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Cost-effectiveness of novel imaging tests to select patients for carotid endarterectomy

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ABSTRACT

Objective: We estimated the cost-effectiveness of novel imaging tests to select patients for carotid endarterectomy (CEA) in patients with significant carotid stenosis using a computer model and explored the minimum prognostic performance that a new confirmatory test must have in order to be cost-effective versus the guideline-based strategy.

Methods: The guidelines recommend initial duplex ultrasonography (DUS) followed by a confirmatory test if DUS shows 30–69% stenosis; a positive CT-angiography (CTA) is an indication for CEA. In an alternative strategy, we replaced CTA with CE-DUS, and in another strategy we replaced it by a hypothetical imaging test and estimated the minimum prognostic performance that the test must have in order to be cost-effective versus the guideline-based strategy. We assessed the potential cost-effectiveness in four age- and sex-specific subpopulations.

Results: For 60-year-old men, a perfect confirmatory test (100% sensitivity and specificity) improves health (0.066 quality-adjusted life years) and reduces costs (€110/$146) versus the guideline-based strategy. Potential health gain is smaller for 80-year-old men, while no health gain is expected for women. Assuming 100% sensitivity, a test must have a specificity of at least 66% for 60-year-old men and 87% for 80-year-old men to be cost-effective. Similarly, assuming 100% specificity, a test must have a sensitivity of at least 58% for 60-year-old men and 66% for 80-year-old men.

Conclusions: Information from new imaging technologies may improve stroke risk prediction and thereby improve decisions about which patients should undergo CEA. However, their cost-effectiveness strongly depends on the current test strategy and choice of patient subpopulation.

Introduction

Carotid endarterectomy (CEA) reduces the risk of recurrent stroke in selected populations: i.e., symptomatic patients with 70–99% stenosis, or patient subpopulations with 50–69% stenosis. The decision to select patients for CEA in daily clinical practice is mainly based on degree of carotid artery stenosis [1,2]. Several published studies have shown that the features of a vulnerable plaque (e.g., intraplaque hemorrhage, thin or ruptured fibrous cap, and large lipid-rich necrotic core) are related to risk of recurrent stroke [3–6].

Imaging of the atherosclerotic plaque with MRI, CT angiography (CTA), duplex ultrasonography (DUS) [7], or biomechanical analysis based on imaging information [8], can yield valuable information. This information can help to improve stroke risk prediction and classify patients into different subpopulations that differ in the risk of recurrent ischemic stroke. These tests can thereby improve decisions about which patients would benefit from CEA. This improvement in patient stratification is an integral part of the promise of precision medicine [9–11].

Abbreviations: CEA, carotid endarterectomy; CE-DUS, contrast-enhanced DUS; CE-MRI, contrast-enhanced MRI; CTA, CT angiography; DUS, duplex ultrasonography; FN, false negative; FP, false positive; ICERs, incremental cost-effectiveness ratios (€/$ per QALY gained); MRA, magnetic resonance angiography; OMT, optimal medical treatment; QALYs, quality-adjusted life years; TN, true negative; TP, true positive.

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However, the prognostic performance (i.e., sensitivity and specificity) of these tests is unknown. Several prospective cohort studies are currently ongoing determining the prognostic performance of various candidate tests (e.g., PARISk [12] and CAPIAS [13]). In this study, we estimated the potential cost-effectiveness of novel imaging tests using a computer model and explored the maximum health gain that these tests could achieve if they were perfect, in comparison with a guideline-based strategy. We also estimated the minimum prognostic performance that a new confirmatory test must have in order to be cost-effective versus the guideline-based strategy.

Methods

We applied the framework with general steps of early-CEAs of medical tests as developed by Buisman et al. [14]. This framework is a useful guidance for researchers performing early-CEAs of medical tests.

Patient population

We defined the patient population as follows: patients with a recent TIA or minor ischemic stroke (mRS $\leq$3). TIA was defined as a focal neurologic deficit of sudden onset lasting less than 24 h and with no signs of recent infarction on CT or MRI. Ischemic stroke was defined as a focal neurological deficit of sudden onset of presumed vascular origin, lasting at least 24 h, with brain imaging showing typical signs of brain infarction or no abnormalities.

Current imaging test strategies (including a guideline-based strategy)

As part of secondary prevention, patients are selected for CEA or optimal medical treatment (OMT) alone. The Dutch national stroke guidelines [15] were examined and interviews were conducted with vascular neurologists from different hospitals to ascertain whether the guidelines were used in clinical practice (see Buisman et al. [16]).

In general, after diagnostic evaluation and treatment in the acute phase, patients with a recent TIA or minor ischemic stroke undergo an assessment of carotid artery stenosis and subsequent treatment as part of secondary prevention (i.e., preventing a recurrent stroke). In the assessment of carotid stenosis, Dutch guidelines recommend DUS as the initial test and CTA or magnetic resonance angiography (MRA) as confirmatory test [15]. According to the initial DUS, the criterion for performing a confirmatory test is moderate (50–69%) carotid stenosis for men or severe (70–99%) carotid stenosis for women [15]. CEA is recommended for both men and women with severe (70–99%) carotid stenosis and a TIA or minor ischemic stroke in the past 6 months. In addition, a CEA is recommended for men with moderate (50–69%) carotid stenosis and a TIA or minor ischemic stroke in the past 3 months [15].

Since multiple imaging test strategies are used in clinical practice [16], we included various strategies in our analysis as comparators, including a guideline-based strategy (initial DUS and confirmatory CTA) and three other strategies: DUS-only, CTA-only, and CE-MRA-only.

New test strategy

Since there are many imaging tests currently being developed to improve risk prediction with imaging features of a vulnerable plaque, leading to a large number of possible combinations of tests, vascular neurologists were queried about the optimal combination of tests. We determined that the most likely application for a new imaging test to improve risk prediction in patients with a recent TIA or minor ischemic stroke would be a confirmatory test for patients with 30–69% stenosis based on an initial DUS. DUS is the preferred initial test since it is often used in current care, relatively cheap and simple to use.

In addition, we used contrast-enhanced DUS (CE-DUS) as a new confirmatory test for patients with 30–69% stenosis based on an initial DUS, because recent studies have shown an association between vulnerable plaque features assessed with CE-DUS and the recurrence of ischemic stroke events in TIA/stroke patients [9].

Model structure

A lifetime cost-effectiveness model was developed to perform the cost-effectiveness analyses. Fig. 1 shows the first part of the model in which use of tests and subsequent treatment were modeled. Patients who test positive, i.e., patients with a high-risk of a recurrent stroke, undergo CEA, whereas others receive OMT alone. Based on the prognostic test performance, patients are classified into four groups: true positive (TP), false positive (FP), false negative (FN), and true negative (TN). Final health outcomes depend on these classifications and subsequent treatment. Fig. 2 shows the health outcomes after CEA and OMT alone. If the test's sensitivity and specificity are less than 100%, the test misclassifies patients, resulting in inappropriate treatments and increased risk of ischemic stroke events. The final health outcomes include minor, major, fatal or no ischemic stroke. Death from other causes is incorporated by using the life expectancy from the Dutch population [17].

Model inputs and assumptions

Test performance

The performance of the imaging tests used in *current care* was based on the sensitivity and specificity to diagnose 70–99% carotid stenosis (see Table 1). The sensitivity and specificity of DUS and CE-MRA were based on a meta-analysis of 41 studies [18]. The performance of CTA was derived from a prospective cohort study of 351 TIA/minor ischemic stroke patients [19].

The performance of CE-DUS was based on the sensitivity and specificity to detect plaque rupture compared to ultrasonography and histological images [20]. The performance of the *new hypothetical* prognostic test was defined in terms of the ability to predict an ischemic stroke based on imaging features of vulnerable carotid plaque. TPs were defined as patients with a *positive test result* and a 100% lifetime risk of an ischemic stroke if they receive OMT alone. Since these patients subsequently undergo CEA, their risk of ischemic stroke is reduced. FNs were defined as patients with a *negative test result* and a 100% lifetime risk of an ischemic stroke if they receive OMT alone. Since these patients do not undergo CEA and instead receive OMT alone, their lifetime risk of ischemic stroke remains 100%. TNs were defined as patients with a *negative test result* and a 0% lifetime risk of an ischemic stroke if they receive OMT alone. Since these patients are correctly identified, they will receive OMT and continue to have a 0% risk of ischemic stroke. FPs were defined as patients with a *positive test result* and a 0% lifetime risk of an ischemic stroke if they receive OMT alone. Although these patients should receive OMT, they are misclassified, undergo CEA and therefore have a short-term risk of ischemic stroke due to surgical complications.

When these definitions are applied, a test with a higher sensitivity increases the chance that patients who will benefit from a CEA are correctly identified and treated. Similarly, a test with a higher specificity increases the chance that patients who will not benefit from a CEA are correctly identified and treated.

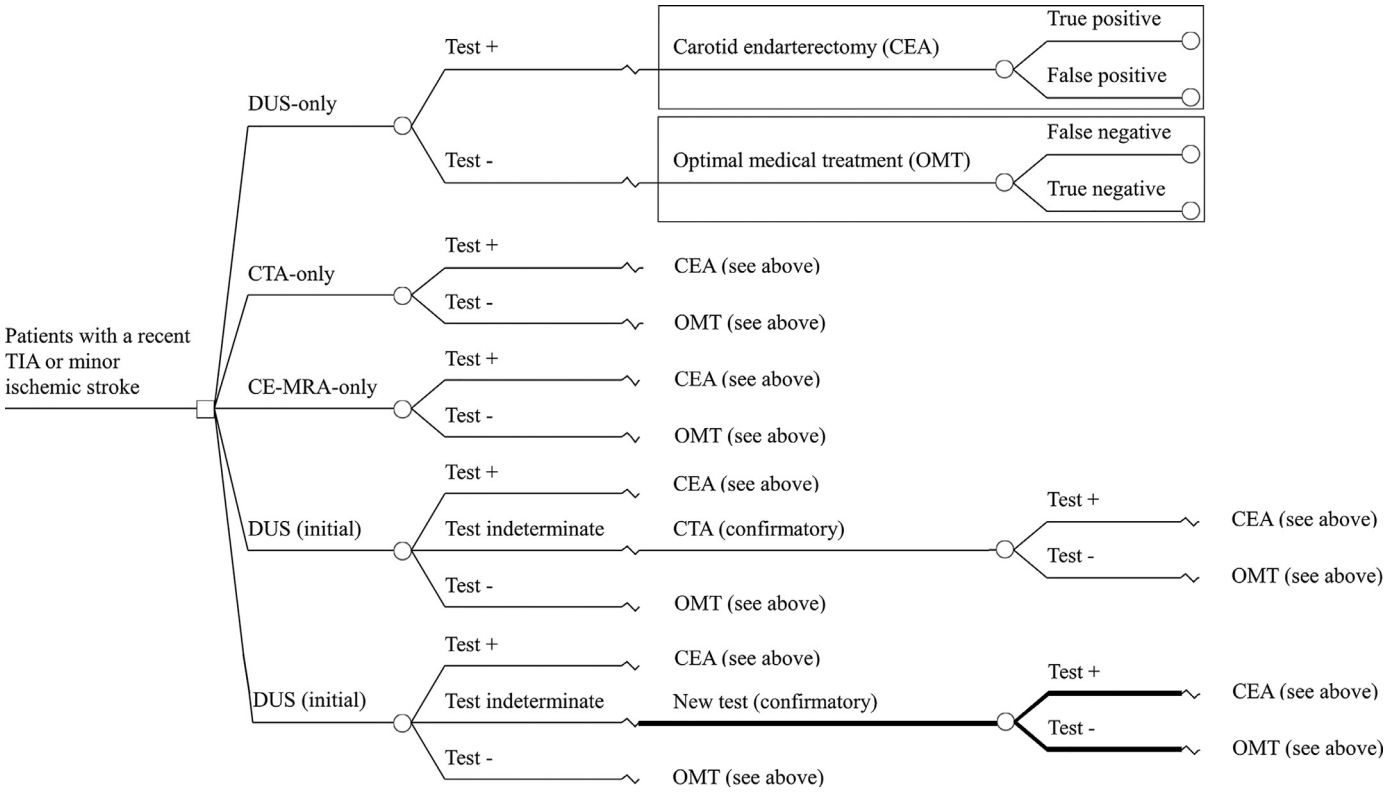

Fig. 1. Decision model – tests and subsequent treatment.
New test (confirmatory) = CE-DUS or hypothetical imaging test.

Table 1
Model input parameters.

Parameter	Value	SE	Distribution (alpha;beta)	Source
Performance of tests				
DUS – sensitivity	0.890	0.015	Beta (371;46)	[18]
– specificity	0.840	0.026	Beta (173;33)	[18]
CTA – sensitivity	0.910	0.041	Beta (44;4)	[19]
– specificity	0.990	0.005	Beta (376;4)	[19]
CE-MRA – sensitivity	0.940	0.015	Beta (225;14)	[18]
– specificity	0.930	0.015	Beta (257;19)	[18]
CE-DUS – sensitivity	0.913	–	–	[20]
– specificity	0.687	–	–	[20]
Health-related quality of life				
Baseline (recent TIA or minor ischemic stroke)	0.710	0.020	Beta (350;143)	[21]
After minor ischemic stroke	0.658	0.015	Beta (631;329)	[21,22]
After major ischemic stroke	0.310	0.015	Beta (283;629)	[21]
Costs (in 2014€)				
DUS	€125	€19	Gamma (€44;€3)	[25]
CTA	€189	€28	Gamma (€44;€4)	[25]
CE-MRA	€243	€36	Gamma (€44;€5)	[25]
CE-MRI (new test)	€362	€54	Gamma (€44;€8)	[25]
CE-DUS (new test)	€244	€37	Gamma (€44;€5)	[25]
Carotid endarterectomy	€7077	€68	Gamma (€10,788;€1)	[26]
Optimal medical treatment (per year)	€120	€18	Gamma (€44;€3)	Expert opinion
Minor ischemic stroke				[27]
first year	€8731	€1113	Gamma (€61;€142)	
subsequent years (per year)	€1494	€190	Gamma (€62;€24)	
Major ischemic stroke				[27]
first year	€49,790	€6350	Gamma (€61;€810)	
subsequent years (per year)	€29,072	€3708	Gamma (€61;€473)	
Fatal ischemic stroke (in year of fatal ischemic stroke)				[28]
Men – aged <65	€6663	€999	Gamma (€44;€150)	
Men – aged 65–74	€10,875	€1631	Gamma (€44;€245)	
Men – aged 75–85	€8735	€1310	Gamma (€44;€197)	
Men – aged >85	€10,640	€1596	Gamma (€44;€239)	
Women – aged <65	€7353	€1103	Gamma (€44;€165)	
Women – aged 65–74	€9984	€1498	Gamma (€44;€225)	
Women – aged 75–84	€12,043	€1806	Gamma (€44;€271)	
Women – aged ≥85	€14,484	€2173	Gamma (€44;€326)	

SE = standard error.

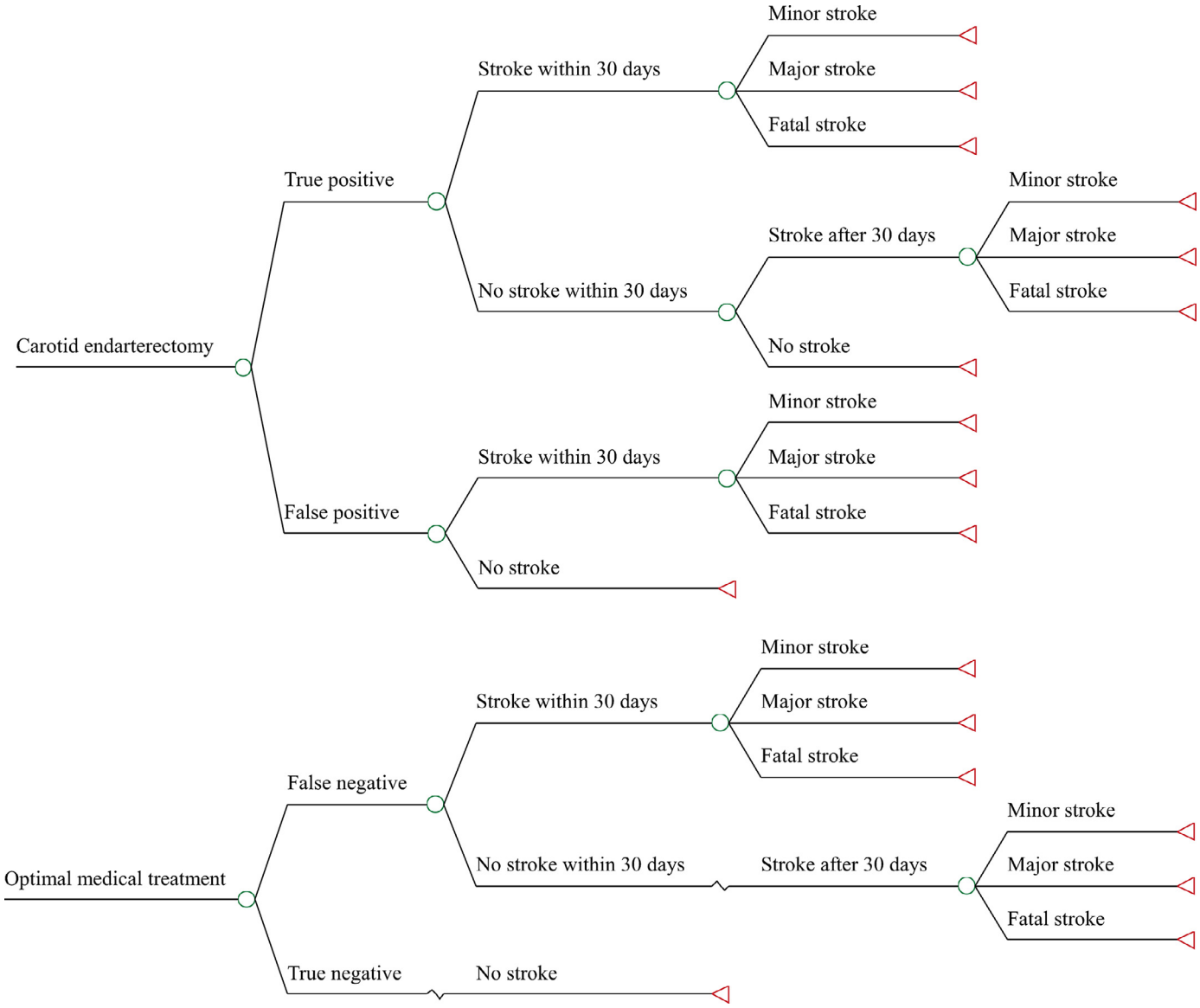

Fig. 2. Decision model – health outcomes after treatment.

Health-related quality of life (utilities) and life expectancy

We included quality-adjusted life years (QALYs) as a measure of health outcomes. Table 1 shows the utility weights by ischemic stroke severity used in our model (at baseline after a recent TIA or minor ischemic stroke, after minor ischemic stroke, and after major ischemic stroke). At baseline, all patients have had a recent TIA or minor ischemic stroke and a utility of 0.71 was assigned [21]. We assigned a utility of 0.66 when a second minor ischemic stroke occurred, which was calculated by combining the utility loss due to a minor ischemic stroke (0.0524) with the baseline utility [22]. We used a utility of 0.31 after major ischemic stroke [21].

Life expectancies of patients after a TIA, minor, or major ischemic stroke were estimated by combining survival data of ischemic stroke patients [23] with the life expectancy from the Dutch population in 2014 [17].

Costs

All costs were calculated in 2014 Euros and converted to US Dollars using a societal perspective (see Table 1). A mean exchange rate of €1 = $1.3285 was used for 2014, because daily exchange rates ranged from €1 = $1.2141 to €1 = $1.3953 in 2014 [24]. The total costs per patient consisted of costs of tests, treatment (i.e., CEA and medicines), and stroke-related societal costs. Test costs were based on tariffs provided by the Dutch Healthcare Authority [25]. Costs of CEA were based on a recent cost-analysis [26], and the costs of OMT were based on expert opinion. Stroke-related costs in the first and subsequent years after a minor or major ischemic stroke, and costs related to a fatal ischemic stroke were based on literature [27,28].

The cost of the new hypothetical confirmatory test was arbitrarily set at €362/$481 which was based on the unit cost of a MRI of the carotid plaque including contrast [25], because recent studies have shown an association between vulnerable plaque features assessed with MRI and the recurrence of ischemic stroke events in TIA/stroke patients [9]. The cost of the new CE-DUS was set at €244/$324 which was based on the unit cost of a DUS of the carotid plaque including contrast [25].

Risk of ischemic stroke

The risk of ischemic stroke after CEA or OMT alone was based on published estimates of the ECST-study [29,30] and reanalyzed according to the NASCET-method [31,32]. These estimates were

combined with a risk reduction of 33% to reflect that medical treatment has improved (e.g., widespread use of statins, better antiplatelet therapy, and lower targets for blood pressure control [33–35]).

Short-term risks referred to the risk of events occurred within 30 days after start of OMT or CEA. Long-term risks referred to the risk of events occurred after 30 days until death. We assumed that the risk after 10 years, in each subsequent year, would be equal to risk in the 10th year (see Supplementary Table e–1).

Analysis

The cost-effectiveness of the new test strategy was assessed versus the different comparators. Incremental cost-effectiveness ratios (ICERs) were calculated using the guideline-based strategy as comparator. ICERs were calculated as the difference in costs divided by the difference in QALYs. Probabilistic sensitivity analysis with 1000 simulations was performed. For each simulation, the values of the input parameters were randomly sampled from the appropriate distributions (see Supplementary Table e–1).

The cost-effectiveness of the new test strategy was assessed in four subpopulations (60-year-old men, 80-year-old men, 60-year-old women, and 80-year-old women). Cost-effectiveness planes were created to show the incremental costs and QALYs of the new imaging test strategies versus the guideline-based strategy. As illustration, we assumed that a perfect confirmatory test (100% sensitivity and specificity) was used. However, a new confirmatory test is unlikely to be perfect. Therefore, we estimated the minimum prognostic performance that a new confirmatory test must have in order to be cost-effective versus the guideline-based strategy using a QALY threshold of €30,000/$39,855. We used this QALY threshold because it is similar to the QALY threshold set by NICE [36]. We created four scenarios by varying the sensitivity and specificity. First, we estimated the minimum required specificity given a test with 100% sensitivity. Second, we estimated the minimum required sensitivity given 100% specificity. In the third and fourth scenarios, we estimated the minimum required specificity given a 90% sensitive test, and the minimum sensitivity required given a 90% specific test. In an alternative strategy, we used CE-DUS with known sensitivity, specificity and costs as a confirmatory test for patients with 30–69% stenosis. Annual discount rates were 4.0% for costs and 1.5% for health outcomes in accordance with the Dutch guidelines [37].

Results

A cost-effectiveness plane represents the difference between the new test strategy and guideline-based test strategy in health outcomes on the horizontal axis and in costs on the vertical axis. Fig. 3 shows a cost-effectiveness plane that summarizes the results for the four subpopulations. For 60-year-old and 80-year-old women, a perfect confirmatory test strategy leads to poorer health outcomes and higher costs than the guideline-based strategy. For 60-year-old and 80-year-old men, the triangles represent all combinations of sensitivity and specificity that a test can have in order to be cost-effective compared to the guideline-based strategy. These triangles show that a cost-effective test (i.e., a test with cost-effective combinations of sensitivity and specificity) usually results in better health outcomes but higher costs. The exception to this rule is the use of a perfect or near-perfect confirmatory test with 60-year-old men, where the result would be better health outcomes and lower costs).

Table 2 shows the cost-effectiveness results of the new test scenarios compared to the guideline-based strategy. The costs and health outcomes are dependent on the sensitivity and specificity of the tests, age, and sex.

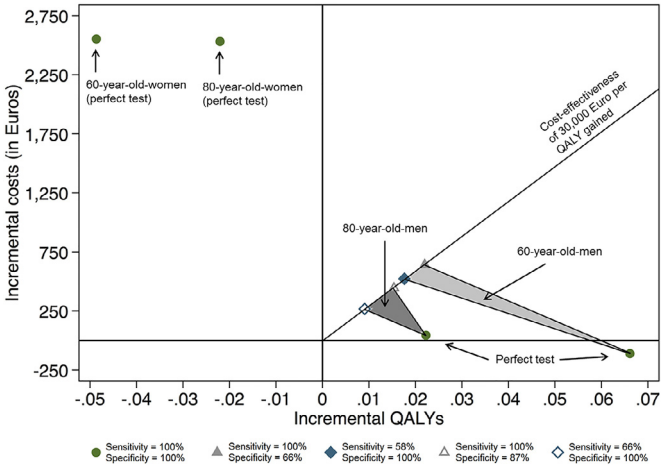

Fig. 3. Cost-effectiveness plane with different subpopulations.
Se = sensitivity; Sp = specificity; QALY = quality-adjusted life year; Cost-effectiveness of 30,000 Euro per QALY gained = QALY threshold line of €30,000/$39,855.

For 60-year-old men, the five new test scenarios and current CTA-only and CE-MRA-only strategies resulted in better health outcomes than the guideline-based strategy, while DUS-only resulted in poorer health outcomes. Furthermore, DUS-only, CTA-only, CE-MRA-only, and a perfect test resulted in lower costs than the guideline-based strategy, whereas the other four new test scenarios led to higher costs. Assuming 100% sensitivity, a test must have a specificity of at least 66% to be cost-effective. Similarly, a test with a specificity of 100% must have a sensitivity of at least 58%. Assuming 90% sensitivity, a test must have a specificity of at least 74% and a test with a specificity of 90% must have a sensitivity of at least 70%. Notice that the new imaging test must have a sufficiently high sensitivity and specificity to be cost-effective, and that the test specificity is more important than the test sensitivity.

For 80-year-old men, the minimum required test performance must be higher than for 60-year-old men. A test with a sensitivity of 100% must have a specificity of at least 87% (versus 66%) and a test with a specificity of 100% must have a sensitivity of at least 66% (versus 58%).

For 60-year-old and 80-year-old women, even a perfect confirmatory test is not cost-effective versus the guideline-based strategy since it leads to poorer health outcomes and higher costs. The poorer health outcomes arise because the new test strategy in women with 30–69% stenosis and not in women with 70–99% stenosis. In the guideline-based strategy, women with 70–99% stenosis based on DUS undergo a confirmatory test. In contrast, in the new test strategy, these women do not undergo a confirmatory test, which means that some of the women are undertreated and therefore show poorer health outcomes and incur higher costs.

We found that the maximum health gain achievable by using a perfect confirmatory test after a DUS is relatively small (i.e., 0.066 QALY in 60-year-old men, 0.022 QALY in 80-year-old men, and no gain in women).

In addition, Table 2 shows the cost-effectiveness of the new CE-DUS as confirmatory test compared to the guideline-based strategy. For all four subpopulations, this new test strategy is not cost-effective because the ICERs are greater than the QALY threshold of €30,000/$39,855 for 60-year-old and 80-year-old men and dominated by the guideline-based strategy for 60-year-old and 80-year-old women (i.e., poorer health outcomes and higher costs).

Discussion

Information from new imaging technologies can help to improve stroke risk prediction and thereby improve decisions about

Table 2
Cost-effectiveness of new test strategy versus current test strategies in different subpopulations.

Sex	Age	Sensitivity	Specificity	Test strategy	QALYs	ΔQALYs (vs GL)	Costs	ΔCosts (vs GL)	ICER (vs. GL)
Men	60			GL	11.589	*Reference*	€29,134/$38,705	*Reference*	*Reference*
				DUS-only	11.556	−0.033	€29,112/$38,675	-€22/–$29	€667/$886
				CTA-only	11.606	0.017	€28,590/$37,982	-€544/–$723	Dominant*
				CE-MRA-only	11.625	0.036	€28,768/$38,218	-€366/–$486	Dominant*
		100%	100%	DUS + new test	11.655	0.066	€29,024/$38,558	-€110/–$146	Dominant*
		100%	**66%**	DUS + new test	11.611	0.022	€29,775/$39,556	€641/$852	€29,136/$38,707
		58%	100%	DUS + new test	11.607	0.018	€29,657/$39,399	€523/$695	€29,056/$38,601
		90%	**74%**	DUS + new test	11.610	0.021	€29,749/$39,522	€615/$817	€29,286/$38,906
		70%	90%	DUS + new test	11.608	0.019	€29,697/$39,452	€563/$748	€29,632/$39,366
		91.3%	68.7%	DUS + CE-DUS	11.604	0.015	€29,813/$39,607	€679/$902	€43,969/$58,413
Men	80			GL	4.705	*Reference*	€19,047/$25,304	*Reference*	*Reference*
				DUS-only	4.694	−0.011	€19,016/$25,263	-€31/–$41	€2818/$3744
				CTA-only	4.712	0.007	€18,360/$24,391	-€687/–$913	Dominant*
				CE-MRA-only	4.718	0.013	€18,654/$24,782	-€393/–$552	Dominant*
		100%	100%	DUS + new test	4.727	0.022	€19,091/$25,362	€44/$58	€2000/$2657
		100%	**87%**	DUS + new test	4.720	0.015	€19,491/$25,894	€444/$590	€29,600/$39,324
		66%	100%	DUS + new test	4.714	0.009	€19,314/$25,659	€267/$355	€29,667/$39,413
		90%	**91%**	DUS + new test	4.718	0.013	€19,434/$25,818	€387/$514	€29,769/$39,548
		91%	90%	DUS + new test	4.718	0.013	€19,458/$25,850	€411/$546	€31,615/$42,001
		91.3%	68.7%	DUS + CE-DUS	4.707	0.002	€20,061/$26,651	€1014/$1347	€439,498/$583,873
Women	60			GL	13.171	*Reference*	€32,957/$43,782	*Reference*	*Reference*
				DUS-only	13.041	−0.130	€37,638/$50,002	€4681/$6219	Dominated**
				CTA-only	13.078	−0.093	€35,897/$47,689	€2940/$3906	Dominated**
				CE-MRA-only	13.096	−0.075	€35,773/$47,524	€2816/$3741	Dominated**
		100%	100%	DUS + new test	13.122	−0.049	€35,526/$47,196	€2569/$3413	Dominated**
		91.3%	68.7%	DUS + CE-DUS	13.081	−0.090	€37,292/$49,542	€4335/$5759	Dominated**
Women	80			GL	5.658	*Reference*	€20,540/$27,287	*Reference*	*Reference*
				DUS-only	5.607	−0.051	€24,083/$31,994	€3543/$4707	Dominated**
				CTA-only	5.622	−0.036	€22,799/$30,288	€2259/$3001	Dominated**
				CE-MRA-only	5.628	−0.030	€22,931/$30,464	€2391/$3176	Dominated**
		100%	100%	DUS + new test	5.636	−0.022	€23,097/$30,684	€2558/$3398	Dominated**
		91.3%	68.7%	DUS + CE-DUS	5.619	0.040	€24,571/$32,643	€4032/$5357	Dominated**

GL = guideline-based strategy (initial DUS + confirmatory CTA); new test = new confirmatory test.
* Dominant = better health outcomes and lower costs.
** Dominated = poorer health outcomes and higher costs.

which patients should undergo CEA. We examined how much these technologies can potentially improve the value of decision-making given the treatment options that are currently available.

We showed that multiple factors determine the cost-effectiveness of a new test strategy. First, the cost-effectiveness of the new confirmatory imaging test depends on which subpopulation is tested. In the two subpopulations of men that we examined a new test may be cost-effective if the test achieves minimum required prognostic performance, whereas even a perfect confirmatory test is not cost-effective among women with 30–69% stenosis. Amongst women, a new confirmatory test is likely to be cost-effective for women with 70–99% stenosis since they have a higher risk of ischemic stroke.

Second, the positioning of new tests (e.g., as initial or confirmatory test) has an impact on the cost-effectiveness. Since new tests are likely to be costly, we examined a test strategy in which patients first undergo DUS and then undergo a new imaging test as confirmatory test only if they have 30–69% stenosis according to DUS. We found that the maximum health gain achievable by using a perfect confirmatory test after a DUS is relatively small per individual (0.066 and 0.022 QALY gain for 60-year-old and 80-year-old men, respectively). While these are small gains per individual, they could be important at a population level and cost-effective to achieve. Obviously, a new imaging test could be used in other ways, including as the initial test; an exploration of other ways to use new tests merits further research.

Third, the choice of current test strategy is important. When DUS-only, CTA-only or CE-MRA-only is used as the current test strategy for 60-year-old women instead of the guideline-based strategy, a perfect confirmatory test strategy leads to better health outcomes and lower costs.

Fourth, clinical effectiveness of existing treatments is important, because a test forms just one part of patient management. The available treatments should be able to reduce the risk of an ischemic stroke; a new test with excellent prognostic performance is useless if the available treatment options are not very effective. On the other hand, if available treatments are both effective and relatively cheap, a test will have no value since all patients could receive treatment without the test. While improvements of medical treatment have reduced the risk of ischemic stroke [33–35], tests are still needed to identify the best candidates for treatment since existing treatments have both advantages and disadvantages.

Our study has some limitations. Only a single recurrent ischemic stroke event was allowed in our model even though patients can have more than one recurrent stroke. Furthermore, our model structure and inputs are based on literature and expert opinion. Ongoing studies such as PARISk [12] and CAPIAS [13] may yield better input for our model. Another limitation is the use of national tariffs instead of unit costs of tests. Hence, some of our results are not generalizable to other countries. The current test strategies used in our study do not necessarily reflect the test strategies seen elsewhere and the model inputs might be different (e.g., higher costs in the US). The US AHA/ASA guidelines recommend the use of at least one of the following tests to select suitable candidates for CEA: DUS, CTA or MRA [38]. Recommendations for the sequence of tests are not specified, which may result in a variety of test combinations. Furthermore, we expect that the life expectancy of ischemic stroke patients is generalizable to most developed countries because of similar overall life expectancies. However, differences in the quality of stroke care (e.g., risk of complications after CEA) might result in differences in QALYs. Therefore, similar analyses should be performed in other countries.

An Expected Value of Partially Perfect Information (EVPPI) can be useful given the uncertainties in the model. We would therefore recommend this for further research.

Conclusions

While new imaging tests can help to select the most appropriate treatments for patients with a recent TIA or ischemic stroke, their impact on costs and health outcomes depends on the current test strategy and the choice of patient subpopulation. Our analyses show that the maximum health gain of a perfect confirmatory test strategy versus the guideline-based test strategy may be limited.

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Competing interests

None declared

Ethical approval

Not required

Supplementary material

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CRediT authorship contribution statement

Leander R. Buisman: Writing - original draft, Writing - review & editing, Conceptualization, Formal analysis, Data curation, Methodology, Supervision. **Adriana J. Rijnsburger:** Writing - review & editing, Conceptualization, Formal analysis, Data curation. **Aad van der Lugt:** Writing - review & editing. **Paul J. Nederkoorn:** Writing - review & editing. **Peter J. Koudstaal:** Writing - review & editing. **William K. Redekop:** Writing - review & editing, Conceptualization, Data curation, Supervision, Funding acquisition.

References

[1] Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003;361:107–16.
[2] European Carotid Surgery Trialists' Collaborative Group Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379–87.
[3] Spagnoli LG, Mauriello A, Sangiorgi G, et al. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. JAMA 2004;292:1845–52.
[4] Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. Circulation 2006;113:2320–8.
[5] Kwee RM, Van Oostenbrugge RJ, Mess WH, et al. MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. J Magn Reson Imaging 2013;37:1189–94.
[6] Wintermark M, Arora S, Tong E, et al. Carotid plaque computed tomography imaging in stroke and nonstroke patients. Ann Neurol 2008;64:149–57.
[7] Van Engelen A, Wannarong T, Parraga G, et al. Three-dimensional carotid ultrasound plaque texture predicts vascular events. Stroke 2014;45:2695–701.
[8] Chai CK, Akyildiz AC, Speelman L, et al. Local axial compressive mechanical properties of human carotid atherosclerotic plaques-characterisation by indentation test and inverse finite element analysis. J Biomech 2013;46:1759–66.
[9] National Research Council. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. Washington, DC: National Academies Press; 2011.
[10] Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015;372:793–5.
[11] Obama B. Remarks by the president on precision medicine, Washington, DC: The White House; 2015. State of the Union speech, January 30 Available at: https://www.whitehouse.gov/the-press-office/2015/01/30/remarks-president-precision-medicine.
[12] Truijman MT, Kooi ME, Van Dijk AC, et al. Plaque At RISK (PARISK): prospective multicenter study to improve diagnosis of high-risk carotid plaques. Int J Stroke 2014;9:747–54.
[13] Bayer-Karpinska A, Schwarz F, Wollenweber FA, et al. The carotid plaque imaging in acute stroke (CAPIAS) study: protocol and initial baseline data. BMC Neurol 2013;13:201.
[14] Buisman LR, Rutten-van Mölken MPMH, Postmus D, et al. The early bird catches the worm: early cost-effectiveness analysis of new medical tests. Int J Technol Assess Health Care 2016;32(1/2).
[15] Dutch Institute for Healthcare Improvement CBO. Guideline: diagnostics, treatment and healthcare for patients with a stroke (in Dutch: Richtlijn: Diagnostiek, behandeling en zorg voor patiënten met een beroerte). Utrecht: Dutch Institute for Healthcare Improvement CBO; 2008.
[16] Buisman LR, Rijnsburger AJ, Den Hertog HM, Van der Lugt A, Redekop WK. Clinical practice variation needs to be considered in cost-effectiveness analyses: a case study of patients with a recent transient ischemic attack or minor ischemic stroke. Appl Health Econ Health Policy 2016;14:67–75.
[17] Statistics Netherlands (in Dutch: Centraal Bureau voor de Statistiek, CBS). CBS Statline. Available at: https://opendata.cbs.nl/statline/#/CBS/en/. Accessed 01 February 2014.
[18] Wardlaw JM, Chappell FM, Best JJ, et al. Non-invasive imaging compared with intra-arterial angiography in the diagnosis of symptomatic carotid stenosis: a meta-analysis. Lancet 2006;367:1503–12.
[19] Tholen ATR, De Monyé C, Genders TSS, et al. Suspected carotid artery stenosis: cost-effectiveness of CT angiography in work-up of patients with recent TIA or minor ischemic stroke. Radiology 2010;256:585–97.
[20] Hamada O, Sakata N, Ogata T, Shimada H, Inoue T. Contrast-enhanced ultrasonography for detecting histological carotid plaque rupture: quantitative analysis of ulcer. Int J Stroke 2016;11(7):791–8.
[21] Hallan S, Asberg A, Indredavik B, Widerøe TE. Quality of life after cerebrovascular stroke: a systematic study of patients' preferences for different functional outcomes. J Intern Med 1999;246:309–16.
[22] Sullivan PW, Ghushchyan V. Mapping the EQ-5D index from the SF-12: US general population preferences in a nationally representative sample. Med Decis Making 2006;26:401–9.
[23] Gattellari M, Goumas C, Garden F, Worthington JM. Relative survival after transient ischaemic attack: results from the Program of Research Informing Stroke Management (PRISM) study. Stroke 2012;43:79–85.
[24] European Central Bank. ECB: Euro foreign exchange reference rates. Available at: https://www.ecb.europa.eu/stats/exchange/eurofxref/html/index.en.html. Accessed 04 September 2015.
[25] Dutch Healthcare Authority (in Dutch: Nederlandse Zorgauthoriteit, NZa). NZa Zorgproducten Tariefapplicatie. Available at: https://zorgproducten.nza.nl/ZoekZorgproduct.aspx. Accessed 03 March 2015.
[26] Buisman LR, Tan SS, Nederkoorn PJ, Koudstaal PJ, Redekop WK. Hospital costs of ischemic stroke and TIA in the Netherlands. Neurology 2015;84:2208–15.
[27] Buskens E, Nederkoorn PJ, Buijs-Van Der Woude T, et al. Imaging of carotid arteries in symptomatic patients: cost-effectiveness of diagnostic strategies. Radiology 2004;233:101–12.
[28] Struijs JN, Van Genugten ML, Evers SM, Ament AJ, Baan CA, Van den Bos GA. Future costs of stroke in the Netherlands: the impact of stroke services. Int J Technol Assess Health Care 2006;22:518–24.
[29] Rothwell PM, Gutnikov SA, Warlow CP. Reanalysis of the final results of the European Carotid Surgery Trial. Stroke 2003;34:514–23.
[30] U-King-Im JM, Hollingworth W, Trivedi RA, et al. Cost-effectiveness of diagnostic strategies prior to carotid endarterectomy. Ann Neurol 2005;58:506–15.
[31] North American Symptomatic Carotid Endarterectomy Trial Collaborators Beneficial effect of carotid endarterectomy in symptomatic patients with high–grade carotid stenosis. N Engl J Med 1991;325:445–53.
[32] 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;339:1415–25.
[33] Sillesen H, Amarenco P, Hennerici MG, et al. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 2008;39:3297–302.
[34] Milionis HJ, Giannopoulos S, Kosmidou M, et al. Statin therapy after first stroke reduces 10-year stroke recurrence and improves survival. Neurology 2009;72:1816–22.
[35] Bonati LH, Dobson J, Featherstone RL, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. Lancet 2015;385:529–38.
[36] Appleby J, Devlin N, Parkin D. NICE's cost effectiveness threshold. BMJ 2007;335:358–9.
[37] College voor zorgverzekeringen (CVZ). Guidelines for pharmacoeconomic research, updated version. Diemen: College voor zorgverzekeringen; 2006.
[38] Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870–947.