Suspected Carotid Artery Stenosis

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Suspected Carotid Artery Stenosis: Cost-effectiveness of CT Angiography in Work-up of Patients with Recent TIA or Minor Ischemic Stroke[1]

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Purpose: To assess the effectiveness and cost-effectiveness of state-of-the-art noninvasive diagnostic imaging strategies in patients with a transient ischemic attack (TIA) or minor stroke who are suspected of having carotid artery stenosis (CAS).

Materials and Methods: All prospectively evaluated patients provided informed consent, and the local ethics committee approved this study. Diagnostic performance, treatment, long-term events, quality of life, and costs resulting from strategies employing duplex ultrasonography (US), computed tomographic (CT) angiography, contrast material–enhanced magnetic resonance (MR) angiography, and combinations of these modalities were modeled in a decision tree and Markov model. Data sources included a prospective diagnostic cohort study, a meta-analysis, and a review of the literature. Outcomes were costs, quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios, and net health benefits (QALY-equivalents), with a willingness-to-pay threshold of €50 000 per QALY and a societal perspective. The strategy with the highest net health benefit was considered the most cost effective. Extensive one-way, two-way, and probabilistic sensitivity analyses to explore the effect of varying parameter values were performed. The reference case analysis assumed that patients underwent surgery 2–4 weeks after the first symptoms, and the effect of earlier intervention was explored.

Results: The reference case analysis showed that duplex US combined with CT angiography and surgery for 70%–99% stenoses was the most cost-effective strategy, with a net health benefit of 13.587 and 15.542 QALY-equivalents in men and women, respectively. In men, the CT angiography strategy with a 70%–99% cutoff yielded slightly more QALYs, at an incremental cost of €71 419 per QALY, compared with duplex US combined with CT angiography. In patients with a high-risk profile, in patients with a high prior probability of disease, and when patients could be treated within 2 weeks after the first symptoms, the CT angiography strategy with surgery for 50%–99% stenoses was the most cost-effective strategy.

Conclusion: In diagnosing CAS, duplex US should be the initial test, and, if its results are positive, CT angiography should be performed; patients with 70%–99% stenoses should then undergo carotid endarterectomy. In patients with a high-risk profile, a high probability of CAS, or who can undergo surgery without delay, immediate CT angiography and surgery for 50%–99% stenoses is indicated.

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In 10%–30% of patients with a transient ischemic attack (TIA) or stroke, the cause is a carotid artery stenosis (CAS) of 70% or greater (1,2). Detection of a CAS is essential to reduce the probability of a (recurrent) stroke. Carotid endarterectomy reduces the absolute risk of ipsilateral ischemic stroke by 18% in patients with 70%–99% symptomatic CAS and by 8% in patients with a stenosis of 50%–69%, as documented in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (3,4).The benefit of carotid endarterectomy, however, depends on the delay between the first symptoms of ischemia and surgery: The benefit from surgery decreases rapidly with an increasing delay (5).

Digital subtraction angiography (DSA) remains the reference standard for diagnosing a CAS, according to several large randomized trials, such as NASCET and the European Carotid Surgery Trial (1,4,6). Because DSA is both invasive and expensive (3), the question arises as to whether alternatives exist that overall would yield better outcomes. Although this question has been studied before, results of an analysis of the effectiveness and cost-effectiveness of, in particular, multidetector computed tomographic (CT) angiography alone and in comparison to duplex ultrasonography (US) and contrast material–enhanced magnetic resonance (MR) angiography have, to our knowledge, not yet been published (3,7–10).

The purpose of this study was to assess the effectiveness and cost-effectiveness of state-of-the-art noninvasive diagnostic imaging strategies in patients with a TIA or a minor stroke who are suspected of having CAS. Particular attention was paid to the time window between the first ischemic symptoms and carotid endarterectomy and the cutoff value chosen as an indication for surgery (70%–99% vs 50%–99% stenosis).

Advances in Knowledge

- The diagnostic performance of multidetector CT angiography is high.
- Multidetector CT angiography alone or combined with duplex US is the most cost-effective diagnostic test strategy for suspected carotid artery stenosis in the work-up of patients with a recent transient ischemic attack (TIA) or minor ischemic stroke.
- Patient sex, risk profile for recurrent stroke, and the time window between the first ischemic symptoms and carotid endarterectomy determine whether CT angiography alone versus the combination strategy of duplex US and CT angiography is the most cost effective and which cutoff value should be chosen as an indication for surgery (50%–99% vs 70%–99% stenosis).
- In women, the results were less sensitive to changes in the input values than in men.

Implications for Patient Care

- Our study results suggest that in patients with a TIA or minor stroke, the diagnostic work-up should be duplex US as the initial diagnostic test; CT angiography should then be performed if the duplex US results are positive, assuming carotid endarterectomy is performed 2–4 weeks after presentation in patients harboring stenoses of 70%–99%.
- Our study suggests that in patients with a high-risk profile, with a high prior probability of carotid artery stenosis, or who can undergo surgery within 2 weeks after the initial symptoms, immediate CT angiography and surgery for stenoses of 50%–99% are indicated.
- The optimal diagnostic strategy depends on the diagnostic tests available, local expertise, the patient's sex, the risk profile for recurrent stroke, and the time window between the first symptoms and carotid endarterectomy.

Materials and Methods

Study Population

The target patient population was patients with a TIA or minor stroke who were suspected of having CAS.

Decision Model

A decision model was developed to evaluate and compare various diagnostic strategies by using decision-analytical software (TreeAge Pro, version 3.5, 2009; TreeAge, Williamstown, Mass). We assessed all feasible strategies in normal practice, all tests separately, and CT angiography or contrast-enhanced MR angiography combined with duplex US. In the combination strategies, if duplex US results appeared positive or uninterpretable, a CT angiography or contrast-enhanced MR angiography examination followed. A noninvasive test with uninterpretable results was followed by a DSA examination in single noninvasive test strategies and if the results of the second test in a combination strategy were uninterpretable. We considered

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Abbreviations:
CAS = carotid artery stenosis
CI = confidence interval
DSA = digital subtraction angiography
EVPI = expected value of perfect information
HRR = hazard rate ratio
ICER = incremental cost-effectiveness ratio
NASCET = North American Symptomatic Carotid Endarterectomy Trial
NHB = net health benefit
QALY = quality-adjusted life-year
TIA = transient ischemic attack
WTP = willingness-to-pay

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two cutoff values for the indication for carotid endarterectomy: 70%–99% or 50%–99% stenosis. These cutoff values were also the positivity criteria used in interpreting test results. In combination strategies, we considered additional strategies by using the 50%–99% positivity criterion in interpreting the duplex US results if the indication for endarterectomy was 70%–99%, to maximize sensitivity (Fig 1). Both the advantages and the disadvantages of diagnostic tests and of treatment with endarterectomy were modeled.

A Markov model with a 1-year cycle length was developed to extrapolate and evaluate long-term outcomes of diagnostic work-up and subsequent treatment. More details about the decision model and Markov model are given in Appendix E1 (online) and Figure E1 (online).

Data Sources and Assumptions

Prior probability.—The prior probability of CAS was based on results of a cross-sectional prospective diagnostic cohort study of 351 patients with a TIA or minor stroke who were admitted between November 2002 and January 2005 to Erasmus University Medical Center, Rotterdam, the Netherlands. Percentage stenosis was categorized by using the NASCET method (1). Data in 194 male and 139 female patients who had a TIA or minor stroke were included in the study. Nineteen (9.8%) male patients and three female patients (2.2%) had a severe stenosis (70%–99%), and four (2.1%) male patients and two female patients (1.4%) had a moderately severe stenosis (50%–69%). To keep the input data consistent, we derived the prior probability from the same study from which we derived the accuracy of CT angiography. Nevertheless, we performed sensitivity analysis by using a wide range of possible prior probabilities to explore the effect of this variable on the decision. On average, male patients were 62 years of age and female patients were 61 years of age. The age range of the entire population was 19–90 years, with an average age of 62 years. All patients underwent duplex US and multidetector CT angiography of the carotid arteries. If one of the examinations showed a stenosis of 50%–99%, a DSA examination of the carotid arteries followed in the context of the prospective diagnostic cohort study. If neither duplex

Figure 1

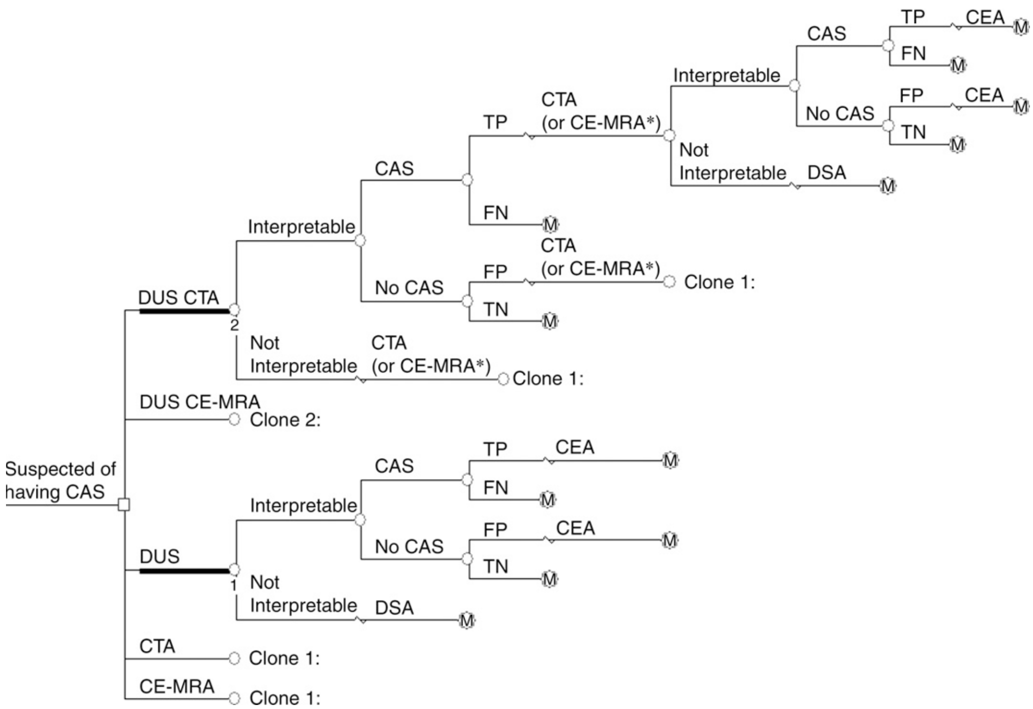

Figure 1: Schematic representation of decision tree. □ = Decision node, ○ = chance node, *M* = Markov node. After a positive result, carotid endarterectomy *(CEA)* is performed. DSA has the same structure as a single-test strategy. *Clone* = the structure of the tree at that point is identical to that of another subtree, which is marked with a black line and a corresponding number. Only one combination strategy (duplex US *[DUS]* plus CT angiography *[CTA]*) and one solo strategy (duplex US) have been expanded to limit the size of this figure. The other strategies have a similar structure, however, when combined with another test. * = For the other combination strategy, (duplex US plus contrast-enhanced MR angiography *[CE-MRA]*), the second test would be contrast-enhanced MR angiography instead of CT angiography. *FN* = false-negative, *FP* = false-positive, *TN* = true-negative, *TP* = true-positive.

Table 1

Prevalence, Diagnostic Tests, and Procedures: Parameter Estimates, Reported Ranges, and Data Sources

Parameter	Point Estimate*	Source
Prevalence of CAS		
0%–49% Stenosis	0.88 (0.84, 0.92)	Prospective diagnostic cohort study
Men	0.84 (0.78, 0.88)	Prospective diagnostic cohort study
Women	0.95 (0.90, 0.98)	Prospective diagnostic cohort study
50%–69% Stenosis	0.02 (0.01, 0.04)	Prospective diagnostic cohort study
Men	0.02 (0.00, 0.05)	Prospective diagnostic cohort study
Women	0.01 (0.00, 0.05)	Prospective diagnostic cohort study
70%–99% Stenosis	0.07 (0.04, 0.10)	Prospective diagnostic cohort study
Men	0.10 (0.06, 0.15)	Prospective diagnostic cohort study
Women	0.02 (0.00, 0.06)	Prospective diagnostic cohort study
100% Stenosis	0.03 (0.02, 0.06)	Prospective diagnostic cohort study
Men	0.05 (0.02, 0.09)	Prospective diagnostic cohort study
Women	0.01 (0.00, 0.05)	Prospective diagnostic cohort study
Carotid endarterectomy		
Risk of stroke in men	0.055 (0.015, 0.15)	Reference 3
Risk of stroke in women	0.070 (0.02, 0.26)	References 3, 11
Mortality	0.0106 (0.003, 0.03)	Reference 3
Costs†	4535 (3402, 5669)	Cost analysis
Time cost for patients (min)	4320 (3240, 5400)	Cost analysis
Contrast-enhanced MR angiography		
Sensitivity for 70%–99% stenosis	0.94 (0.88, 0.97)	Reference 8
Specificity for 70%–99% stenosis	0.93 (0.89, 0.96)	Reference 8
Sensitivity for 50%–99% stenosis	0.96 (0.90, 0.99)	Reference 8
Specificity for 50%–99% stenosis	0.96 (0.90, 0.99)	Reference 8
Uninterpretable (%)	0.114 (0.09, 0.143)	Reference 3
Mortality due to contrast agent allergy	0.0000007 (0, 0.000016)	Reference 12
Costs†	384 (288, 480)	Cost analysis
Time cost for patients (min)	120 (90, 150)	Cost analysis
CT angiography		
Sensitivity for 70%–99% stenosis	0.91 (0.71, 0.99)	Prospective diagnostic cohort study
Specificity for 70%–99% stenosis	0.99 (0.98, 1.00)	Prospective diagnostic cohort study
Sensitivity for 50%–99% stenosis	1.00 (0.88, 1.00)	Prospective diagnostic cohort study
Specificity for 50%–99% stenosis	0.98 (0.96, 0.99)	Prospective diagnostic cohort study
Uninterpretable (%)	0.003 (0, 0.02)	Prospective diagnostic cohort study
Mortality due to contrast agent allergy	0.0000007 (0, 0.000016)	Reference 12
Costs†	198 (146, 247)	Cost analysis
Time cost for patients (min)	90 (67.5, 112.5)	Cost analysis
DSA		
Sensitivity	1	Assumption
Specificity	1	Assumption
Risk of stroke	0.05 (0.003, 0.008)	Reference 13
Mortality due to contrast agent allergy	0.0000007 (0, 0.000016)	Reference 12
Mortality	0.001 (0.0003, 0.003)	Reference 13
Costs†	906 (680, 1133)	Cost analysis
Time cost for patients (min)	285 (214, 356)	Cost analysis
Duplex US		
Sensitivity for 70%–99% stenosis	0.89 (0.85, 0.92)	Prospective diagnostic cohort study
Specificity for 70%–99% stenosis	0.84 (0.77, 0.89)	Prospective diagnostic cohort study
Sensitivity for 50%–99% stenosis	0.84 (0.62, 0.95)	Prospective diagnostic cohort study
Specificity for 50%–99% stenosis	0.83 (0.73, 0.90)	Prospective diagnostic cohort study

Table 1 (continues)

Table 1 (continued)

Prevalence, Diagnostic Tests, and Procedures: Parameter Estimates, Reported Ranges, and Data Sources

Parameter	Point Estimate*	Source
Uninterpretable (%)	0.02 (0.008, 0.04)	Prospective diagnostic cohort study
Costs†	42 (32, 53)	Cost analysis
Time cost for patients (min)	80 (60, 100)	Cost analysis

* Data in parentheses are 95% confidence intervals (CIs).

† All costs were converted to 2007 euros.

US nor CT angiography showed a stenosis of greater than 50%, or if both examinations showed a stenosis of greater than 80%, DSA was not performed, to avoid unnecessary risk to the patient. Results of duplex US and CT angiography were interpreted independently. In the model, we used sex-specific prior probabilities of CAS (Table 1).

Diagnostic test performance.—Data on the performance of CT angiography were derived from the same cross-sectional study mentioned above. The sensitivity and specificity of CT angiography at a cutoff point of 70%–99% stenosis were 0.91 (95% CI: 0.71, 0.99) and 0.99 (95% CI: 0.98, 1.00), respectively. Sensitivity and specificity at a cutoff point of 50%–99% stenosis were 1.00 (95% CI: 0.88, 1.00) and 0.98 (95% CI: 0.96, 0.99), respectively.

Written informed consent for the prospective diagnostic cohort study was obtained from all 351 patients, and the local ethics committee approved the study.

The diagnostic performances of duplex US and contrast-enhanced MR angiography were based on results of a meta-analysis (8) that included 41 studies (2541 patients, 4876 arteries) published between January 1987 and April 2004. All studies included in the meta-analysis compared noninvasive imaging with intra-arterial angiography and met Standards for Reporting of Diagnostic Accuracy criteria; this ensured that only good-quality studies were included (14). Percentage stenosis was categorized by using the NASCET method (4). The sensitivity and specificity, respectively, of duplex US were 0.89 (95% CI: 0.85, 0.92) and 0.84 (95% CI: 0.77, 0.89) at a cutoff point of 70%–99% stenosis and 0.84 (95% CI: 0.62, 0.95) and 0.83 (95% CI: 0.73, 0.90) at a cutoff point of 50%–99% stenosis (Table 1). The sensitivity and specificity, respectively, of contrast-enhanced MR angiography were 0.94 (95% CI: 0.88, 0.97) and 0.93 (95% CI: 0.89, 0.96) at a cutoff point of 70%–99% stenosis and 0.96 (95% CI: 0.90, 0.99) and 0.96 (95% CI: 0.90, 0.99) at a cutoff point of 50%–99% stenosis (Table 1).

Information on the disadvantages of the tests was obtained from the prospective diagnostic cohort study and from the literature (13,15). The percentage of uninterpretable test results with duplex US was based on findings from the prospective diagnostic cohort study and was 1.99% (seven of 351 patients). Contrast-enhanced MR angiography cannot be performed in patients who are claustrophobic; this applied to 40 (11.4%) of 350 patients (3). Allergy to contrast medium confers a very small probability of dying (5.9×10^{-6}) (12), which applies to contrast-enhanced MR angiography, CT angiography, and DSA. DSA as such imposes a risk of inducing a major stroke or death; this risk was modeled (Table 1) (13).

Treatment results.—According to the latest publications on the treatment of CAS, carotid endarterectomy is still reported to be the best treatment (16–18). Consequently, we modeled carotid endarterectomy as the treatment for CAS. The periprocedural probability of stroke was modeled in a sex-specific fashion (Table 1) (11). Long-term outcomes were calculated in the same fashion as in the previous cost-effectiveness study by Buskens et al (3) (Table 2). Buskens et al combined published clinical NASCET trial data with expert opinion and age- and sex-specific national survival statistics. The benefit of surgical treatment as compared with medical treatment was calculated. From the same national survival statistics, we calculated the risk of dying of a noncerebrovascular accident.

Prognosis and patient risk profile.—In addition, we estimated the hazard rate ratios (HRRs) for stroke and death in patients with high-risk profiles compared with patients with low-risk profiles and explored their effect on the decision (Table 3) (20). A high-risk profile was defined as either unilateral weakness or a symptom duration of 60 minutes or longer or at least two of the following: age 60 years or greater, blood pressure 140/90 mm Hg or higher, speech impairment without weakness, a symptom duration of 10–59 minutes, and diabetes. High risk was associated with an HRR of 2.0 or greater. Finally, we explored the effect of time between first symptoms and treatment (Table 3) (1,3,5).

Quality of Life

Scores on a utility scale for quality of life after a TIA, after a minor stroke, and after a major stroke were estimated from several published studies (3,7,23). After a TIA or carotid endarterectomy, we assumed that patients had a utility of 0.88, which is similar to the mean utility in the general population of the same age (26). We estimated the utility after a minor stroke (0.71) from the literature, and we used a utility of 0.31 for after a major stroke (Table 3) (7,22,23). We also included disutilities for the events: For a TIA, we used a disutility of 0.0017, which we calculated in the same way as Buskens et al (3). For a minor or major stroke, we used

Table 2

HRRs and Event Rates: Parameter Estimates and Data Sources

Parameter	Year 0	Year 1	Year 2	Year 3	Long Term
HRR of CVA-related mortality after carotid endarterectomy	1.01	1.01	1.01	1.01	1.01
HRR of CVA-related mortality with 100% stenosis	1.175	1.09	1.04	1.03	1.03
HRR of CVA-related mortality with 70%–99% stenosis	1.14	1.07	1.03	1.02	1.02
HRR of CVA-related mortality with 50%–69% stenosis	1.06	1.03	1.015	1.015	1.015
HRR of CVA-related mortality with 0%–49% stenosis	1.02	1.01	1.01	1.01	1.01
Probability of stroke after carotid endarterectomy	0.02	0.02	0.02	0.02	0.02
Probability of stroke with 100% stenosis	0	0	0	0	0
Probability of stroke with 70%–99% stenosis	0.14	0.07	0.03	0.02	0.02
Probability of stroke with 50%–69% stenosis	0.08	0.04	0.02	0.02	0.02
Probability of stroke with 0%–49% stenosis	0.04	0.02	0.02	0.02	0.02
Probability of TIA after carotid endarterectomy	0.01	0.01	0.01	0.01	0.01
Probability of TIA with 100% stenosis	0	0	0	0	0
Probability of TIA with 70%–99% stenosis	0.07	0.04	0.02	0.01	0.01
Probability of TIA with 50%–69% stenosis	0.04	0.02	0.02	0.01	0.01
Probability of TIA with 0%–49% stenosis	0.02	0.01	0.01	0.01	0.01

Note.—Age- and sex-specific annual non–cerebrovascular accident (CVA)-related mortality data (in Appendix E1 [online]) were obtained from reference 19; all other data were obtained from reference 3.

Table 3

Quality of Life and Costs: Parameter Estimates, Reported Ranges, and Data Sources

Parameter	Point Estimate*	Source
HRRs for stroke		
Low- to high-risk profile	1.0 (1, 10.6)	Reference 20
Early or late treatment after first symptoms	1.0 (0.5, 2.0)	Reference 21
Quality-of-life weights		
After TIA	0.88 (0.84, 0.92)	References 7, 22, 23
After minor stroke	0.71 (0.68, 0.74)	Reference 23
After major stroke	0.31 (0.28, 0.34)	Reference 23
Disutility for TIA	0.0017 (0.0015, 0.0019)	Reference 3
Disutility for minor stroke	0.0524 (0.0523, 0.0525)	Reference 22
Disutility for major stroke	0.0524 (0.0523, 0.0525)	Reference 22
Costs†		
Medication per year	20 (15, 25)	Reference 24
Minor stroke during 1st year	7654 (5740, 9567)	Reference 3
Minor stroke subsequent year	1310 (982, 1637)	Reference 3
Major stroke during 1st year	43 650 (32 737, 54 562)	Reference 3
Major stroke subsequent year	25 487 (19 116, 31 859)	Reference 3
Travel cost per visit	5 (4, 6)	Estimation
Time cost per hour	18 (13, 22)	Estimation
Friction period (wk)	22	Reference 25
Friction cost per hour		
Men	51 (38, 63)	Reference 25
Women	39 (29, 48)	Reference 25

* Data in parentheses are 95% CIs.

† All costs were converted to 2007 euros

a disutility of 0.0524—a value we found in the literature (22).

Costs

We estimated the costs of duplex US, CT angiography, and DSA, including hospitalization, if applicable, in 2007 euros. Current costs, which included expenditures for personnel, equipment, materials, maintenance, housing, cleaning, administration, and overhead, were determined at the Erasmus Medical Center. Additional estimates of costs associated with hospitalization and stroke in the Dutch setting were obtained from the study of Buskens et al (3). For assessment of the costs of contrast-enhanced MR angiography and carotid endarterectomy, we performed a systematic review of the published literature (Table 1) (27).

Data Analysis

The reference-case analysis was performed for a 60-year-old man. We assumed that the average patient had a low-risk profile and underwent surgery between 2 and 4 weeks after the first symptoms (3,28). Diagnostic strategies were compared in terms of costs, effects (in quality-adjusted life-years [QALYs]), incremental cost-effectiveness ratios (ICERs), and net health benefit (NHB) by using a threshold willingness-to-pay (WTP) of €50 000 per QALY. NHB is a multiattribute outcome that combines effectiveness and costs in one measure, with NHB = QALYs − (costs/WTP). A strategy with the highest NHB was considered to be the most cost effective, which was equivalent to the highest QALYs at an ICER of less than the WTP of €50 000 per QALY. The reference case analysis was performed by using cost estimates and recommendations for cost-effectiveness analyses from the Netherlands that took productivity losses (friction costs) into account and discounted future costs and effectiveness at 4% and 1.5%, respectively (25). Also, a second WTP threshold of €80 000 per QALY was considered, as recommended by the Dutch Council for Public Health (29).

Subsequently, we performed the cost-effectiveness analysis from the societal perspective according to United

States recommendations, considering QALYs, health care costs, and direct non–health care costs (patient time and travel costs), and we discounted both future costs and effectiveness at 3% (30–32). Finally, we performed an analysis according to United Kingdom recommendations, discounting both future costs and effectiveness at 3.5% (33,34).

We performed extensive sensitivity analyses in which we explored varying assumptions about the risk profile of the patient, the timing of surgery after the first symptoms, and the prior probability of CAS. In addition, we performed a probabilistic sensitivity analysis by using 1000 Monte Carlo simulations in which we sampled from distributions of all uncertain variable values. We calculated the probability that a certain strategy was cost effective compared with other strategies with varying WTP thresholds and present acceptability curves. The expected value of perfect information (EVPI) (simulation with 1000 samples) was calculated to assess the value of performing further research (35). The population EVPI was calculated for the European Union by assuming an annual absolute stroke incidence of 1 million among women and 1 million among men and considering 5 years (36,37).

Figure 2

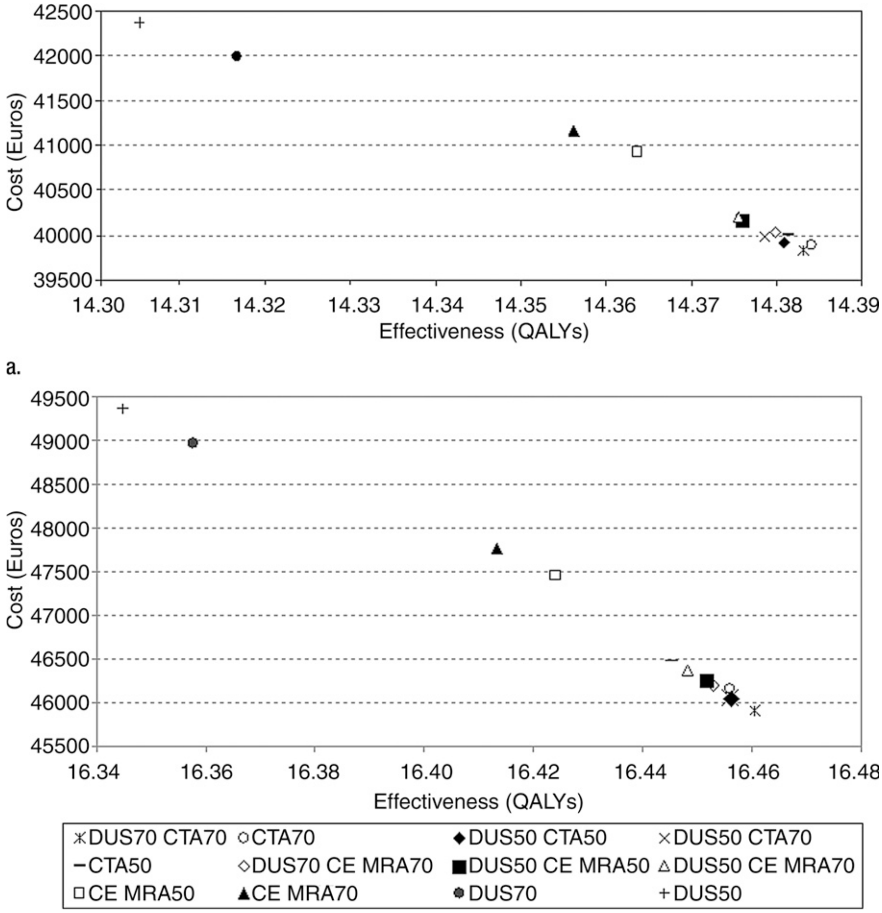

Figure 2: Cost-effectiveness graphs obtained by using the Dutch recommendations for cost-effectiveness analyses in **(a)** men and **(b)** women show expected lifetime cost versus QALYs for the various strategies. **(a)** In men, the combination strategy of duplex US *(DUS)* and CT angiography *(CTA)* with a cutoff of 70%–99% stenosis *(70)* yielded the highest effectiveness at the lowest costs compared with all other strategies except the solo CT angiography strategy with a cutoff of 70%–99% stenosis, which yielded slightly more QALYs, for €71 419 per QALY gained. **(b)** In women, the combination strategy of duplex US and CT angiography with a cutoff of 70%–99% stenosis yielded the highest effectiveness at the lowest costs compared with all other strategies. *50* = 50%–99% Stenosis, *CE MRA* = contrast-enhanced MR angiography.

Results

Reference Case Analysis

All strategies that used CT angiography or contrast-enhanced MR angiography, either as a solo strategy or in combination with an initial duplex US examination, demonstrated similar costs and effectiveness, presuming a 2–4 week delay in surgery. In men in similar conditions, the combination strategy of duplex US followed by CT angiography with a cutoff of 70%–99% stenosis dominated all other strategies, except the solo CT angiography strategy with a cutoff of 70%–99% stenosis, which yielded slightly more QALYs, for €71 419 per QALY gained (Fig 2a, Table 4). Likewise, in women, the duplex US–CT angiography combination strategy with a cutoff of 70%–99% stenosis dominated all other strategies (Fig 2b, Table 4). With a WTP of €50 000 per QALY, the duplex US–CT angiography strategy yielded the highest NHB in both men and women, whereas with a higher WTP of €80 000 per QALY, the solo CT angiography strategy would be preferable in men (Table 4). In both men and women, the least cost-effective strategy was duplex US performed as a solo test. Furthermore, all strategies employing contrast-enhanced MR angiography were dominated by the corresponding strategies employing CT angiography (Table 4).

Probabilistic Sensitivity Analysis

In men, the acceptability curve of the combination strategy of duplex US and CT angiography with a cutoff of 70%–99% stenosis was highest (33%–48%) for all WTP values of less than €100 000 per QALY (Fig 3a). The solo CT angiography strategy showed an increasing chance of being most cost effective with increasing WTP values. The value-of-information analysis demonstrated an EVPI for further research of €318 per male patient, which implies

Table 4

Reference Case Analysis Results

Patient and Strategy	Costs (€)	QALYs	ICER	NHB for WTP of €50 000 per QALY	NHB for WTP of €80 000 per QALY
60-Year-old man					
Duplex US and CT angiography for 70%–99% stenosis (reference strategy)	39 826	14.3832		13.587	13.885
CT angiography for 70%–99% stenosis	39 893	14.3841	€71 419	13.586	13.885
Duplex US and CT angiography for 50%–99% stenosis	39 914	14.3809	Dominated	13.583	13.882
Duplex US for 50%–99% stenosis and CT angiography for 70%–99% stenosis	39 986	14.3787	Dominated	13.579	13.879
CT angiography for 50%–99% stenosis	40 004	14.3815	Dominated	13.581	13.881
Duplex US and contrast-enhanced MR angiography for 70%–99% stenosis	40 028	14.3799	Dominated	13.579	13.880
Duplex US and contrast-enhanced MR angiography for 50%–99% stenosis	40 162	14.3761	Dominated	13.573	13.874
Duplex US for 50%–99% stenosis and contrast-enhanced MR angiography for 70%–99% stenosis	40 193	14.3755	Dominated	13.572	13.873
Contrast-enhanced MR angiography for 50%–99% stenosis	40 924	14.3637	Dominated	13.545	13.852
Contrast-enhanced MR angiography for 70%–99% stenosis	41 166	14.3562	Dominated	13.533	13.842
Duplex US for 70%–99% stenosis	41 997	14.3167	Dominated	13.477	13.792
Duplex US for 50%–99% stenosis	42 368	14.3052	Dominated	13.458	13.776
60-Year-old woman					
Duplex US and CT angiography for 70%–99% stenosis (reference strategy)	45 911	16.4605		15.542	15.887
Duplex US and CT angiography for 50%–99% stenosis	46 046	16.4562	Dominated	15.535	15.881
Duplex US for 50%–99% stenosis and CT angiography for 70%–99% stenosis	46 057	16.4559	Dominated	15.535	15.880
CT angiography for 70%–99% stenosis	46 153	16.4559	Dominated	15.533	15.879
Duplex US and contrast-enhanced MR angiography for 70%–99% stenosis	46 199	16.4531	Dominated	15.529	15.876
Duplex US and contrast-enhanced MR angiography for 50%–99% stenosis	46 256	16.4517	Dominated	15.527	15.873
Duplex US for 50%–99% stenosis and contrast-enhanced MR angiography for 70%–99% stenosis	46 362	16.4482	Dominated	15.521	15.869
CT angiography for 50%–99% stenosis	46 475	16.4452	Dominated	15.516	15.864
Contrast-enhanced MR angiography for 50%–99% stenosis	47 454	16.4239	Dominated	15.475	15.831
Contrast-enhanced MR angiography for 70%–99% stenosis	47 772	16.4133	Dominated	15.458	15.816
Duplex US for 70%–99% stenosis	48 965	16.3577	Dominated	15.378	15.746
Duplex US for 50%–99% stenosis	49 362	16.3448	Dominated	15.358	15.728

Note.—The cost-effectiveness analysis was performed by using recommendations from the Netherlands. Note that all strategies are dominated by the combination strategy of duplex US and CT angiography for 70%–99% stenosis (ie, this strategy is more or equally effective and less costly) except for CT angiography of 70%–99% stenosis in men, which had an ICER that was higher than the chosen threshold WTP. The percentages refer to the degree of stenosis that was considered a positive test result.

a population EVPI of €1.5 billion for the European Union.

In women, the acceptability curve showed that the duplex US–CT angiography combination strategy with a cutoff of 70%–99% stenosis was most cost effective, with an 80% probability, irrespective of the WTP (Fig 3b). The value-of-information analysis demonstrated an EVPI for further research of €40 per female patient, which implies a population EVPI of €193 million for the European Union.

Sensitivity Analysis

United Kingdom and United States recommendations.—Analyses performed by using United Kingdom and United States recommendations yielded the same results as the analysis performed by using the Dutch recommendations.

Patient risk profile.—For men, if the HRR for the risk profile was 1.03, indicating a low-risk profile, the duplex US–CT angiography combination strategy with a cutoff of 70%–99% stenosis yielded the highest NHB. For HRRs that were slightly higher but still close to 1.03, the solo CT angiography strategy with a cutoff of 70%–99% stenosis was the most cost effective. For HRRs

Figure 3

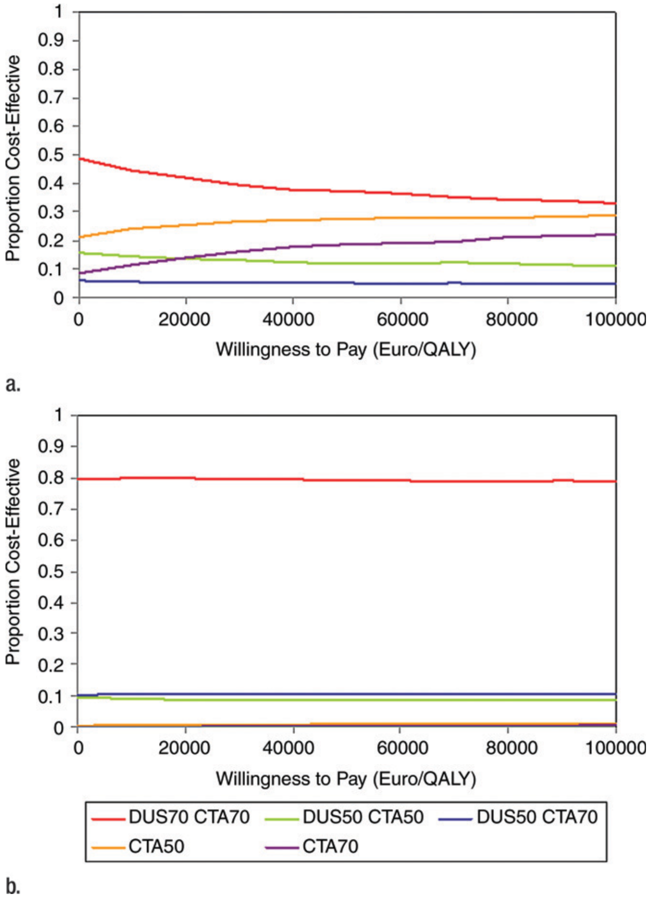

Figure 3: Acceptability curves with the five most competitive strategies for **(a)** men and **(b)** women. The graphs plot the proportion of simulated scenarios in the probabilistic sensitivity analysis for which each of the strategies is the most cost effective for varying thresholds of WTP. The probabilistic sensitivity analysis included all strategies. Strategies with a very low probability of being cost effective are not shown. *50* = 50%–99% Stenosis, *70* = 70%–99% stenosis, *CTA* = CT angiography, *DUS* = duplex US.

Figure 4

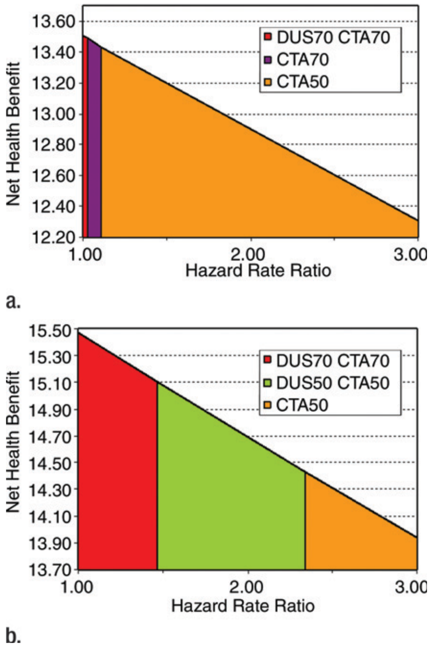

Figure 4: Graphs show results of sensitivity analysis exploring the effect of different patient risk profiles in **(a)** men and **(b)** women. Higher-risk profiles are represented with increasing HRRs on the x-axis. The outcome is expressed in NHB on the y-axis with a WTP of €50 000 per QALY. Shading = optimal strategy. *50* = 50%–99% Stenosis, *70* = 70%–99% stenosis, *CTA* = CT angiography, *DUS* = duplex US.

that were clearly greater than 1.11, the CT angiography solo strategy with a cutoff for surgery of 50%–99% stenosis yielded a higher NHB (Fig 4). For women, the duplex US–CT angiography combination strategy with a cutoff of 70%–99% stenosis was most cost effective for an HRR of 1.47 or less; above this threshold, the duplex US–CT angiography combination strategy with a cutoff of 50%–99% stenosis had a higher NHB. If the HRR was greater than 2.34, the solo CT angiography strategy with a cutoff of 50%–99% stenosis was the most cost effective (Fig 4).

Prior probability.—The prior probability of CAS was derived from the prospective diagnostic cohort study and was clearly lower than that in the study of Buskens et al (3). For men with a low prior probability of disease, the duplex US–CT angiography combination strategy with a cutoff of 70%–99% stenosis had the highest NHB. When the prior probability was greater than 0.20, the solo CT angiography strategy had the highest NHB, and when the prior probability was greater than 0.30, CT angiography with a cutoff of 50%–99% stenosis was optimal (Fig 5a). For women, the solo CT angiography strategy with a cutoff of 70%–99% stenosis had the highest NHB when the prior probability increased above 0.30; with a lower prior probability, the duplex US–CT angiography combination strategy with a cutoff of 70%–99% stenosis had the highest NHB (Fig 5b).

Timing of surgery.—For men undergoing surgery without delay, the solo CT angiography strategy with a cutoff of 50%–99% stenosis yielded the highest NHB (Fig 6a). With a longer delay, the solo CT angiography strategy with a cutoff of 70%–99% stenosis yielded the highest NHB, followed by the duplex US–CT angiography combination strategy with a cutoff of 70%–99% stenosis, if surgery was performed more than 4 weeks after first symptoms. For women undergoing surgery without delay, the duplex US–CT angiography combination strategy with a cutoff of 50%–99%

Figure 5

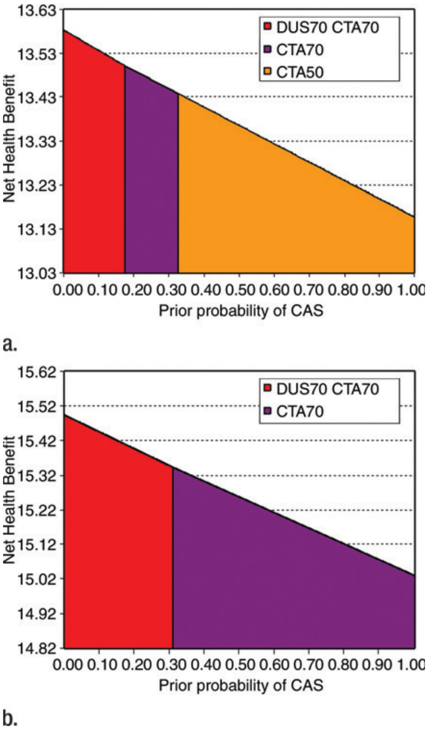

Figure 5: Graphs show results of sensitivity analysis exploring the effect of the prior probability of CAS (x-axis) on the NHB (y-axis) with a WTP of €50 000 per QALY in **(a)** men and **(b)** women. Shading = corresponding optimal strategy. *50* = 50%–99% Stenosis, *70* = 70%–99% stenosis, *CTA* = CT angiography, *DUS* = duplex US.

Figure 6

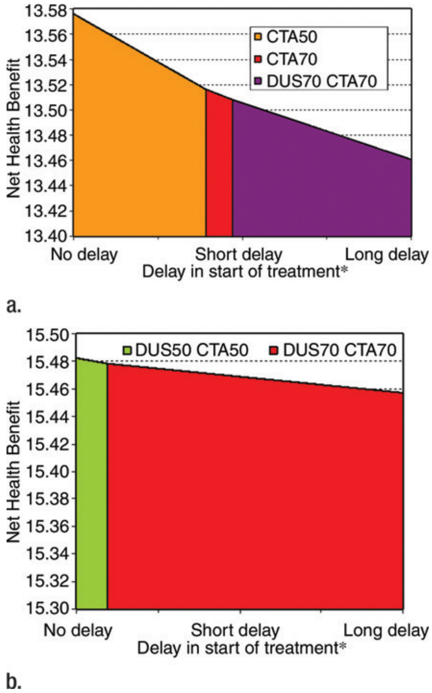

Figure 6: Graphs show results of sensitivity analysis exploring the effect of a delay in treatment after the first symptoms in weeks (x-axis) on the NHB (y-axis) with a WTP of €50 000 per QALY in **(a)** men and **(b)** women. Shading = corresponding optimal strategy. *"Short delay" = delay in treatment ranging from 2 to 4 weeks; "long delay" = delay in treatment of more than 4 weeks.

stenosis had the highest NHB, whereas a cutoff of 70%–99% stenosis would be best if surgery cannot be performed within 2 weeks (Fig 6b).

Discussion

Our study evaluated the cost-effectiveness of various noninvasive tests. The results demonstrated that the duplex US–CT angiography combination strategy with a cutoff of 70%–99% stenosis is the most cost-effective strategy. If the WTP is higher than we assumed—that is, €80 000 per QALY instead of €50 000 per QALY—then the solo CT angiography strategy would be more effective than the combination strategy at an acceptable ICER in men, whereas in women, the combination strategy would remain optimal. The sensitivity analysis demonstrated that with an increase in patient risk profile or with a higher prior probability of disease, the criterion to perform surgery should be more lenient (50%–99% stenosis) and the solo CT angiography strategy would be preferred to a combination test strategy. Also, if surgery can be performed without delay, a more lenient criterion (50%–99%) for surgery and a single-test strategy with CT angiography would be preferred. Notably, we found that all strategies employing contrast-enhanced MR angiography were dominated by the corresponding CT angiography strategies.

Although we found very small differences in QALYs across the strategies, there were clear differences in costs. This phenomenon is generally found in diagnostic test evaluation (38). Even though differences are small on average, they are nevertheless important because they pertain to a large group of patients and in aggregate can have large consequences. Note that a small average difference in the context of diagnostic test strategies implies that for most patients there is no difference between the evaluated strategies, but for a few patients the consequence can be very large in that a serious complication or event may be avoided with the optimal strategy.

In women, results were less sensitive to changes in the input values than in men. The probabilistic sensitivity analysis demonstrated that whereas for women results were fairly robust, results for men were less certain. The prior probability was lower among women and the risk of surgery was higher, implying that the mean expected gain of performing a diagnostic work-up is less in women; this led to more consistent results favoring less invasive imaging in the sensitivity analysis. This is also reflected in the results of the value-of-information analysis, which demonstrated a high value, especially in men, which suggests that it is worth exploring this issue and performing further studies in this area, especially for men.

As with all decision- and cost-effectiveness models, several assumptions had to be made to keep the model coherent. In finding parameter estimates, we chose to stay as close as possible to the primary data (especially with respect to costs) to ensure the internal consistency of the model, rather than using data from diverse published sources. This may have reduced the generalizability of our results. One assumption concerned the follow-up period and event rates, which were based on the article by Buskens et al (3). Their results dated from 1998, and since then a great deal of new information about event rates in the follow-up period has been published. We adjusted event rates for this new data by including HRRs that were found in the literature for the patient's risk profile and delay between first symptoms and surgery.

Radiation risk was not considered in our model. Although radiation risk is an important consideration in performing CT, the risk for this particular clinical patient population is small in comparison to their risk of cardiovascular events. In particular, the amount of radiation at neck CT angiography is low, only the thyroid is at risk, and the average age of patients with a TIA or minor stroke is high. With a latency period of about 12 years before cancer develops and the high probability that these patients will die of cardiovascular disease before a radiation-induced cancer can develop, radiation risk is unlikely to influence the decision (39). Finally, the risk of nephrotoxicity was not considered because this is a very small risk, with in most cases only temporary consequences. In patients with renal insufficiency, CT angiography and contrast-enhanced MR angiography are contraindicated; such patients were not considered in this analysis.

For the sensitivity and specificity of duplex US and contrast-enhanced MR angiography, we used data from the meta-analysis by Wardlaw et al (8). Other sources of diagnostic performance results of duplex US, CT angiography, and MR angiography were not applicable to our model because they did not report sensitivity and specificity for the criteria that we examined (both 70%–99% and 50%–99% stenoses), because they did not report results with state-of-the-art imaging techniques (ie, contrast-enhanced rather than nonenhanced MR angiography and multidetector instead of single-detector CT angiography), or because the results were not from a large prospectively performed clinical study (40,41). In the current analysis, we used sensitivity and specificity data for multidetector CT angiography from a recently completed prospective cohort study rather than from a meta-analysis because to our knowledge, no meta-analysis involving multidetector CT angiography has been published. A meta-analysis involving single-section CT angiography has been performed (42), but single-section CT angiography is currently no longer a state-of-the-art technique. One small retrospective pilot study of multidetector CT angiography of the carotid arteries (43) was published in 2009. This study showed high sensitivity and specificity and supports our estimates.

It is remarkable that in our study, duplex US turned out to be the most costly strategy; this is in stark contrast to the results reported by Buskens et al (3), which clearly showed that duplex US was the most effective and least costly strategy. Buskens et al, however, compared duplex US with nonenhanced rather than contrast-enhanced MR angiography and did not consider CT angiography. Similarly, Wardlaw et al (7,8) concluded that duplex US is the most cost-effective strategy. Their data were, however, based on a combination of single- and multidetector CT angiography instead of solely multidetector CT angiography, and only a limited number of studies reporting CT angiography results were available at the time of their analysis. We therefore used a higher sensitivity (91% vs 77%) and a higher specificity (99% vs 95%) for CT angiography than Wardlaw et al; this was justified by a recent study of multidetector CT angiography (43) that demonstrated similar values.

Two controversies in the management of CAS were considered in our analysis and proved to be important in choosing a diagnostic work-up: the cutoff value chosen as the indication for surgery (50%–99% vs 70%–99% stenosis) and the delay between first symptoms and surgery. The results highlight how the benefit that can be gained with treatment should influence the diagnostic work-up. Our results suggest that if the patient cannot undergo surgery in a timely fashion, an initial duplex US examination and a 70%–99% stenosis criterion for surgery is indicated. On the other hand, if the patient can undergo surgery in a timely fashion, immediate CT angiography and the use of a lenient criterion (50%–99% stenosis) as the surgery indication is beneficial.

Implementing the results of this study should always be done with consideration of the individual patient and the local situation. The prior probability of CAS and the risk profile of the individual patient or as observed in the local patient population may be very different and affect the choice of work-up. Similarly, logistics and waiting lists may influence the diagnostic work-up. Furthermore, local expertise with duplex US, CT angiography, and contrast-enhanced MR angiography may influence the decision: If, for example, no local expertise exists with CT angiography of the carotid arteries, whereas contrast-enhanced MR angiography can be performed at low cost, without delay, with good quality, and with high diagnostic performance, then our results justify the use of contrast-enhanced MR angiography instead of CT angiography. Finally, patient behavior, patient preferences, and local treatment options should be considered. Of note, our analysis highlights that if patients present rapidly after their first symptoms and local treatment of patients with TIA or minor stroke is streamlined, a solo CT angiography strategy with lenient criteria for surgery is indicated. The fact that benefit can be gained by streamlining the work-up of patients with TIA or stroke has been pointed out before, but as yet, not all centers are able to organize TIA and stroke care efficiently (5,28).

In conclusion, patients with a TIA or minor stroke should undergo duplex US as an initial diagnostic test, followed by CT angiography if the duplex US results are positive, with surgery for 70%–99% stenoses, while in patients with a high risk profile, with a high prior probability of carotid stenosis, or who can undergo surgery without delay, immediate CT angiography and surgery for 50%–99% stenoses are indicated.

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