				
CEA indicated for ≥70% stenosis	96.8–98.4	100	60.9–67.5	0
CEA indicated for ≥50% stenosis	89.0–98.3	100	60.9–67.5	0
Duplex US plus MR angiography performed. If both examinations have positive results, confirm results by performing DSA. If MR angiography impossible or has discordant results, perform DSA.				
CEA indicated for ≥70% stenosis	96.3–98.4	100	66.7–74.1	0
CEA indicated for ≥50% stenosis	85.9–97.1	100	66.7–74.1	0
Only DSA (reference strategy) performed.				
CEA indicated for ≥70% stenosis	100	100	100	0
CEA indicated for ≥50% stenosis	100	100	100	0

Note.—All estimates of examination characteristics for individual examinations, as well as for combinations of examinations, were derived directly or by performing further analysis of the data presented in our previous report on the accuracy of noninvasive testing (14). The 13 strategies presented in this table can be expanded by considering different cutoff levels for positive examination results, with the associated sensitivity and specificity, and different criteria for endarterectomy. A total of 62 diagnostic strategies were analyzed.

* The ranges presented for the major strategies pertain to all underlying and coherent combinations of sensitivity and specificity of the substrategies conceived by using cutoff values for a positive examination result. All data, except values of 100%, are ranges.

† All data, except values of 0% and 100%, are ranges.

‡ With strategy in which MR angiography is impossible and thus duplex US results are relied on, somewhat higher sensitivity and lower specificity are expected. Accordingly, the overall examination characteristics similarly will change marginally. Also, the proportion of patients who undergo unnecessary CEA will increase marginally; this effect is accounted for in the model.

§ With strategy in which MR angiography is impossible and thus DSA is performed, overall sensitivity and specificity will increase marginally. This effect is accounted for in the model.

alone, would generate $2000 in additional costs and cause a 0.06 QALY loss.

Sensitivity Analysis

We took into account the variability of criteria used to indicate positive examination results and of criteria indicating the need for surgery in a sensitivity analysis of coherent combinations of sensitivity, specificity, and indication to operate. Within the major categories of the diagnostic strategies, varying the above criteria resulted in a move along the negatively sloped lines observed in Figures 2–4. Figure 4 illustrates this finding for the strategy of performing duplex US alone. Using both a lower diagnostic threshold and a lower threshold indication to perform surgery would lead to lower costs and improved health outcomes. The rank of strategies in terms of incremental cost-effectiveness ratios, however, would remain the same.

Additionally performed sensitivity analyses revealed that the results were robust. The ranges for the sensitivity analysis are presented in Table 4. The utilities for minor and major stroke were varied by ±0.1, and this variability did not alter the order of preference. Similarly, the age of symptomatic patients was varied between 45 and 65 years, and the discount rate was varied between 0% and 10%, and these variances had no effect on the order of preference. The cost estimates of the diagnostic examinations were varied by a factor of 0.5–2.0, and these variances did not alter the order of preference among the strategies. As expected, increasing the cost of MR angiography resulted in even more unfavorable incremental cost-effectiveness ratios. Likewise, varying the costs of surgery did not cause a substantial altering of the results. However, with high surgery costs (>$6550 per procedure), strategies involving the use of higher threshold values for positive examination results—that is, those involving the use of strict positivity criteria implying lower sensitivity and higher specificity—became slightly more favorable.

TABLE 2
Cost Estimates Used in Markov and/or Decision Model

Cost Component	Cost Estimate Used ($)*	Data Source
Duplex US	53 (27–107)	Current cost study
DSA†	1169 (584–2338)	Current cost study
MR angiography‡	256 (128–512)	Current cost study
CEA	3062 (1531–6125)	Current cost study
Procedure to treat minor stroke	4056 (2028–8112)	References 18–21
TIA after CEA or major stroke§	78 (39–155)	Expert opinion
TIA in patients treated nonsurgically	1168 (584–2335)	Expert opinion
Minor stroke during 1st year	5652 (2826–11 305)	References 18–21
Minor stroke during subsequent years	967 (484–1935)	References 18–21
Major stroke during 1st year	32 233 (16 117–64 467)	References 18–21
Major stroke during subsequent years	18 821 (9411–37 642)	References 18–21
Death‖	2404 (1202–4809)	Expert opinion

* Numbers in parentheses are cost ranges, in U.S. dollars.
† Includes hospitalization.
‡ Excludes contrast material–induced enhancement.
§ Limited diagnostic work-up and consultation with general practitioner are assumed, whereas consultations with general practitioner and specialist and diagnostic examinations are assumed for potential candidates for surgery—that is, those treated nonsurgically.
‖ Consultation with general practitioner and specialist, and for half the patients, emergency transportation and admittance to intensive care unit or general ward and diagnostic examinations are accounted for. In the model, the costs associated with death are accounted for as transition costs—a one-time event with associated costs.

TABLE 3
Initial Health States in Markov Model and Associated Expected Life-Years, QALYs, and Lifetime Costs

Initial Health States in Markov Model*	No. of Life-Years	No. of QALYs	Lifetime Costs ($)
0%–49% Stenosis treated with aspirin after TIA	14.0	12.9	23 271
50%–69% Stenosis treated with aspirin after TIA	14.0	12.5	29 577
70%–99% Stenosis treated with aspirin after TIA	13.9	11.9	40 606
Occlusion treated with aspirin after TIA†	13.9	13.9	2 399
0%–49% Stenosis treated with aspirin after minor stroke‡	14.0	10.6	34 188
50%–69% Stenosis treated with aspirin after minor stroke‡	14.0	10.4	39 784
70%–99% Stenosis treated with aspirin after minor stroke‡	13.9	10.1	49 284
Occlusion treated with aspirin after minor stroke†	13.9	11.1	15 855
CEA after TIA	14.0	13.0	20 977
CEA after minor stroke‡	14.0	10.7	32 105
Major stroke treated with aspirin§	13.9	2.8	264 360
Death (absorbing state)	0	0	0

Note.—Estimates were obtained by using the prognostic Markov model. The estimated (quality adjusted) life expectancies, as well as the costs, were estimated with Markov modeling by using data reported in the literature (18–21, 23–26).
* The initial health states reflect the outcomes after diagnostic work-up and treatment.
† Occlusion is assumed not to result in further ipsilateral events; contralateral events were not taken into account.
‡ Minor stroke as initial event or as a result of diagnostic work-up or treatment.
§ Regardless of underlying stenosis, no further treatment or serious prognosis assumed.

The likelihood of complications associated with DSA was varied by a factor of 0.3–3.0, and little effect was observed. At very low stroke rates (<1%), incremental cost-effectiveness ratios decreased substantially. The likelihood of complications associated with CEA was varied by a factor of 0.3–3.0, and the variances did not change the order of preference. At low periprocedural mortality (<1%) and stroke (<5%) rates, duplex US dominated all other strategies. At high stroke rates (>10%), strategies with high threshold values for positive results became favorable.

The proportion of patients who were unfit or unwilling to undergo MR angiography, which varied between 3% and 30%, had no effect on the rank of the strategies. At high estimates of this range of proportions, the incremental cost-effectiveness ratio for the combination strategies became increasingly unfavorable. Similarly, the proportion of strokes classified as major had little effect. Only at implausibly high proportions of major stroke (>50%) did the combination strategy reach an acceptable incremental cost-effectiveness ratio (<$27 750 per QALY gained).

DISCUSSION

The results of this study show that in terms of the balance between costs and

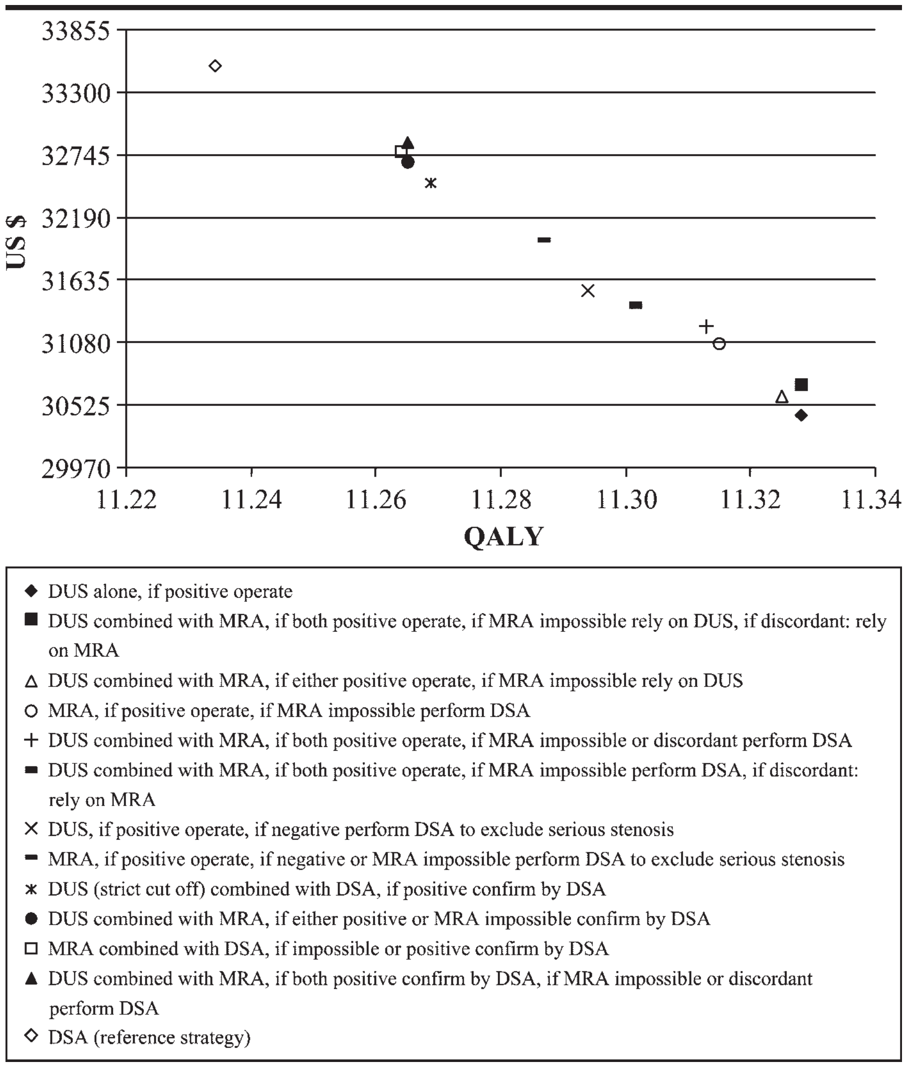

Figure 2. Graph illustrates expected lifetime costs versus lifetime QALYs at 50% stenosis threshold for surgery. For all the major groups of similar strategies, the optimal strategy at this low threshold for surgery is presented. Duplex US *(DUS)* alone appears to be the optimal strategy. *MRA* = MR angiography.

effects, the single-examination duplex US strategy is optimal for establishing a final diagnosis and a treatment plan for patients with symptomatic carotid artery stenosis. The combination strategy of duplex US and MR angiography has a slight benefit in terms of clinical outcome but at extremely high additional costs. To fully comprehend this result, several key issues should be considered. Endarterectomy has a substantial treatment benefit and generally is associated with relatively low risk. Patients with moderate-grade stenosis who are inadvertently judged to have high-grade stenosis (ie, false-positive cases) can, on average, expect a minor benefit from endarterectomy. Therefore, the gain from decreasing the rate of false-positive cases by means of verification with MR angiography or DSA is quite limited.

Another important finding was that the use of various positivity criteria had limited effect on the overall results of the study. At higher stenosis thresholds, specificity increased, with the result being a lower proportion of patients who underwent surgery. Since patients with moderate-grade stenosis may benefit from surgery, high thresholds for both the diagnostic examinations and the policy to perform surgery actually yield less favorable cost-effectiveness ratios. Accordingly, warnings regarding the misclassifications and overtreatments that may result from using a "nonperfect" examination (ie, examination that, according to strict criteria to perform surgery for 70%–99% stenosis, would result in overtreatment) in symptomatic patients may not be clinically relevant (28).

Also, sensitivity analyses of the likelihood of complications resulting from DSA or surgery, and the cost estimates in general, revealed that the rank of the strategies was barely altered. The conventional strategy to always perform DSA as the final examination after duplex US was clearly inferior. Various other combined examination strategies, including performing DSA in cases of discrepancy between duplex US and MR angiographic findings or to confirm or rule out severe stenosis, also were inferior.

A comparable study by Kent et al (8) was published before the results regarding intermediate-grade (50%–69%) stenoses and the long-term results from the NASCET became available. The authors used a less complex model, assessed fewer strategies, and based the examination diagnostic characteristics on findings in a small sample of patients. Kent et al found that a combination strategy of duplex US and MR angiography, including DSA performed in cases of discordant findings, was favorable. However, they assumed a constant high risk of stroke in patients with severe stenosis—and consequently projected overly optimistic long-term benefits of endarterectomy—and underestimated the benefits for patients with intermediate-grade stenoses. Both the assumed high stroke risk and the underestimated benefits call for high specificity and justify the small risk associated with the diagnostic work-up. Thus, their acceptable incremental cost-effectiveness ratio for the combination strategy, including DSA, can be explained.

An interesting finding that is not often observed was the apparent negative correlation between costs and QALYs across the strategies. The ranks of the diagnostic strategies were determined on the basis of the prevention of incident (ie, major) strokes. Strokes are associated with both high costs and a reduced quality of life, which explain the negative correlation. In the analysis of costs and life-years, strokes still direct the costs incurred, but their effect on longevity is less apparent, leading to a scattered, noncorrelated distribution of costs and effects.

A point of surgical and technical interest that we cannot substantiate or reject on the basis of the available data pertains to anatomy—for example, that of the extracranial or intracranial part of the carotid arteries. Surgeons who perform surgery on the basis of duplex US results do so without detailed anatomic information. Some may argue that this information has no relevance in terms of the surgical approach or outcome, whereas others may challenge this opinion. The fact is that in all of the CEAs performed as a part of this study, the surgeons had detailed anatomic information because DSA was routinely performed. Single-examination duplex US will remain the optimal examination only if neither the complication rate nor the effectiveness is altered in the absence of anatomic information. We have not come across publications addressing this issue specifically; however, at present, numerous surgeries are performed solely on the basis of duplex US information.

With regard to the reliability of the above findings and the associated inferences made, we believe that although considerable extrapolation occurred while using the modeling techniques described in the Methods section, the results do not indicate a specific "sensitive" parameter that when used alters the ranking of strategies. The described diagnostic study was performed by using a large representative and consecutive sample of symptomatic patients. Moreover, the diagnostic values of the examinations were calculated on the basis of findings in the ipsilateral (symptomatic) carotid artery only, and, thus, the overestimation of specificity that would have resulted from also including the asymptomatic carotid arteries was avoided.

Some limitations of our study should be recognized. The included patients were selected on the basis of duplex US findings. Accordingly, the prevalence of severe stenosis and the diagnostic values of the examinations might be biased because not all of the symptomatic patients underwent MR angiography and DSA. Selective verification could have resulted in an overestimation of the sensitivity, particularly that of duplex US but also that of MR angiography, and an underestimation of the specificity. However, because these possible results apply to both duplex US (in this study, with duplex US considered a stringent "final" examination) and MR angiography, it is very likely that the examination characteristics would have changed proportionally. Accordingly, the ranking of the diagnostic strategies in terms of clinical outcomes would not have been affected. Because cost estimates were not affected, the ranking of cost-effectiveness ratios remained stable. Similarly, the combination of duplex US and MR angiography would still be associated with high additional costs that might well be considered unacceptable.

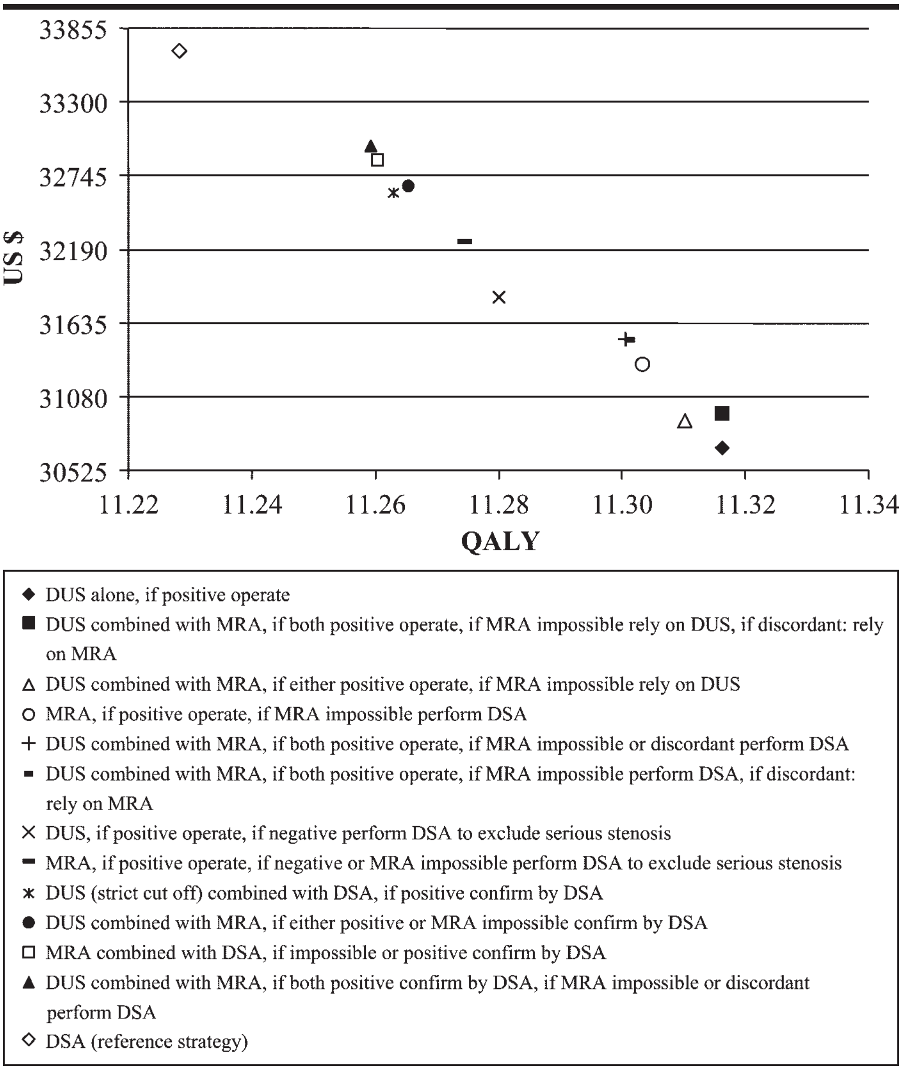

Figure 3. Graph illustrates expected lifetime costs versus lifetime QALYs at 70% stenosis threshold for surgery. For all the major groups of similar strategies, the optimal strategy at this high threshold for surgery is presented. Duplex US *(DUS)* alone appears to be the optimal strategy. *MRA* = MR angiography.

Also recall that the use of less stringent positivity criteria (which are associated with higher sensitivity and lower specificity) results in a move toward lower costs and better outcome along the cost-effectiveness line. A comparable but opposite effect would have been observed had we been able to obtain unbiased estimates of sensitivity (somewhat lower) and specificity (higher). The strategies that included DSA were inferior as a result of complications. Adjusting for verification bias would not have altered the results obtained in this respect.

Finally, we would like to stress that although strictly speaking the presented examination diagnostic values may not be correct, they do apply to the population of interest—that is, patients who are preselected and considered for surgery after undergoing an initial duplex US examination. We argue that in spite of possibly imperfect point estimates of examination diagnostic values, interpretations would remain the same. Also, a relatively recent report by a U.S. group who used data from a comparable setting supports our findings and adds to the credibility and robustness of our study results (28).

A limitation of our analyses is that our event-free survival estimates—for both the patients treated nonsurgically and those who underwent surgery—were based on trial results. The treatment results in a trial setting generally are better than those in routine practice, and this is especially true for nonsurgical therapies. However,

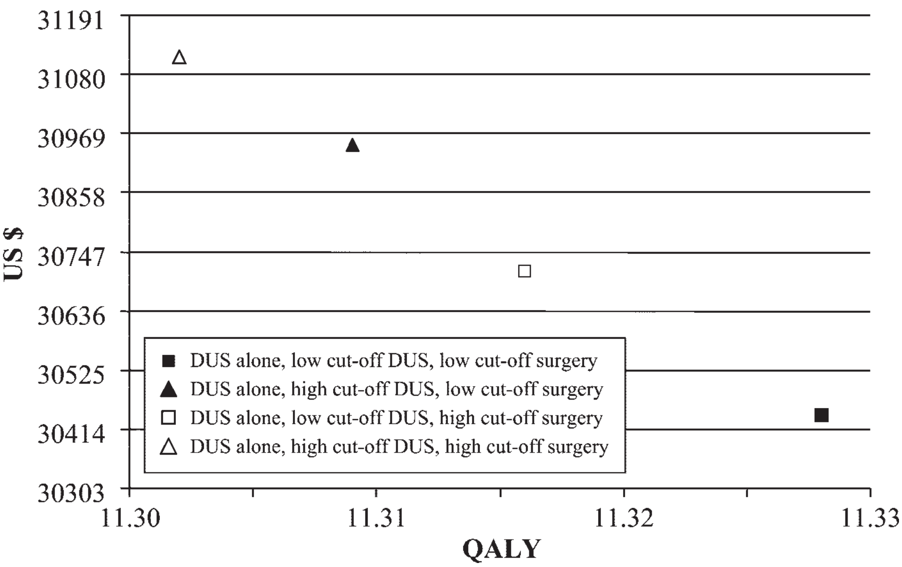

Figure 4. Graph illustrates expected lifetime costs versus lifetime QALYs for duplex US *(DUS)* alone at variable thresholds of the diagnostic examination and for surgery. For the optimal duplex US alone strategy, the effects of using different diagnostic thresholds (high and low cutoffs) and different thresholds for surgery (70%–99% and 50%–99% stenoses) are illustrated. The combination of a low cutoff for duplex US and a low threshold for surgery yields optimal results.

TABLE 4
Point Estimates and Ranges for Sensitivity Analysis

Variable	Point Estimate*	Data Source
Mean age at diagnosis (y)	55 (45–65)	Assumed
Utility health states		References 25, 26
Major stroke	0.2 (0.1–0.3)	
Minor stroke	0.8 (0.7–0.9)	
Discount rate	0.04 (0.0–0.10)	References 16, 24
Probability of stroke after DSA	0.03 (0.01–0.09)	Current study, references 3, 4
Probability of death after DSA	0.001 (0.0003–0.003)	Current study, references 3, 4
Probability of stroke after CEA	0.055 (0.015–0.15)	Current study, references 3, 4
Probability of death after CEA	0.0106 (0.003–0.03)	Current study, references 3, 4
Proportion of major strokes in cases of stroke	0.33 (0.10–0.66)	References 3, 15

* Numbers in parentheses are ranges.

since such “trial bias” would have affected all diagnostic strategies in a similar way, it is unlikely that it affected our cost-effectiveness results in a major way.

An additional limitation might be the fact that unrelated medical and nonmedical costs, such as the costs associated with and the effects of nonfatal contralateral strokes, were not accounted for. We reason, however, that regardless of whether endarterectomy was performed, the long-term prognosis associated with contralateral strokes or other cardiovascular outcomes would not have been altered. This reasoning obviously does not apply to periprocedural complications, but these were taken into account. We recognize that high-grade contralateral stenosis and associated high-competing morbidity and mortality might reduce the yield from CEA. We reason that this effect was accounted for, however, because differential cardiovascular risks based on the ipsilateral stenosis grade were incorporated. Moreover, in an incremental comparison of strategies, the long-term outcomes that are equivalent across strategies will “drop out” of the equation.

U.S. cost estimates may be different from European and particularly Dutch cost estimates. However, a more or less global increase in costs, in accordance with differences in U.S. and Dutch cost estimates, would not change the overall conclusions. In fact, if anything, the incremental cost-effectiveness ratio for the combination strategy would probably be even higher, and this higher ratio would strengthen our argument that adding MR angiography to the work-up is not cost-effective. Furthermore, our estimates reflect actual costs rather than reimbursements or charges, such as those available from Medicare, which may differ considerably. Moreover, our sensitivity analysis of cost estimates revealed that the costs of diagnostic examinations can vary across a wide range of settings, including U.S. clinical settings, without affecting the overall ranking of strategies.

Finally, we chose not to perform an extensive sensitivity analysis in the prognostic model. The results obtained in the prognostic Markov model were used as input for the diagnostic model. We believe this was an acceptable simplification because the underlying estimates used in the prognostic model are based on the results of large-scale multicenter trials. Taking into account the very certain trial results would have added substantially to the complexity of the modeling. However, one would not expect a change in overall results. We also did not perform any multivariable probabilistic sensitivity analyses and therefore cannot present formal measures of uncertainty. However, given the unambiguous results of the current univariate sensitivity analyses, this simplification seems justified.

An issue that has not been validated and that was alluded to earlier in this article is the usefulness of a strict stenosis grade threshold for surgery. Results from the NASCET (3) indicate that this threshold has limited benefit, particularly for male symptomatic patients with 50%–69% carotid stenosis who have had a TIA or minor stroke. This conclusion is based on results that show favorable cost-effectiveness ratios with use of a 50% stenosis threshold as compared with those associated with the use of a 70% stenosis threshold. Sensitivity analyses specifically addressing the complication rates of endarterectomy, however, revealed that when periprocedural stroke rates surpass 10%, the high stenosis threshold will yield more favorable outcomes. This finding is in accordance with previously expressed concerns that the advantages of surgery may be outweighed by complications (3,29). CEA, as well as the more recently available percutaneous interventions, should be performed only in centers that are able to maintain a stable and low complication rate (30). In our opinion, this requires continued

TABLE A1
Yearly Risk of Various Events Given Underlying Cardiovascular Status and Carotid Stenosis Percentage

Event	Probability Estimates				
	Stable Phase	Year 0	Year 1	Year 2	Year 3
Stroke after aspirin therapy in patient who had <50% stenosis and TIA	0.02	0.04	0.02	0.02	0.02
Stroke after aspirin therapy in patient who had 50–69% stenosis and TIA	0.02	0.08	0.04	0.02	0.02
Stroke after aspirin therapy in patient who had 70–99% stenosis and TIA	0.02	0.14	0.07	0.03	0.02
Stroke after aspirin therapy in patient who had occlusion and TIA	0	0	0	0	0
Stroke after aspirin therapy in patient who had <50% stenosis and minor stroke	0.02	0.04	0.02	0.02	0.02
Stroke after aspirin therapy in patient who had 50–69% stenosis and minor stroke	0.02	0.08	0.04	0.02	0.02
Stroke after aspirin therapy in patient who had 70–99% stenosis and minor stroke	0.02	0.14	0.07	0.03	0.02
Stroke after aspirin therapy in patient who had occlusion and minor stroke	0	0	0	0	0
Stroke after CEA in patient who had TIA	0.02	0.02	0.02	0.02	0.02
Stroke after CEA in patient who had minor stroke	0.02	0.02	0.02	0.02	0.02
Stroke after aspirin therapy in patient who had major stroke	0.02	0.14	0.07	0.03	0.02
TIA after aspirin therapy in patient who had <50% stenosis and TIA	0.01	0.02	0.01	0.01	0.01
TIA after aspirin therapy in patient who had 50–69% stenosis and TIA	0.01	0.04	0.02	0.01	0.01
TIA after aspirin therapy in patient who had 70–99% stenosis and TIA	0.01	0.07	0.035	0.015	0.01
TIA after aspirin therapy in patient who had occlusion and TIA	0	0	0	0	0
TIA after aspirin therapy in patient who had <50% stenosis and minor stroke	0.01	0.02	0.01	0.01	0.01
TIA after aspirin therapy in patient who had 50–69% stenosis and minor stroke	0.01	0.04	0.02	0.01	0.01
TIA after aspirin therapy in patient who had 70–99% stenosis and minor stroke	0.01	0.07	0.035	0.015	0.01
TIA after aspirin therapy in patient who had occlusion and minor stroke	0	0	0	0	0
TIA after CEA in patient who had TIA	0.01	0.01	0.01	0.01	0.01
TIA after CEA in patient who had minor stroke	0.01	0.01	0.01	0.01	0.01
TIA after aspirin therapy in patient who had major stroke	0.01	0.07	0.035	0.015	0.01

monitoring of complication rates and specific (ie, local) deliberations regarding optimal diagnostic and treatment strategies.

Finally, the emergence of contrast material–enhanced MR angiography should be addressed. Around the time that our study began, time-of-flight MR angiography was considered a state-of-the-art examination. By enabling one to avoid so-called flow voids, which at times may result in poor-quality images and difficulties in determining the stenosis grade, contrast enhancement could contribute to even higher accuracy of MR angiography, especially in terms of specificity. Yet, as our analysis results indicated, such a gain in accuracy would result in only a marginal gain in QALYs. Furthermore, contrast enhancement would increase the cost of MR angiography substantially, and, therefore, a very unfavorable incremental cost-effectiveness ratio would be expected.

We conclude that the use of duplex US as a single-examination strategy results in an optimal trade-off between costs and effectiveness and that only if society is willing to pay extraordinarily high sums of money per QALY gained should one consider performing MR angiography additionally. We believe that owing to the risk of complications, DSA should no longer be routinely performed in the process of selecting patients for CEA.

TABLE A2
Rate Differences for General Cardiovascular Events and Cerebrovascular Events Given Carotid Artery Stenosis Percentage and Vascular Status

Event	Rate Difference Estimates				
	Stable Phase	Year 0	Year 1	Year 2	Year 3
General cardiovascular mortality					
Associated with <50% stenosis	0.01	ND	ND	ND	ND
Associated with 50%–69% stenosis	0.015	ND	ND	ND	ND
Associated with 70%–99% stenosis	0.02	ND	ND	ND	ND
Associated with occlusion	0.025	ND	ND	ND	ND
Associated with CEA	0.015	ND	ND	ND	ND
Associated with major stroke*	0.02	ND	ND	ND	ND
Cerebrovascular mortality					
Associated with <50% stenosis	0.01	0.02	0.01	0.01	0.01
Associated with 50%–69% stenosis	0.015	0.06	0.03	0.015	0.015
Associated with 70%–99% stenosis	0.02	0.14	0.07	0.03	0.02
Associated with occlusion	0.025	0.175	0.0875	0.0375	0.025
Associated with CEA	0.01	0.01	0.01	0.01	0.01
Associated with major stroke*	0.02	0.14	0.07	0.03	0.02

Note.—ND = no data.
* No further diagnostic work-up or treatment other than aspirin therapy assumed.

APPENDIX

The probabilities of future ipsilateral events, with treatment, stenosis grade, and initial symptoms taken into account, are presented in Table A1. Data in the first row show that the likelihood of stroke occurring in a patient with less than 50% stenosis who was being treated with aspirin and whose first symptom was a TIA in the first year (year 0) after becoming symptomatic is 4%. The presented estimates were used in the prognostic Markov model.

Differences in rates of general cardiovascular mortality and cerebrovascular mortality for patients with symptomatic carotid artery stenosis are presented in Table A2. The cerebrovascular mortality rate is assumed to decrease to a baseline level by 4 years after the patient becomes symptomatic. These estimates are based on expert opinion and were used to adjust the mortality rates observed in the general population according to the fact that these patients have vascular disease. Mortality rates were adjusted according to the following formula: Age-specific mortality multiplied by rate ratio specific for carotid artery ste-

TABLE A3
Probabilities of Various Vascular Events and Prevalence Estimates according to Procedure and Carotid Artery Stenosis Percentage

Parameter	Estimate	Data Source
Probability of DSA resulting in stroke	0.03	NASCET, current study
Probability of DSA resulting in death	0.001	NASCET, current study
Probability of CEA resulting in stroke	0.055	NASCET, current study
Probability of CEA resulting in death	0.0106	NASCET, current study
Prevalence of 0%–49% stenosis	0.2267	NASCET, current study
Prevalence of 50%–69% stenosis	0.1828	NASCET, current study
Prevalence of 70%–99% stenosis	0.3849	NASCET, current study
Prevalence of occlusion	0.2056	Current study
Proportion of cases of major stroke in cases of stroke	0.333	NASCET, current study
Proportion of TIAs in symptomatic patients	0.333	Expert opinion
Proportion of cases in which MR angiography impossible*	0.1145	Current study

* These patients were assumed to have undergone DSA in most strategies.

TABLE A4
Proportions of Uninterpretable Combination Examination Results

Examination	Estimated Probability*
Duplex US assuming 50% stenosis threshold plus MR angiography assuming 50% stenosis threshold	
Of 0%–49% stenosis	0.0578
Of 50%–69% stenosis	0.0667
Of 70%–99% stenosis	0.0059
Of occlusion	0.0686
Duplex US assuming 50% stenosis threshold plus MR angiography assuming 70% threshold	
Of 0%–49% stenosis	0.1422
Of 50%–69% stenosis	0.4095
Of 70%–99% stenosis	0.0765
Of occlusion	0.0686
Duplex US assuming 70% stenosis threshold plus MR angiography assuming 70% stenosis threshold	
Of 0%–49% stenosis	0.0489
Of 50%–69% stenosis	0.2286
Of 70%–99% stenosis	0.0706
Of occlusion	0.0588
Duplex US assuming 70% stenosis threshold plus MR angiography assuming 50% stenosis threshold	
Of 0%–49% stenosis	0.0222
Of 50%–69% stenosis	0.0286
Of 70%–99% stenosis	0.0059
Of occlusion	0.0588

* Estimated probability of given examination having uninterpretable results.

nosis grade, where the rate ratio is calculated as $1 + RD_{cardio} + RD_{cerebro}$. RD_{cardio} is the general cardiovascular mortality rate difference, and $RD_{cerebro}$ is the cerebrovascular mortality rate difference. These estimates were used in the prognostic Markov model.

Estimates of the various probabilities and proportions used in the diagnostic decision model are presented in Table A3.

The proportions of patients in whom various combination strategies would have resulted in discordant duplex US and MR angiographic results are presented in Table A4. For each combination strategy, the various stenosis thresholds and stenosis grades were taken into account. All estimates were derived from actual data obtained in the current study. In the strategy in which DSA is used to make a final diagnosis in cases of discordance, the patients would have to undergo DSA. These estimates were used in the diagnostic decision model.

References

1. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325:445–453.
2. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991; 337:1235–1243.
3. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998; 339: 1415–1425.
4. Hankey GJ, Warlow CP, Molyneux AJ. Complications of cerebral angiography for patients with mild carotid territory ischaemia being considered for carotid endarterectomy. J Neurol Neurosurg Psychiatry 1990; 53:542–548.
5. Bendszus M, Koltzenburg M, Burger R, Warmuth-Metz M, Hofmann E, Solymosi L. Silent embolism in diagnostic cerebral angiography and neurointerventional procedures: a prospective study. Lancet 1999; 354:1594–1597.
6. 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; 26:1747–1752.
7. Blakeley DD, Oddone EZ, Hasselblad V, Simel DL, Matchar DB. Noninvasive carotid artery testing: a meta-analytic review. Ann Intern Med 1995; 122:360–367.
8. 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; 274:888–893.
9. Kagawa R, Moritake K, Shima T, Okada Y. Validity of B-mode ultrasonographic findings in patients undergoing carotid endarterectomy in comparison with angiographic and clinicopathologic features. Stroke 1996; 27:700–705.
10. AbuRahma AF, Robinson PA, Strickler DL, Alberts S, Young L. Proposed new duplex classification for threshold stenoses used in various symptomatic and asymptomatic carotid endarterectomy trials. Ann Vasc Surg 1998; 12:349–358.
11. Back MR, Wilson JS, Rushing G, et al. Magnetic resonance angiography is an accurate imaging adjunct to duplex ultrasound scan in patient selection for carotid endarterectomy. J Vasc Surg 2000; 32:429–438.
12. Modaresi KB, Cox TC, Summers PE, et al. Comparison of intra-arterial digital subtraction angiography, magnetic resonance angiography and duplex ultrasonography for measuring carotid artery stenosis. Br J Surg 1999; 86:1422–1426.
13. Kallmes DF, Omary RA, Dix JE, Evans AJ, Hillman BJ. Specificity of MR angiography as a confirmatory test of carotid artery stenosis. AJNR Am J Neuroradiol 1996; 17:1501–1506.
14. Nederkoorn PJ, Mali WP, Eikelboom BC, et al. Pre-operative diagnosis of carotid artery stenosis: accuracy of non-invasive testing. Stroke 2002; 33:2003–2008.
15. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351: 1379–1387.
16. Drummond MF, O'Brien BJ, Stoddart G, Torrance GW, eds. In: Methods for the

economic evaluation in health care. 2nd ed. New York, NY: Oxford University Press, 1997.
17. Oostenbrink JB, Koopmanschap MA, Rutten FH. Standardisation of costs: the Dutch manual for costing in economic evaluations. Pharmacoeconomics 2002; 20:443–454.
18. Bergman L, van der Meulen JH, Limburg M, Habbema JD. Costs of medical care after first-ever stroke in the Netherlands. Stroke 1995; 26:1830–1836.
19. de Haan R, Limburg M, van der MJ, van den Bos GA. Use of health care services after stroke. Qual Health Care 1993; 2:222–227.
20. van Straten A, van der Meulen JH, van den Bos GA, Limburg M. Length of hospital stay and discharge delays in stroke patients. Stroke 1997; 28:137–140.
21. Tung CY, Granger CB, Sloan MA, et al. Effects of stroke on medical resource use and costs in acute myocardial infarction. GUSTO I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Study. Circulation 1999; 99:370–376.
22. Hunink MGM, Glasziou PP, Siegel JE, et al. Decision making in health and medicine: integrating evidence and values. Cambridge, England: Cambridge University Press, 2001.
23. Central Bureau of Statistics. Lifetables Dutch population, men and women, 1998 and 1994–1998: monthly population statistics. Heerlen, the Netherlands: Central Bureau of Statistics, 1999; 9:19–23.
24. Oostenbrink JB, Koopmanschap MA, Rutten FF. Instructions for cost assessment, methods and directive of prices for economic evaluation in health care. Amstelveen, the Netherlands: Health Insurance Council, 2000.
25. Samsa GP, Matchar DB, Goldstein L, et al. Utilities for major stroke: results from a survey of preferences among persons at increased risk for stroke. Am Heart J 1998; 136:703–713.
26. Matchar DB, Pauker SG. Endarterectomy in carotid artery disease: a decision analysis. JAMA 1987; 258:793–798.
27. Elgersma OE, van Leersum M, Buijs PC, et al. Changes over time in optimal duplex threshold for the identification of patients eligible for carotid endarterectomy. Stroke 1998; 29:2352–2356.
28. Johnston DC, Goldstein LB. Clinical carotid endarterectomy decision making: noninvasive vascular imaging versus angiography. Neurology 2001; 56:1009–1015.
29. Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. BMJ 1997; 315:1571–1577.
30. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001; 357:1729–1737.