

Different Imaging Strategies in Patients With Possible Basilar Artery Occlusion

Cost-Effectiveness Analysis

Sebastian E. Beyer; Myriam G. Hunink, MD, PhD; Florian Schöberl, MD; Louisa von Baumgarten, MD; Steffen E. Petersen, MD, DPhil; Martin Dichgans, MD; Hendrik Janssen, MD; Birgit Ertl-Wagner, MD; Maximilian F. Reiser, MD; Wieland H. Sommer, MD, MPH

Background and Purpose—This study evaluated the cost-effectiveness of different noninvasive imaging strategies in patients with possible basilar artery occlusion.

Methods—A Markov decision analytic model was used to evaluate long-term outcomes resulting from strategies using computed tomographic angiography (CTA), magnetic resonance imaging, nonenhanced CT, or duplex ultrasound with intravenous (IV) thrombolysis being administered after positive findings. The analysis was performed from the societal perspective based on US recommendations. Input parameters were derived from the literature. Costs were obtained from United States costing sources and published literature. Outcomes were lifetime costs, quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios, and net monetary benefits, with a willingness-to-pay threshold of \$80 000 per QALY. The strategy with the highest net monetary benefit was considered the most cost-effective. Extensive deterministic and probabilistic sensitivity analyses were performed to explore the effect of varying parameter values.

Results—In the reference case analysis, CTA dominated all other imaging strategies. CTA yielded 0.02 QALYs more than magnetic resonance imaging and 0.04 QALYs more than duplex ultrasound followed by CTA. At a willingness-to-pay threshold of \$80 000 per QALY, CTA yielded the highest net monetary benefits. The probability that CTA is cost-effective was 96% at a willingness-to-pay threshold of \$80 000/QALY. Sensitivity analyses showed that duplex ultrasound was cost-effective only for a prior probability of ≤ 0.02 and that these results were only minimally influenced by duplex ultrasound sensitivity and specificity. Nonenhanced CT and magnetic resonance imaging never became the most cost-effective strategy.

Conclusions—Our results suggest that CTA in patients with possible basilar artery occlusion is cost-effective.

(*Stroke*. 2015;46:1840-1849. DOI: 10.1161/STROKEAHA.115.008841.)

Key Words: cost-effectiveness analysis ■ economics ■ stroke

Basilar artery occlusion (BAO) is a life-threatening condition. Without treatment, a fatal outcome must be expected in >90% of patients.^{1,2} Even if treated, mortality rates of 30% to 40% have been reported.^{3,4} In view of these poor outcomes, treatment, if attempted, must not be delayed.⁵ Notably, $\approx 75\%$ of the survivors have a favorable functional long-term outcome with an acceptable quality of life.¹

Symptoms of BAO include almost the entire spectrum of neurological deficits, such as altered consciousness, dysarthria, diplopia, dysphagia, ataxia, visual (field) disturbances,

sensory deficits, and paresis.³ However, the main presenting and sometimes even only symptoms, especially in the early stage, can be vertigo or unspecific dizziness and unsteadiness of stance and gait. The often subacute symptom onset, the varying time course, as well as the subtle, unspecific, and partly fluctuating symptoms in up to >90% of the patients can be challenging for the clinician and delay correct diagnosis.⁶

Depending on the clinical setting, nonenhanced computed tomography (NECT) or transcranial Doppler and color-coded duplex ultrasound (DUS) are used in the acute setting,⁷

Received January 21, 2015; final revision received April 1, 2015; accepted April 2, 2015.

From the Institute of Clinical Radiology (S.E.B., B.E.-W., M.F.R., W.H.S.), Department of Neurology (F.S., L.B.), Institute for Stroke and Dementia Research (M.D.), and Department of Neuroradiology (H.J.), Ludwig-Maximilian University of Munich Hospitals, Munich, Germany; Advanced Cardiovascular Imaging, William Harvey Research Institute, National Institute for Health Research, Cardiovascular Biomedical Research Unit at Barts, The London Chest Hospital, London, United Kingdom (S.E.P.); Department of Radiology (M.G.H.) and Department of Epidemiology (M.G.H.), Erasmus University Medical Center, Rotterdam, The Netherlands; and Department of Health Policy and Management, Harvard School of Public Health, Harvard University, Boston, MA (M.G.H.).

The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.008841/-/DC1>.

Correspondence to Wieland H. Sommer, MD, MPH, Institute of Clinical Radiology, Ludwig-Maximilian University of Munich Hospitals, Marchioninistr. 15, 81377 Munich, Germany. E-mail Wieland.Sommer@med.uni-muenchen.de

© 2015 The Authors. *Stroke* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.115.008841

especially if the pretest probability of BAO is relatively low. However, DUS of the basilar artery is uninterpretable in $\leq 50\%$ of patients if standard noncontrast enhanced techniques are applied.⁸ In NECT, the hyperdense basilar artery sign alone has a low sensitivity ranging from 61% to 71%.^{9,10} Direct assessment using the more expensive computed tomographic angiography (CTA) or magnetic resonance (MR) angiography may thus be warranted in the acute setting, even if BAO is not likely because outcome crucially depends on prompt diagnosis and successful recanalization without delays.^{3,5}

CTA and magnetic resonance imaging (MRI) (including standard nonenhanced, as well as angiographic sequences) are acknowledged as reference standard noninvasive imaging modalities for BAO. Among these, CTA generally has a higher availability, faster acquisition time, and lower costs, but uses ionizing radiation and is especially associated with a greater risk of contrast medium-induced complications. This raises the question whether a more costly diagnostic technique such as MRI is justified in all patients even if the diagnosis of BAO is rather unlikely. Higher costs of CTA and MRI must be weighed against the risk of false-negative results leading to delayed diagnosis with NECT and DUS.

The aim of this study was to determine the cost effectiveness of different imaging strategies using NECT, DUS, CTA, MRI, or combinations of these tests in patients with possible BAO.

Materials and Methods

Decision Model

We developed a decision model using decision-analytic software (TreeAge Pro 2014, version 14.1.1.0; TreeAge, Williamstown, MA) to evaluate the cost-effectiveness of different imaging strategies for the diagnostic work-up of possible BAO in 63-year-old men³ (Figure 1). We assessed NECT, CTA, and MRI separately, as well as duplex US combined with CTA or MRI. MRI for the exclusion of BAO both consists of unenhanced sequences to exclude an intracranial hemorrhage, as well as time-of-flight MR angiography. In the combination strategies, CTA or MRI followed any abnormal duplex US result. Treatment was initiated if the test result of NECT, CTA, or MRI was positive. The time delay of treatment associated with each strategy, as well as other advantages and disadvantages were modeled. Treatment was with IV thrombolysis or antithrombotics if there

were contraindications for IV thrombolysis. The 1-month modified rankin Scale (mRS) score was used to measure short-term outcome. A Markov model with a 1-year cycle length was developed to estimate long-term outcomes and costs. Further details about the decision model are given in the online-only Data Supplement.

Data Sources and Input Parameters

The input data were based on the best available evidence in the literature. Clinical trial data and published clinical studies were used to estimate the input parameters (Tables 1 and 2; Table I in the online-only Data Supplement).

Prior Probability

As BAO can present with an extremely broad spectrum of symptoms, the prior probability may vary significantly depending on the clinical symptoms at the time of presentation.^{6,10,11} We, therefore, assessed a broad range of prior probabilities in deterministic and probabilistic sensitivity analyses. Furthermore, as low prior probabilities are encountered mostly among patients with mild symptoms, we performed a subgroup analysis for this patient group, thereby also accounting for different outcomes among patients with different presentations. The corresponding input parameters for our model are presented in Table 1.

Diagnostic Test Performance

Data on the performance of NECT and DUS were derived from cross-sectional studies that compared NECT^{9,10} and DUS^{8,11,27} to CTA as reference standard. Differences in the assessment of DUS originated from the application of contrast-enhanced techniques,^{11,27} which is still experimental and probably not readily available in the emergency department but prompted us to perform extensive sensitivity analyses.

CTA and MR angiography are considered noninvasive standard tests with a sensitivity and specificity of close to 1.0.¹⁴⁻¹⁶ Further detail about the diagnostic test performances is given in the online-only Data Supplement. The corresponding test performances that served as input parameters for our model are presented in Table 1.

Treatment Results

We modeled IV thrombolysis as treatment for BAO. As randomized trials on the optimal treatment of BAO treatment are still underway, there is currently no clear evidence for the superiority of endovascular treatment for IV thrombolysis.^{3,28,29} Thus, we modeled only IV thrombolysis.

We derived the 1-month mRS outcomes for patients with BAO depending on the type of treatment performed from a study

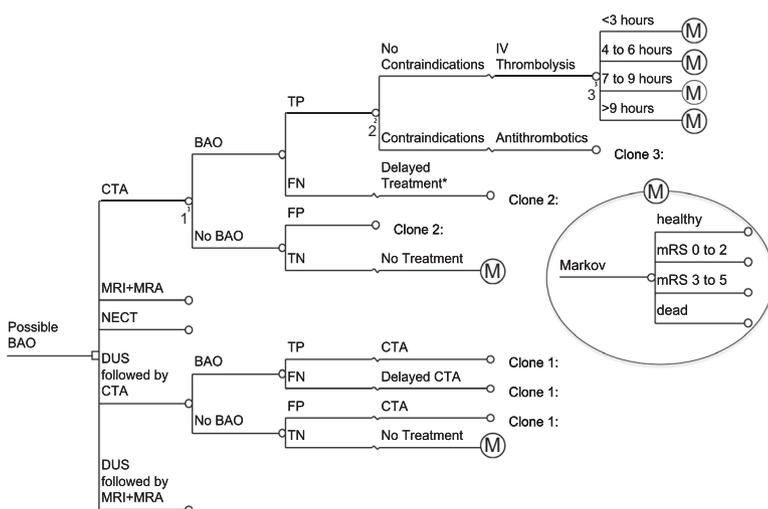


Figure 1. Schematic model overview. □, decision node; ○, chance node; M, Markov node; clone, the structure of the tree at that point is identical to the structure of a sub tree (marked with a thick black line and a corresponding number) but the input parameters are adjusted to apply to that specific situation. MRI+MR angiography (MRA) and NECT have a similar structure to computed tomographic angiography (CTA). DUS followed by MRI+MRA has a similar structure to DUS followed by CTA. *Delayed treatment follows after reimaging but has poorer long-term outcomes than immediate treatment. BAO indicates basilar artery occlusion; DUS, duplex US; FN, false-negative; FP, false-positive; IV, intravenous; MRI, magnetic resonance imaging; NECT, nonenhanced CT; TN, true-negative; and TP, true-positive.

Table 1. Summary of Input Parameters for the Decision Model With SE and Distribution Type, as well as References

Model Parameter	Expected Value	SE	Distribution	References
Age	63	±10%	Normal	Schonewille et al ³
Pretest probability	0.3	0.01–0.5	Uniform	Estimated from the study by Goldmakher et al ¹⁰ and Kermer et al ¹¹
Test performances				
NECT sensitivity	0.66	±10%	β	Connell et al ⁹ and Goldmakher et al ¹⁰
NECT specificity	0.85	±10%	β	Connell et al ⁹ and Goldmakher et al ¹⁰
DUS sensitivity	0.95	0.89–1.0	Triangular	Brandt et al, ⁸ Stolz et al, ¹² and Hoksbergen et al ¹³
DUS specificity	0.70	0.5–0.9	Triangular	Brandt et al, ⁸ Stolz et al, ¹² and Hoksbergen et al ¹³
CTA sensitivity	1.00	0.99–1.0	Triangular	Ng et al ¹⁴ and Bonatti et al ¹⁵
CTA specificity	1.00	0.99–1.0	Triangular	Ng et al ¹⁴ and Bonatti et al ¹⁵
MRI sensitivity	1.00	0.99–1.0	Triangular	Wentz et al ¹⁶
MRI specificity	1.00	0.99–1.0	Triangular	Wentz et al ¹⁶
Outcome probabilities				
BAO, thrombolysis 0–3 h				
mRS, 0–2	0.29	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
mRS, 3–5	0.35	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
Death	0.36	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
BAO, thrombolysis 4–6 h				
mRS, 0–2	0.26	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
mRS, 3–5	0.36	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
Death	0.38	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
BAO, thrombolysis 7–9 h				
mRS, 0–2	0.11	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
mRS, 3–5	0.50	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
Death	0.39	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
BAO, thrombolysis >9 h				
mRS, 0–2	0.09	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
mRS, 3–5	0.45	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
Death	0.46	±20%	β	Schonewille et al ³ and Vergouwen et al ⁵
BAO, antithrombotics 0–3 h				
mRS, 0–2	0.35	±20%	β	Schonewille et al ³
mRS, 3–5	0.38	±20%	β	Schonewille et al ³
Death	0.27	±20%	β	Schonewille et al ³
BAO, antithrombotics 4–6 h				
mRS, 0–2	0.31	±20%	β	Schonewille et al ³
mRS, 3–5	0.39	±20%	β	Schonewille et al ³
Death	0.30	±20%	β	Schonewille et al ³
BAO, antithrombotics 7 to 9 h				
mRS, 0–2	0.14	±20%	β	Schonewille et al ³
mRS, 3–5	0.56	±20%	β	Schonewille et al ³
Death	0.30	±20%	β	Schonewille et al ³
BAO, antithrombotics > 9 h				
mRS, 0–2	0.12	±20%	β	Schonewille et al ³
mRS, 3–5	0.51	±20%	β	Schonewille et al ³
Death	0.37	±20%	β	Schonewille et al ³
No BAO				
Healthy	1	Assumption
Death	0	Assumption

(Continued)

Table 1. Continued

Model Parameter	Expected Value	SE	Distribution	References
Timing data, min				
Time from symptom onset	312	±240	γ	Vergouwen et al ⁵
Perform and interpret NECT	10	5–15	Triangular	Expert opinion
Perform and interpret CTA	15	10–20	Triangular	Expert opinion
Perform and interpret MRI	45	20–60	Triangular	Earnshaw et al ¹⁷
Perform and interpret DUS	30	20–50	Triangular	Expert opinion
Delay if false-negative	180	10–360	Uniform	Expert opinion
Utility values				
Healthy	1
mRS, 0–2	0.81	±0.081	β	Earnshaw et al, ¹⁷ Stahl et al, ¹⁸ and Gage et al ¹⁹
mRS, 3–5	0.33	±0.033	β	Earnshaw et al, ¹⁷ Stahl et al, ¹⁸ and Gage et al ¹⁹
Death	0
Death HRR				
mRS, 0–1	1.00	1.0–1.2	Triangular	Earnshaw et al ¹⁷ and Samsa et al ²⁰
mRS, 2	1.11	1.0–1.2	Triangular	Earnshaw et al ¹⁷ and Samsa et al ²⁰
mRS, 3	1.27	1.2–1.4	Triangular	Earnshaw et al ¹⁷ and Samsa et al ²⁰
mRS, 4	1.71	1.3–2.0	Triangular	Earnshaw et al ¹⁷ and Samsa et al ²⁰
mRS, 5	2.37	1.5–4.0	Triangular	Earnshaw et al ¹⁷ and Samsa et al ²⁰
Complication probabilities				
Contrast-induced nephropathy	0.005	0–0.02	Triangular	Jackson et al ²¹
Contraindications for IV thrombolysis	0.05	±20%	β	Katzen et al ²²
Lifetime attributable risk of cancer after NECT scanning	0.0001	±0.00001	Normal	Holmes et al ²³
Lifetime attributable risk of cancer after CTA scanning	0.0002	±0.00002	Normal	Holmes et al ²³

BAO indicates basilar artery occlusion; CTA, computed tomographic angiography; DUS, duplex ultrasound; HRR, hazard rate ratios; MRI, magnetic resonance imaging; mRS, modified rankin Scale; and NECT, nonenhanced computed tomography.

by Vergouwen et al⁵ investigating the data of the Basilar Artery International Cooperation Study (BASICS), a large prospective registry study.³ These outcomes were similar to previously published 90-days outcomes after IV thrombolysis⁴ but allowed a separate evaluation of patients receiving thrombolytic and patients receiving antithrombotic therapy as well as analysis of prognostic factors, such as time from symptom onset to treatment.

On the basis of a study by Katzen et al,²² we estimated that 5% of patients with BAO would have contraindications for thrombolytic therapy (ie, active gastro intestinal tract bleeding, uncontrolled hypertension, oral anticoagulation with international normalized ratio >1.7, or recent brain injury). This number is considerably lower than the total number of ineligible patients in their study because (1) in BAO there is no clear time window for the administration of thrombolytic therapy and (2) contraindications, such as minor symptoms (National Institutes of Health Stroke Scale <4) and rapidly resolving symptoms would not apply for patients with BAO.

The BASICS study evaluated outcomes separately for patients with mild-to-moderate and severe symptoms.³ In our model, we performed an overall analysis using the pooled data from these 2 groups, as well as a subgroup analysis for patients with mild symptoms. The corresponding input parameters for the overall analysis and for the subgroup analysis for patients with mild symptoms are presented in Table 1 and in Table I in the online-only Data Supplement, respectively.

Age- and sex-specific life tables were obtained for the US population of 2007. The hazard rate ratios for the different health states (mRS, 0–5) were derived from the literature.^{17,20}

Timing to Treatment

Time from symptom onset predicts the success of thrombolytic therapy in the anterior circulation³⁰ and influences the treatment outcome in patients with BAO.^{5,31} Consequently, we modeled time from symptom

onset as a factor determining the outcome after initiation of treatment. Detailed information is available in the online-only Data Supplement.

For each imaging strategy, a corresponding delay was added to the time from symptom onset. The respective input parameters are presented in Table 1.

Adverse Events

Information on the adverse events was obtained from the literature.^{21,23,32,33} We modeled contrast-induced nephropathy because of administration of contrast media during CTA²¹ and risk of fatal radiation-induced cancer because of CT scanning.^{23,32} The respective input parameters are given in Table 1. Detailed information is available in the online-only Data Supplement.

Health Benefit

Health benefits were measured using quality-adjusted life years (QALY). Lifetime QALYs were derived by multiplication of the number of years spent in each health state by the utility assigned to that health state. Utility weights range from 0.0 to 1.0, with 1.0 representing perfect health and 0.0 representing death. The utilities were obtained from 2 previously published studies,^{18,19} which have been used repeatedly in prior cost-effectiveness analyses.^{17,34} The utilities were calculated as averages weighted by the proportions of patients with the respective mRS outcome. The utility of a minor disability (mRS, 0–2) was 0.81 and the utility of a major disability (mRS, 3–5) was 0.33. Death (mRS, 6) was assigned a value of 0. The values are summarized in Table 1.

Costs

The model included costs for imaging with NECT, DUS, CTA, and MRI, complications from imaging, treatment with IV thrombolysis, and disability from BAO, including both short- and long-term care.

Table 2. Costs in 2013 USD for Imaging, Complications From Imaging, Treatment and Disability From BAO, Including Both Short- and Long-Term Care

Model Parameter	Expected Value	SE	Distribution	References
Imaging				
NECT	167	±16.7	γ	Medicare 2013
DUS	211	±21.1	γ	Medicare 2013
CTA+NECT	424	±42.4	γ	Medicare 2013
MRI+MRA	804	±80.4	γ	Medicare 2013
Treatment				
IV tPA	3829.55	±382.96	γ	Earnshaw et al ¹⁷
Administration of IV tPA	354.30	±35.43	γ	Earnshaw et al ¹⁷
Physician time to monitor IV tPA administration	711.97	±71.20	γ	Earnshaw et al ¹⁷
Hospitalization				
Inpatient costs for patients with BAO	9809	4200–16 800	Triangular	Young et al ²⁴
Post-hospitalization				
Annual post hospitalization costs for patients with mRS 0–2	8174	1–17 500	Triangular	Young et al ²⁴
Annual post hospitalization costs for patients with mRS, 3–5, first year	68 897	46 700–93 500	Triangular	Young et al ²⁴
Annual post hospitalization costs for patients with mRS 3–5, 2+ year	40 014	17 500–64 300	Triangular	Young et al ²⁴
Complications				
Cost for contrast induced nephropathy	13 323	±1332	γ	Jackson et al ²¹
Cost for cancer	45 000	1–100 000	Triangular	Estimated from ^{23,25,26}

BAO indicates basilar artery occlusion; CTA, computed tomographic angiography; DUS, duplex ultrasound; IV, intravenous; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified rankin Scale; NECT, nonenhanced computed tomography; and tPA, tissue-type plasminogen activator.

Costs for imaging were based on the 2013 Medicare reimbursement rates, including both technical and professional fees. Costs for complications from imaging have been described above. Costs for hospitalization have been reported in the literature.²⁴ These costs included all costs incurred while in a hospital and total costs were obtained by stroke type and discharge status. The costs for treatment with IV thrombolysis were obtained from Earnshaw et al.¹⁷ Costs for IV thrombolysis included physician work and practice expense.

Annual post hospitalization costs have been repeatedly reported in the literature.^{17,24,35,36} These costs were obtained based on the patient's health state. Death (mRS, 6) was assigned no annual post hospitalization cost. All costs were converted into 2013 USD using the consumer price index for medical care. Benefits and costs were discounted at a rate of 3% per year as recommended for cost-effectiveness analyses in the United States.³⁷ A summary of all costs used in this model is presented in Table 2.

Cost-Effectiveness and Sensitivity Analyses

Diagnostic strategies were compared in terms of costs, effectiveness (QALYs), incremental cost-effectiveness ratios, and net monetary benefit (NMB=QALY×willingness-to-pay [WTP]–costs), using a WTP threshold of \$80 000 per QALY. NMB combines costs and effectiveness in 1 measure (NMB=(QALY×WTP)–costs) with a higher NMB implying greater cost-effectiveness. QALYs and costs were calculated from the perspective of a healthcare payer.

We performed extensive sensitivity analyses to explore the robustness of the model's assumptions. We used 1-way deterministic sensitivity analysis to identify variables with a significant influence on the model outcome. In addition, we performed 2- and 3-way sensitivity analyses by altering the input values for 2 and 3 variables, respectively. A WTP threshold of \$80,000 was used for these sensitivity analyses.

In addition to deterministic sensitivity analysis, we also performed probabilistic sensitivity analyses, in which we altered the input values of all parameters simultaneously. Each parameter was assigned a distribution (β, triangular, or γ) and was varied according to this distribution. In addition, we calculated the probability of cost-effectiveness for each strategy for varying WTP values using acceptability curves.

Results

Reference Case Analysis

In the reference-case analysis for male patients of 63 years old with possible BAO, CTA dominated all other strategies (Figure 2A). With a WTP threshold of \$80 000 per QALY, CTA yielded the highest NMB, followed by MRI. The least cost-effective strategy was to perform NECT. In the reference-case analysis for patients with mild symptoms, CTA also dominated all other strategies (Figure 2C), albeit with smaller differences in QALYs and total costs compared with the overall analysis. A summary of the results is presented in Table 3. The results were similar for women (Table II; Figure I in the online-only Data Supplement).

Probabilistic Sensitivity Analysis

Results of the probabilistic sensitivity analysis showed that in men CTA was most cost effective in 96% of the simulation runs in the overall analysis and 80% of the mild symptoms analysis. DUS followed by CTA and DUS followed by MRI were the strategies of choice in only 2.6% and 0.07% of simulation runs

in the overall analysis and 13% and 4.1% of simulation runs in the mild symptoms analysis, respectively. Those results were similar for women. The cost-effectiveness acceptability curves showing the most cost-effective strategy depending on the WTP threshold are given in Figure 2B and 2C for men and in Figure 1B and 1C in the online-only Data Supplement for women.

Deterministic Sensitivity Analyses

Prior Probability and Age

The model outcome was sensitive to varying the prior probability. With a WTP threshold of \$80,000/QALY, CTA was more effective with an incremental cost-effectiveness ratio below the WTP threshold if the prior probability was >0.018 for the overall analysis or >0.024 for patients with mild symptoms. With prior probabilities less than 0.018 and 0.024, DUS followed by CTA was more cost effective.

Model outcome was also influenced by the age of the patient. Varying age together with the prior probability in 2-way sensitivity analyses showed that at a younger age <40 years the MRI strategy was increasingly favored, whereas at age ≥80 years DUS followed by CTA was increasingly favored, at least in patients with a low prior probability. However, changes were minimal between the age of 45 and 80 years—the age group, in which the vast majority of BAO cases occur (Figure II in the online-only Data Supplement).

DUS Sensitivity and Specificity

The choice between CTA and DUS followed by CTA was also affected by the sensitivity and specificity of DUS. Altering these 2 parameters together with the prior probability in 3-way sensitivity analyses showed that DUS followed by CTA would be cost-effective also at higher prior probabilities if sensitivity and specificity increased. However, even with perfect sensitivity and specificity, the prior probabilities at which DUS followed by CTA was cost effective were low. Above a prior probability of ≈0.04 CTA was always the most cost-effective strategy (Figure 3 for men and Figure III in the online-only Data Supplement for women). In contrast, there was no change in cost-effectiveness if the sensitivity of CTA was varied between 0.95 and 1.0 together with the prior probability. Varying the specificity of CTA between 0.95 and 1.0 resulted in slight changes of the cost-effectiveness between prior probabilities of 0.02 and 0.03 for both analyses, favoring DUS followed by CTA also for higher probabilities if the specificity of CTA decreased. Varying the sensitivity or specificity of MRI between 0.95 and 1.0 did not result in any changes of the model outcome.

Radiation Risk

Figure IV in the online-only Data Supplement shows the 2-way sensitivity analyses exploring the influence of the lifetime attributable risk of cancer because of CT scanning.

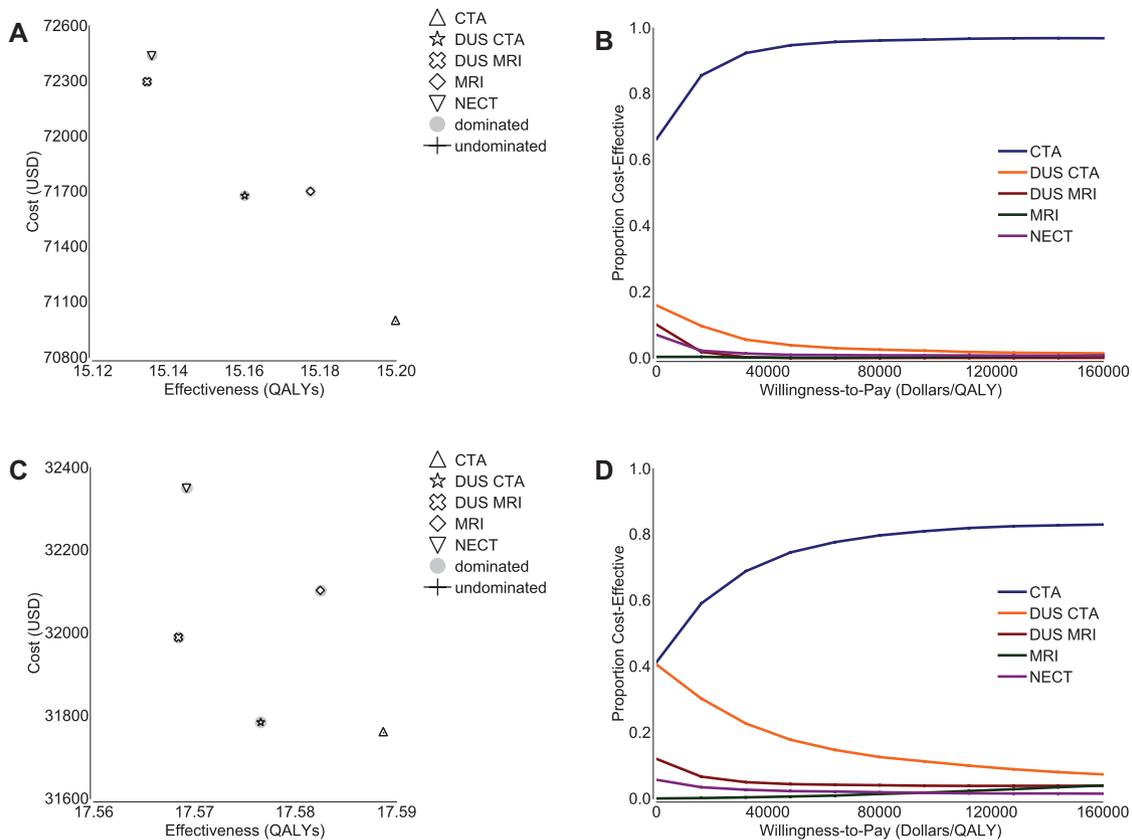


Figure 2. Cost-effectiveness graphs and acceptability curves in male patients. **A** and **B**, The results of the overall analysis. **C** and **D**, The results of the mild symptoms subgroup analysis. Cost-effectiveness graphs are shown in (A) and (C), acceptability curves are shown in (B) and (D). CTA is the optimal strategy in the overall analysis (A and B) and for patients with mild symptoms (C and D). CTA indicates computed tomographic angiography; DUS, duplex US; MRI, unenhanced magnetic resonance sequences+magnetic resonance angiography; NECT, nonenhanced CT; and QALY, quality-adjusted life-year.

Varying the lifetime attributable risk (LAR) after a single CT scan between 0 and 0.0003, the upper value corresponding to 3× the estimated risk, resulted in a change of the most cost-effective strategy between prior probabilities of 0.01 and 0.04, favoring DUS followed by CTA, as well as MRI as the LAR increased. Above a prior probability of 0.04, CTA was the most cost-effective strategy. There was only a marginal difference between the overall analysis and the analysis of patients with mild symptoms.

Timing to Treatment

Performing deterministic 2-way sensitivity analysis on the time to image and interpret MRI did not result in a change of the most cost-effective strategy at any prior probability in the overall analysis or in the analysis of patients with mild symptoms. Nor did performing sensitivity analysis on the time to image and interpret CTA result in a change of the most cost-effective strategy because both CTA as well as DUS followed by CTA were influenced by this analysis. Longer times to perform DUS resulted in changes of the most cost-effective strategy around a prior probability of 0.02, favoring direct CTA also in case of lower prior probabilities because the time to perform DUS increased (Figure V in the online-only Data Supplement).

Discussion

In our study on the cost-effectiveness of different noninvasive imaging tests for patients with possible BAO, we found direct CTA to be the most cost-effective strategy for a WTP threshold of \$80 000/QALY. CTA yielded the most QALYs and although CTA was associated with higher initial imaging costs, total costs were lower compared with other imaging strategies as costs for long-term treatment were less. It, therefore, represented a dominant strategy. Cost-effectiveness acceptability curves showed that CTA remained cost-effective even for higher WTP thresholds.

Sensitivity analysis showed that DUS followed by CTA in case of a positive test result is cost effective for low prior

probabilities. Depending on the sensitivity and specificity of DUS, the cut-off value of the prior probability below which DUS followed by CTA became the preferred strategy, varied between 1% and 4%. Notably, even if perfect sensitivity and specificity were assumed, which would also require DUS to always yield interpretable results, CTA was still the most cost-effective strategy for prior probabilities above 4%. Considering more realistic values for an acute setting, in which DUS may be uninterpretable in ≤50% when using noncontrast enhanced techniques,⁸ performing DUS because the initial test may only be cost-effective if the prior probability is <1%. These results remained nearly unchanged for females and for patients with mild symptoms at initial presentation.

Our results emphasize the paramount importance of a fast diagnostic work-up in BAO, also in relation to the cost of the imaging examination or potential risks, such as renal nephropathy or radiation-induced cancer. In our model, the delay was the key driver determining the most cost-effective strategy. It was the reason why performing DUS was only cost-effective at low prior probabilities—in combination with higher costs—why MRI never became the preferred strategy. Although there is no data available on the prior probability of BAO in patients only exhibiting mild symptoms to date, clinical experience indicates that the probability may be ≥1%.

There are limitations of this study that need to be taken into account when interpreting the data. Because of limited evidence in the literature, several assumptions had to be made. First, as BAO is a rare disease, which can present with a vast variety of clinical symptoms,^{3,6} it is difficult to estimate the prior probability. This may question the generalizability of this model. Sensitivity analyses, however, showed that CTA remained cost-effective for most prior probabilities, whereas DUS became cost-effective only at low prior probabilities of around 1% to 2%. This indicates that CTA is cost-effective for many patients but implementation of the results of this study should be done cautiously for patients in whom BAO is unlikely. Our findings may thus work as a framework to help the physician in the initial decision-making process.

Second, the performance of imaging tests has only been described in studies with small numbers of patients.^{8,9} Especially for DUS there is only limited data available. Sensitivity analysis, however, showed that the outcomes were robust to changes of these input parameters and that CTA was the most cost-effective strategy in the vast majority of scenarios tested. The outcome between DUS and CTA was mainly driven by the effect of the time to perform and interpret test results and thus alterations of the values of test performance of DUS only resulted in slight changes in cost-effectiveness at prior probabilities between 1% and 4%.

Third, the predicted cancer risk associated with cranial CT scanning was derived from a study²³ that used extrapolation of risks of cancers found in a meta-analysis for pediatric patients.³⁸ In general, there is still uncertainty about the risk attributable to cranial CT scanning. Current estimates commonly use organ radiation doses and apply organ-specific cancer incidences, which are derived from studies of

Table 3. Costs and Outcomes for Men

	Total Costs (USD)	QALYs	ICER	NMB for WTP of \$80 000/QALY
Overall				
CTA	70 996	15.20	Dominant	1 144 992
DUS+CTA	71 678	15.16	Dominated	1 141 130
DUS+MRI	72 295	15.13	Dominated	1 138 455
MRI	71 701	15.18	Dominated	1 142 496
NECT	72 438	15.14	Dominated	1 138 415
Mild symptoms				
CTA	31 759	17.59	Dominant	1 375 338
DUS+CTA	31 785	17.58	Dominated	1 374 339
DUS+MRI	31 989	17.57	Dominated	1 374 484
MRI	32 102	17.58	Dominated	1 374 498
NECT	32 351	17.57	Dominated	1 373 187

CTA indicates computed tomographic angiography; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; NECT, nonenhanced computed tomography; NMB, net monetary benefit; QALY, quality-adjusted life-year; and WTP, willingness-to-pay.

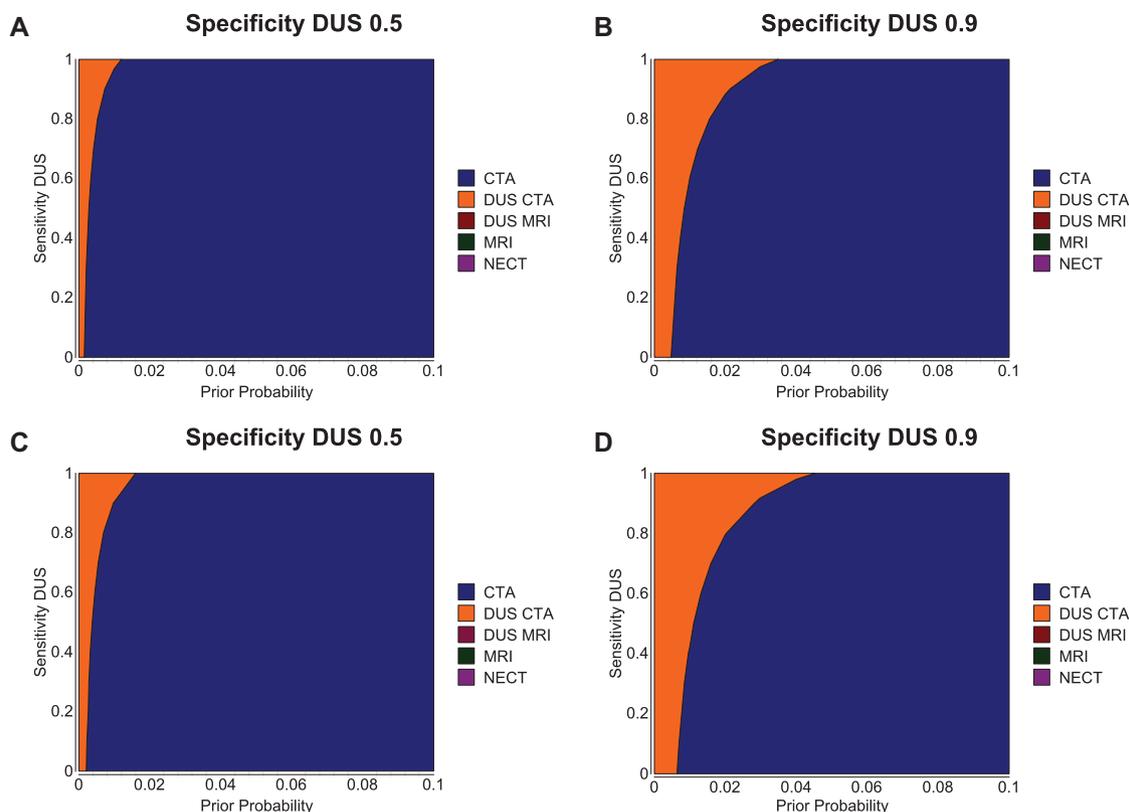


Figure 3. Three-way sensitivity analyses exploring different sensitivities and specificities of duplex US (DUS) and different prior probabilities with a willingness-to-pay of \$80 000 per quality-adjusted life-year in men. **A** and **B**, The results of the overall analysis. **C** and **D**, The results of the mild symptoms subgroup analysis. Shading, optimal strategy. CTA indicates computed tomographic angiography; MRI, nonenhanced magnetic resonance sequences+magnetic resonance angiography; and NECT, nonenhanced CT.

atomic-bomb survivors.³⁹ The LAR of 0.0001 used in our study was derived from Holmes et al.²³ who extrapolated the higher risks found for patients between the ages 0 and 20 years by Stein et al.³⁸ The estimates of Stein et al are in line with earlier reports.⁴⁰ Nevertheless, there is still ambiguity about the LAR for adult patients we used in our study. However, sensitivity analyses showed that even an LAR 2× higher than the estimate only slightly influenced the model outcome, therefore, indicating only a minor role in the decision process for the diagnostic work-up of such a fatal disease, such as BAO.

Fourth, we only modeled IV thrombolysis as outcome, omitting potential intra-arterial treatment options. Therefore, we are not able to extrapolate the results to strategies guiding those treatment options. The rationale was that this study intended to focus on the initial diagnostic imaging work-up by highlighting the influence of potential advantages and disadvantages associated with each of the different imaging strategies. Therefore, it was necessary to use the best evidence on outcome estimates available to date. This is provided by the BASICS study.³ Because this study did not find any significant differences in the outcome between IV and IA thrombolysis, we limited the treatment in our model to IV therapy. It should be noted that our findings were robust, remaining nearly unchanged independent of whether outcome estimates for all patients or for patients with mild symptoms were used, thereby indicating that better outcomes

achieved with intra-arterial therapy may not change the decision of the initial imaging strategy. However, direct catheter angiography with the opportunity for an immediate intervention may become cost-effective if the prior probability is high. Currently, a randomized controlled trial is being performed investigating the added value of IA therapy after IV therapy in patients with an acute symptomatic BAO.⁴¹ As soon as these data become available, our model can be easily adapted and updated.

Finally, the model assumed that CT, MRI, and DUS are available 24 hours a day, 7 days a week. Such an assumption may only be valid for a stroke center and not for a small, rural hospital. However, as CT-based imaging is still the recommended standard for acute stroke work-up, CTA as the most cost-effective strategy in our model is likely to be available more readily than MRI or DUS. Furthermore, the model assumed that CT and MRI always yield interpretable results. This is in fact an oversimplified assumption because CT may be uninterpretable, for example, because of beam-hardening artifacts⁸ and MRI, for example, because of motion artifacts. We chose to refrain from modeling this because there is uncertainty about the risk of scans being uninterpretable. Sensitivity analyses, however, showed that results remained nearly unchanged even if CTA sensitivity and specificity were altered between 0.95 and 1.0, which may be used as an indicator of limited influence of uninterpretable test results.

In conclusion, we demonstrated CTA to be cost-effective as the initial imaging test in many patients with possible BAO in an US American setting. When using standard noncontrast enhanced DUS techniques, DUS followed by CTA in case of an abnormal result is only cost-effective if the prior probability is less than $\approx 1\%$. NECT and MRI are not cost-effective for this indication.

Disclosures

None.

References

- Ottomeyer C, Zeller J, Fesl G, Holtmannspötter M, Opherck C, Bender A, et al. Multimodal recanalization therapy in acute basilar artery occlusion: long-term functional outcome and quality of life. *Stroke*. 2012;43:2130–2135. doi: 10.1161/STROKEAHA.112.651281.
- Baird TA, Muir KW, Bone I. Basilar artery occlusion. *Neurocrit Care*. 2004;1:319–329. doi: 10.1385/NCC.1.3:319.
- Schonewille WJ, Wijman CA, Michel P, Rueckert CM, Weimar C, Mattle HP, et al; BASICS study group. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. *Lancet Neurol*. 2009;8:724–730. doi: 10.1016/S1474-4422(09)70173-5.
- Sairanen T, Strbian D, Soenne L, Silvennoinen H, Salonen O, Arto V, et al; Helsinki Stroke Thrombolysis Registry (HSTR) Group. Intravenous thrombolysis of basilar artery occlusion: predictors of recanalization and outcome. *Stroke*. 2011;42:2175–2179. doi: 10.1161/STROKEAHA.110.605584.
- Vergouwen MD, Algra A, Pfefferkorn T, Weimar C, Rueckert CM, Thijs V, et al; Basilar Artery International Cooperation Study (BASICS) Study Group. Time is brain(stem) in basilar artery occlusion. *Stroke*. 2012;43:3003–3006. doi: 10.1161/STROKEAHA.112.666867.
- von Campe G, Regli F, Bogousslavsky J. Heraldng manifestations of basilar artery occlusion with lethal or severe stroke. *J Neurol Neurosurg Psychiatry*. 2003;74:1621–1626.
- Mortimer AM, Saunders T, Cook JL. Cross-sectional imaging for diagnosis and clinical outcome prediction of acute basilar artery thrombosis. *Clin Radiol*. 2011;66:551–558. doi: 10.1016/j.crad.2010.09.022.
- Brandt T, Knauth M, Wildermuth S, Winter R, von Kummer R, Sartor K, et al. CT angiography and Doppler sonography for emergency assessment in acute basilar artery ischemia. *Stroke*. 1999;30:606–612.
- Connell L, Koerte IK, Laubender RP, Morhard D, Linn J, Becker HC, et al. Hyperdense basilar artery sign—a reliable sign of basilar artery occlusion. *Neuroradiology*. 2012;54:321–327. doi: 10.1007/s00234-011-0887-6.
- Goldmacher GV, Camargo EC, Furie KL, Singhal AB, Roccatagliata L, Halpern EF, et al. Hyperdense basilar artery sign on unenhanced CT predicts thrombus and outcome in acute posterior circulation stroke. *Stroke*. 2009;40:134–139. doi: 10.1161/STROKEAHA.108.516690.
- Kermer P, Wellmer A, Crome O, Mohr A, Knauth M, Bähr M. Transcranial color-coded duplex sonography in suspected acute basilar artery occlusion. *Ultrasound Med Biol*. 2006;32:315–320. doi: 10.1016/j.ultrasmedbio.2005.12.004.
- Stolz E, Nüchel M, Mendes I, Gerriets T, Kaps M. Vertebrobasilar transcranial color-coded duplex ultrasonography: improvement with echo enhancement. *AJNR Am J Neuroradiol*. 2002;23:1051–1054.
- Hoksbergen AW, Legemate DA, Ubbink DT, Jacobs MJ. Success rate of transcranial color-coded duplex ultrasonography in visualizing the basal cerebral arteries in vascular patients over 60 years of age. *Stroke*. 1999;30:1450–1455.
- Ng KW, Venketasubramanian N, Yeo LL, Ahmad A, Loh PK, Seet RC, et al. Usefulness of CT angiography for therapeutic decision making in thrombolysing intubated patients with suspected basilar artery thrombosis. *J Neuroimaging*. 2012;22:351–354. doi: 10.1111/j.1552-6569.2011.00689.x.
- Bonatti G, Ferro F, Haglmüller T, Pernter P, Naibo L. Basilar artery thrombosis: imaging and endovascular therapy. *Radiol Med*. 2010;115:1219–1233. doi: 10.1007/s11547-010-0568-2.
- Wentz KU, Röther J, Schwartz A, Mattle HP, Suchalla R, Edelman RR. Intracranial vertebrobasilar system: MR angiography. *Radiology*. 1994;190:105–110. doi: 10.1148/radiology.190.1.8259384.
- Earnshaw SR, Jackson D, Farkouh R, Schwamm L. Cost-effectiveness of patient selection using penumbral-based MRI for intravenous thrombolysis. *Stroke*. 2009;40:1710–1720. doi: 10.1161/STROKEAHA.108.540138.
- Stahl JE, Furie KL, Gleason S, Gazelle GS. Stroke: Effect of implementing an evaluation and treatment protocol compliant with NINDS recommendations. *Radiology*. 2003;228:659–668. doi: 10.1148/radiol.2283021557.
- Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. *Stroke*. 1998;29:1083–1091.
- Samsa GP, Reutter RA, Parmigiani G, Ancukiewicz M, Abrahamse P, Lipscomb J, et al. Performing cost-effectiveness analysis by integrating randomized trial data with a comprehensive decision model: application to treatment of acute ischemic stroke. *J Clin Epidemiol*. 1999;52:259–271.
- Jackson D, Earnshaw SR, Farkouh R, Schwamm L. Cost-effectiveness of CT perfusion for selecting patients for intravenous thrombolysis: a US hospital perspective. *AJNR Am J Neuroradiol*. 2010;31:1669–1674. doi: 10.3174/ajnr.A2138.
- Katzan IL, Hammer MD, Hixson ED, Furlan AJ, Abou-Chebl A, Nadzam DM; Cleveland Clinic Health System Stroke Quality Improvement Team. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol*. 2004;61:346–350. doi: 10.1001/archneur.61.3.346.
- Holmes MW, Goodacre S, Stevenson MD, Pandor A, Pickering A. The cost-effectiveness of diagnostic management strategies for adults with minor head injury. *Injury*. 2012;43:1423–1431. doi: 10.1016/j.injury.2011.07.017.
- Young KC, Benesch CG, Jahromi BS. Cost-effectiveness of multimodal CT for evaluating acute stroke. *Neurology*. 2010;75:1678–1685. doi: 10.1212/WNL.0b013e3181fc2838.
- Lester SC, Taksler GB, Kuremsky JG, Lucas JT Jr, Ayala-Peacock DN, Randolph DM II, et al. Clinical and economic outcomes of patients with brain metastases based on symptoms: an argument for routine brain screening of those treated with upfront radiosurgery. *Cancer*. 2014;120:433–441. doi: 10.1002/ncr.28422.
- Ray S, Bonafede MM, Mohile NA. Treatment Patterns, Survival, and Healthcare Costs of Patients with Malignant Gliomas in a Large US Commercially Insured Population. *Am Health Drug Benefits*. 2014;7:140–149.
- Koga M, Kimura K, Minematsu K, Yamaguchi T. Relationship between findings of conventional and contrast-enhanced transcranial color-coded real-time sonography and angiography in patients with basilar artery occlusion. *AJNR Am J Neuroradiol*. 2002;23:568–571.
- Mattle HP, Arnold M, Lindsberg PJ, Schonewille WJ, Schroth G. Basilar artery occlusion. *Lancet Neurol*. 2011;10:1002–1014. doi: 10.1016/S1474-4422(11)70229-0.
- Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. *Stroke*. 2006;37:922–928. doi: 10.1161/01.STR.0000202582.29510.6b.
- Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al; ECASS, ATLANTIS, NINDS and EPITHEX rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHEX trials. *Lancet*. 2010;375:1695–1703. doi: 10.1016/S0140-6736(10)60491-6.
- Greving JP, Schonewille WJ, Wijman CA, Michel P, Kappelle LJ, Algra A; BASICS Study Group. Predicting outcome after acute basilar artery occlusion based on admission characteristics. *Neurology*. 2012;78:1058–1063. doi: 10.1212/WNL.0b013e31824e8f40.
- Genders TS, Meijboom WB, Meijs MF, Schuijff JD, Mollet NR, Weustink AC, et al. CT coronary angiography in patients suspected of having coronary artery disease: decision making from various perspectives in the face of uncertainty. *Radiology*. 2009;253:734–744. doi: 10.1148/radiol.2533090507.
- Ottomeyer C, Sick C, Hennerici MG, Szabo K. Orolingual angioedema under systemic thrombolysis with rt-PA: an underestimated side effect. *Nervenarzt*. 2009;80:459–463. doi: 10.1007/s00115-009-2685-5.
- Boudreau DM, Guzauskas GF, Chen E, Lalla D, Tayama D, Fagan SC, et al. Cost-effectiveness of recombinant tissue-type plasminogen activator within 3 hours of acute ischemic stroke: current evidence. *Stroke*. 2014;45:3032–3039. doi: 10.1161/STROKEAHA.114.005852.
- Post PN, Kievit J, van Baalen JM, van den Hout WB, van Bockel JH. Routine duplex surveillance does not improve the outcome after carotid endarterectomy: a decision and cost utility analysis. *Stroke*. 2002;33:749–755.

36. Kilaru S, Korn P, Kasirajan K, Lee TY, Beavers FP, Lyon RT, et al. Is carotid angioplasty and stenting more cost effective than carotid endarterectomy? *J Vasc Surg*. 2003;37:331–339. doi: 10.1067/mva.2003.124.
37. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA*. 1996;276:1253–1258.
38. Stein SC, Hurst RW, Sonnad SS. Meta-analysis of cranial CT scans in children. A mathematical model to predict radiation-induced tumors. *Pediatr Neurosurg*. 2008;44:448–457. doi: 10.1159/000172967.
39. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med*. 2007;357:2277–2284. doi: 10.1056/NEJMra072149.
40. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol*. 2001;176:289–296. doi: 10.2214/ajr.176.2.1760289.
41. van der Hoeven EJ, Schonewille WJ, Vos JA, Algra A, Audebert HJ, Berge E, et al; BASICS Study Group. The Basilar Artery International Cooperation Study (BASICS): study protocol for a randomised controlled trial. *Trials*. 2013;14:200. doi: 10.1186/1745-6215-14-200.