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Is the Cost-Effectiveness of Stroke Thrombolysis Affected by Proportion of Stroke Mimics?

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Abstract

Background and Purpose: Differentiating ischemic stroke patients from stroke mimics (SM), non-vascular conditions which simulate stroke, can be challenging in the acute setting. We sought to model the cost-effectiveness of treating suspected acute ischemic stroke patients before a definitive diagnosis could be made. We hypothesized that we would identify threshold proportions of SM among suspected stroke patients arriving to an emergency department (ED) above which administration of intravenous thrombolysis was no longer cost-effective.

Methods: We constructed a decision-analytic model to examine various ED thrombolytic treatment scenarios. The main variables were: proportion of SM to true stroke patients, time from symptom onset to treatment, and complication rates. Costs, reimbursement rates, and expected clinical outcomes of ischemic stroke and SM patients were estimated from published data. We report the 90-day incremental cost-effectiveness ratio (ICER) of administering intravenous thrombolysis compared to no acute treatment from a healthcare sector perspective as well as the cost-reimbursement ratio (CRR) from a hospital-level perspective. Cost-effectiveness was defined as a willingness to pay <$100,000 USD per quality adjusted life year (QALY) gained and high CRR was defined as >1.5.

Results: There was an increase in ICERs as the proportion of SM cases increased in the 3-hour time window. The threshold proportion of SM above which the decision to administer thrombolysis was no longer cost-effective was 30%. The threshold proportion of SM above which the decision to administer thrombolysis resulted in high CRR was 75%. Results were similar for patients arriving within 0-90 minutes of symptom onset as compared to 91-180 minutes but were significantly affected by cost of alteplase in sensitivity analyses.

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Disclosures: none

Conclusions: We identified thresholds of SM above which thrombolysis was no longer cost-effective from two analytic perspectives. Hospitals should monitor SM rates and establish performance metrics to prevent rising acute stroke care costs and avoid potential patient harms.

Keywords

cost-effectiveness analysis; ischemic stroke; stroke mimic; acute ischemic stroke; thrombolysis; cost-effectiveness

Introduction

Prior analyses have uniformly found that treatment of acute ischemic stroke (AIS) patients with intravenous thrombolysis is cost-effective.[1–3] When the diagnosis of stroke is uncertain, the clinical benefits of thrombolysis are widely thought to outweigh the minimal risks of complications associated with treatment of stroke mimics (SM).[4, 5] There is additional pressure on providers to broadly administer thrombolysis to suspected stroke patients since failure to treat eligible patients is one of the most frequent stroke related malpractice claims by plaintiffs.[6] However, a recent cost analysis found significant financial burdens at the hospital-level associated with SM thrombolysis.[7] Published studies on the proportion of SM treated vary from 0% when MRI is utilized pre-thrombolysis to as high as 25%.[8–13] Therefore, concerns about the cost of treating SM patients with thrombolysis may impact provider decision making and, thereby, impact patient care.

While the decision to administer thrombolysis in the emergency department (ED) is influenced by regional practice patterns, individual practitioner experience, and treatment protocols, concerns about cost-effectiveness also exist. The perceived cost-effectiveness of various healthcare interventions and treatments may influence there use in clinical practice. We, therefore, sought to model the cost-effectiveness of treating suspected stroke patients before a definitive clinical diagnosis of AIS or SM could be made. We hypothesized that we would identify threshold proportions of SM among suspected stroke patients above which administering intravenous thrombolysis was no longer cost-effective despite the proven benefits of thrombolysis in true AIS patients.[14]

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Analytical measures

We use the incremental cost-effectiveness ratio (ICER) to identify proportions of SM among suspected stroke patients where administering intravenous thrombolysis remains favored from a healthcare sector perspective.[15] We calculate ICER as total costs divided by quality adjusted life years (QALY) comparing treatment with thrombolysis (intervention) to no acute treatment (control) at the 90-day time horizon. The intervention is considered cost-effective if the ICER was less than $100,000 USD per QALY gained.

To identify the proportion of SM among suspected stroke patients above which costs are unacceptably high from an individual hospital-level perspective, we use the cost-reimbursement ratio (CRR). The CRR is the ratio of total cost per patient to total reimbursement per patient. CRR results greater than 1 reflect costs that exceed reimbursement; results less than 1 reflect reimbursement that exceeds costs. We consider scenarios where CRR >1.5 as those with unacceptably high costs.

Model construction

We constructed a decision-analytic model using TreeAge Pro (2018, R2. TreeAge Software, Williamstown, MA) to encompass various potential stroke patient treatment scenarios; the choice node was either treat with thrombolysis or not (Figure 1). The main variables in our model were: (1) the proportion of SM to true stroke patients among arriving ED patients with suspected stroke, (2) time from symptom onset to treatment (OTT), and (3) complication rates among treated patients. We evaluated the role of OTT using two patient subgroups: group 1 with time from symptom onset of 0-90 minutes and group 2 with time from symptom onset of 91-180 minutes. The base case in our model is a 67 year old man at the time of his index stroke in keeping with prior research.[1, 3]

Model end nodes were partially defined based on expected patient outcomes measured by 90-day modified Rankin Scale (mRS). Outcomes of treated and untreated AIS patients were determined based on published severity distributions accounting for OTT.[16] For treated SM patients, outcomes were estimated from published data: 75% of SM with a mRS of 0, 10% with an mRS of 1, 10% with a mRS of 2, 2% with a mRS of 3, 2% with a mRS of 4, 1% with a mRS of 5, and 0% with a mRS of 6 provided no treatment complications occurred.[4] Any SM patient not treated with thrombolysis was assigned a mRS of 0. Previously published data were used to determine the QALY for each mRS level (Table 1).[1]

Model assumptions

To improve the generalizability of our model, we assumed that: (1) only a non-contrast head CT is obtained prior to the thrombolysis treatment decision, (2) all patients are admitted to the hospital, and (3) thrombolytics were never given if there were any treatment contraindications. To simplify our model, we assumed that: (1) once discharged from the hospital no patients subsequently returned, (2) no patients refused thrombolysis treatment when it was offered, (3) no patient had both angioedema and symptomatic intracranial hemorrhage after thrombolysis, and (4) the final diagnosis of SM versus true AIS could be ascertained with complete certainty in all patients after the treatment decision was made, but not before the treatment decision.

Cost calculations

To calculate costs, the payer perspective was assumed which includes only direct healthcare costs typically incurred by healthcare payers (e.g., pharmacy costs or inpatient care) and not indirect costs (e.g., productivity loss or caregiver time). All costs were estimated from published rates of inpatient hospitalization for AIS and SM, treatment complications for SM and AIS, as well as non-treatment of AIS.[2–4, 16–19, 21–23, 26] ED-based costs and those associated with neurological consultation were not included in our analyses as they are

likely to be similar for all suspected stroke patients. All costs and reimbursements have been re-adjusted for inflation to December 2017 dollars using the Consumer Price Index (Table 1).[27]

Reimbursement calculations

We assumed that all payers in our analysis were Medicare and that all charges made by the hospital were paid in full. Reimbursements for treated and untreated AIS were estimated from published national Medicare payment rates from the Centers for Medicare & Medicaid Services.[24, 25] Since there is no diagnosis-related group (DRG) for untreated or treated SM, we estimated reimbursement rates for untreated SM by averaging the DRGs for seizure, headache, TIA, and other disorders of the nervous system all without major comorbidity (DRGs 069, 093, 101, 103). We estimated reimbursement rates for treated SM by averaging the DRGs for AIS treated with thrombolysis, seizure, headache, TIA, and other disorders of the nervous system all without major comorbidity (DRGs 063, 069, 093, 101, 103) (Table 1).[25]

Sensitivity Analyses

Deterministic one-way and two-way sensitivity analyses were performed to test the robustness of the model. Parameter ranges were obtained from the literature and by varying costs and probabilities as detailed in Table 1. Additionally, we evaluated the effect of decreasing the overall reimbursement rate from 100% to 72% of Medicare rates. This allowed us to explore the effects of a Medicaid payer mix (which overall pays at an average of 78% of Medicare)[28] and to account for uncompensated care (approximately 6%).[29]

Results

We found an increasing trend of ICER as the proportion of SM cases increased. For patients treated in the 3-hour time window, thrombolysis was cost-effective until a SM threshold of approximately 30% was exceeded (Figure 2). The threshold did not differ by more than 3% comparing patients with symptom onset between 0-90 minutes and 91-180 minutes.

From a hospital-level perspective, the threshold proportion above which treatment of SM resulted in a CRR >1.5 was approximately 75% (Figure 3A). The threshold of SM where CRR> 1.5 did not differ by more than 2% comparing patients with symptom onset between 0-90 minutes and those with symptom onset between 91-180 minutes.

In sensitivity analysis at the healthcare sector level, the SM threshold at which administration of thrombolysis is cost-effective was only significantly impacted by cost of alteplase with an SM threshold of 13% when alteplase cost $7,000 USD and 48% when alteplase cost $0 USD (Figure 4). Changes in all other cost variables did not alter SM threshold by greater than approximately 3%. At the hospital-level, when reimbursement rate decreased to 72% to account for Medicaid payer mix and uncompensated care, CRR was >1.5 with a threshold of SM of greater than approximately 65% (Figure 3B).

Discussion

The penalty for treating stroke mimics with thrombolysis was significantly less than the penalty of failing to treat true AIS until specific thresholds of SM proportions were reached. Up to a threshold of greater than 30% of stroke mimics, thrombolysis for suspected stroke in the 0-3 hour window remains cost-effective in a majority scenarios. At the hospital-level, the cost reimbursement ratio for stroke thrombolysis became unacceptable with a higher proportion of stroke mimics (>75%).

We are not aware of any prior studies that sought to determine the proportion of SM among suspected stroke patients above which thrombolytic treatment is not cost-effective or associated with high hospital-level costs. A single study of four primary stroke centers in Tennessee evaluated the indirect and direct hospital costs associated with acute SM thrombolysis and reported a median excess cost of $5,401 per treated SM patient as compared to other neurological conditions.[7] Our data suggest that thrombolysis in the 0-3 hour window provides a margin of diagnostic error up to approximately 30%. Of note, we did not explore the cost-effectiveness of thrombolysis in the 3-4.5 hour window in these analyses largely due to our reliance on randomized control trial data wherein patients enrolled within the 3-4.5 hours differed from those enrolled within 3 hours based on study inclusion and exclusion criteria.[16] Treatment of SM may have a more significant effect in the extended time window as the odds of a favorable 90 day outcome are substantially lower among true AIS patients than in the 0-3 hour window.[16, 30] Beyond 3 hours, a lower margin of diagnostic error may be warranted.

Cost-effective analyses are an important lens through which the problem of balancing speed and diagnostic accuracy in acute stroke decision making can be viewed.[30] Finding the appropriate balance of under-treating, perhaps at the cost of missing treatment for true stroke patients, and over-treating, which may become expensive, requires addition considerations. Though hemorrhagic complication rates among SM patients are low,[4] the ethical principles of beneficence and non-maleficence must be weighed carefully when attempting to identify acceptable SM treatment thresholds.[31] An in-depth discussion of medical ethics is lacking in this current study and represents an important area of future research. From a policy standpoint, our finding that with increasing costs of alteplase itself, lower thresholds of SM are needed to maintain treatment cost-effectiveness is important. Our range of drug costs included the most recent cost estimated for a 100 mg vial of alteplase.[19]

In addition to traditional cost-effectiveness analyses, hospital-level analyses carry a great deal of practical importance. The current US healthcare system’s reimbursement structure is sharply divided between inpatient and outpatient care. As such, while emergency treatments may be cost-effective, hospitals caring for stroke patients may not be appropriately reimbursed or incentivized to make efficacious emergency treatments a priority.[19] In the long term, high CRRs due to thrombolysis of SM could undermine recent improvements in thrombolysis treatment rates among stroke patients.[26] Based on our analyses, hospitals with less advantageous payer mixes (e.g., Medicaid payers and/or uncompensated care) may be more dis-incentivized to treat suspected stroke patients with thrombolysis than centers with a more advantageous payer mix. To better understand current hospital-level SM treatment

rates, uniform reporting guidelines for the diagnosis of SM, particularly after thrombolysis, are needed.[32] We are not aware of any certification agencies or national registries which currently require reporting rates of treated SM.

Our study has a number of limitations. First, we did not account for the potential role of advanced early imaging or other diagnostic testing to differentiate true AIS from SM prior to thrombolysis.[10, 33] We also did not account for the cost of any angiographic studies in the ED. Though emergent vessel imaging can be obtained to guide acute stroke treatment decision making in clinical practice, our model assumed that the decision to administer thrombolysis was made independently of advanced imaging data. Second, we did not consider the effect of endovascular therapy on patient outcomes or hospital costs. Third, we primarily used Medicare reimbursement rates (e.g., not those of private insurers), did not adjust for the effects of supplemental payments to hospitals, and did not perform additional analyses to more carefully account for state differences. Additionally, the DRGs that we used for treated and untreated SM were estimates and we did not update DRGs when a treatment complication occurred. Fourth, we did not account for race-ethnic differences in thrombolysis treatment in our model. Fifth, we evaluated only the 90-day time horizon, which likely led to an under-estimation of the lifetime cost-effectiveness of stroke thrombolysis.[1, 3] Since the costs and benefits of stroke thrombolysis are generally up-front and there are a number of uncertainties introduced with longer time horizons, we chose 90 days in our study. Finally, we exclusively focused on the US healthcare system and limited our perspective to that of the payer. In countries with a single public payer such as the United Kingdom, Canada, and many European countries, our model would likely include additional costs. Both of our analytical perspectives, the healthcare sector and the hospital-level, omit many societal costs including those of the informal healthcare sector (e.g., unpaid caregiver costs) and the non-health care sector (e.g., cost of uncompensated household production or future patient consumption unrelated to health).[15] In particular, we did not account for the downstream effects and costs of SM thrombolysis which may include delays in the diagnosis and management of alternative neurological diseases.[34] Better quantification of the societal effects of SM diagnosis and treatment would improve future cost-effectiveness analyses.

Conclusion

We found that stroke thrombolysis in the 3 hour window is cost-effective from the healthcare sector perspective when SM proportions among arriving patients are less than 30%. From a hospital-level perspective, costs may rise to greater than 1.5 times reimbursement depending on the proportion of SM among arriving patients and the payer mix. Hospitals should, therefore, carefully monitor the proportions of SM among suspected stroke patients undergoing thrombolysis and establish performance metrics to prevent rising acute stroke care costs and potential patient harms.

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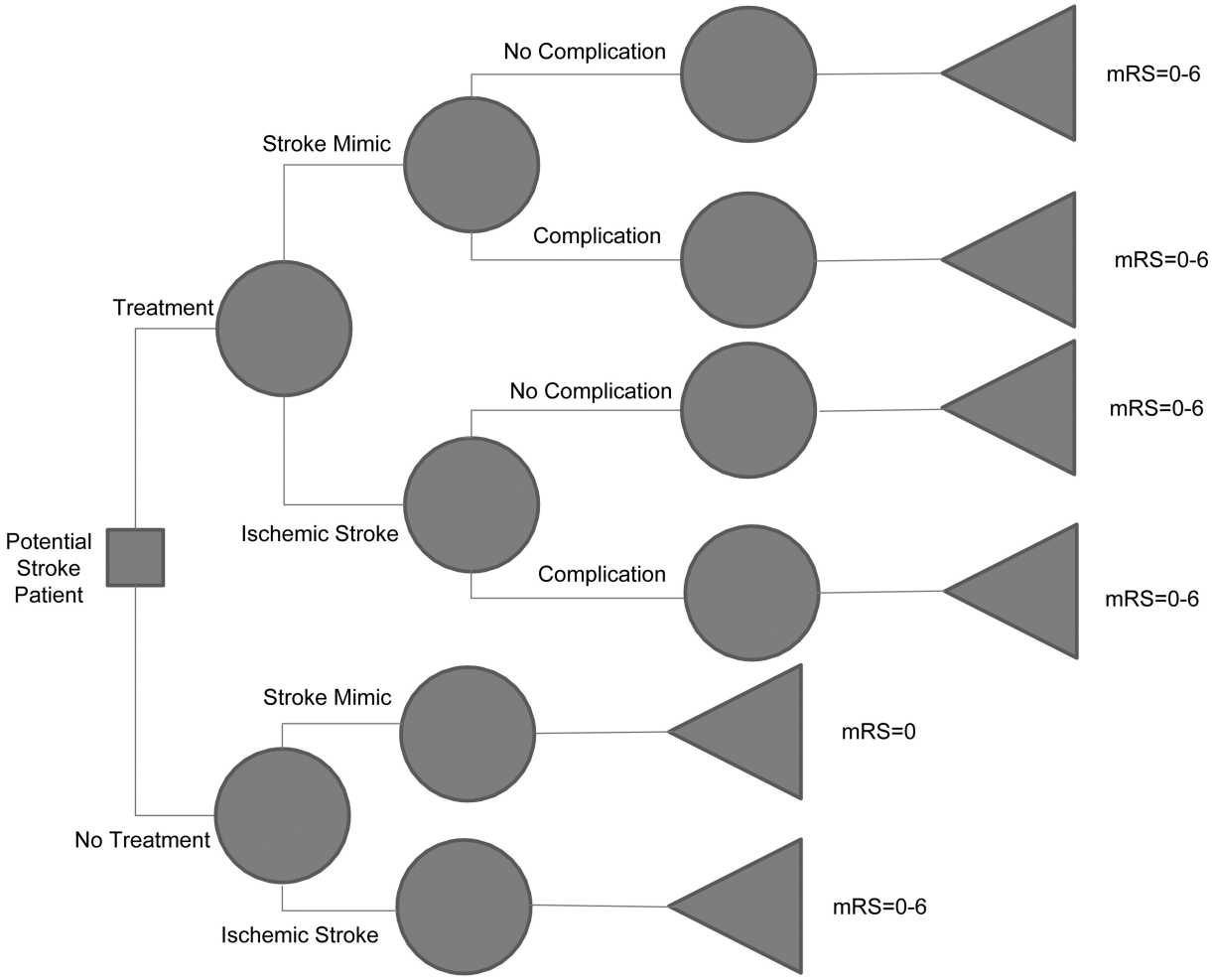

Figure 1.
Decision Tree Schematic

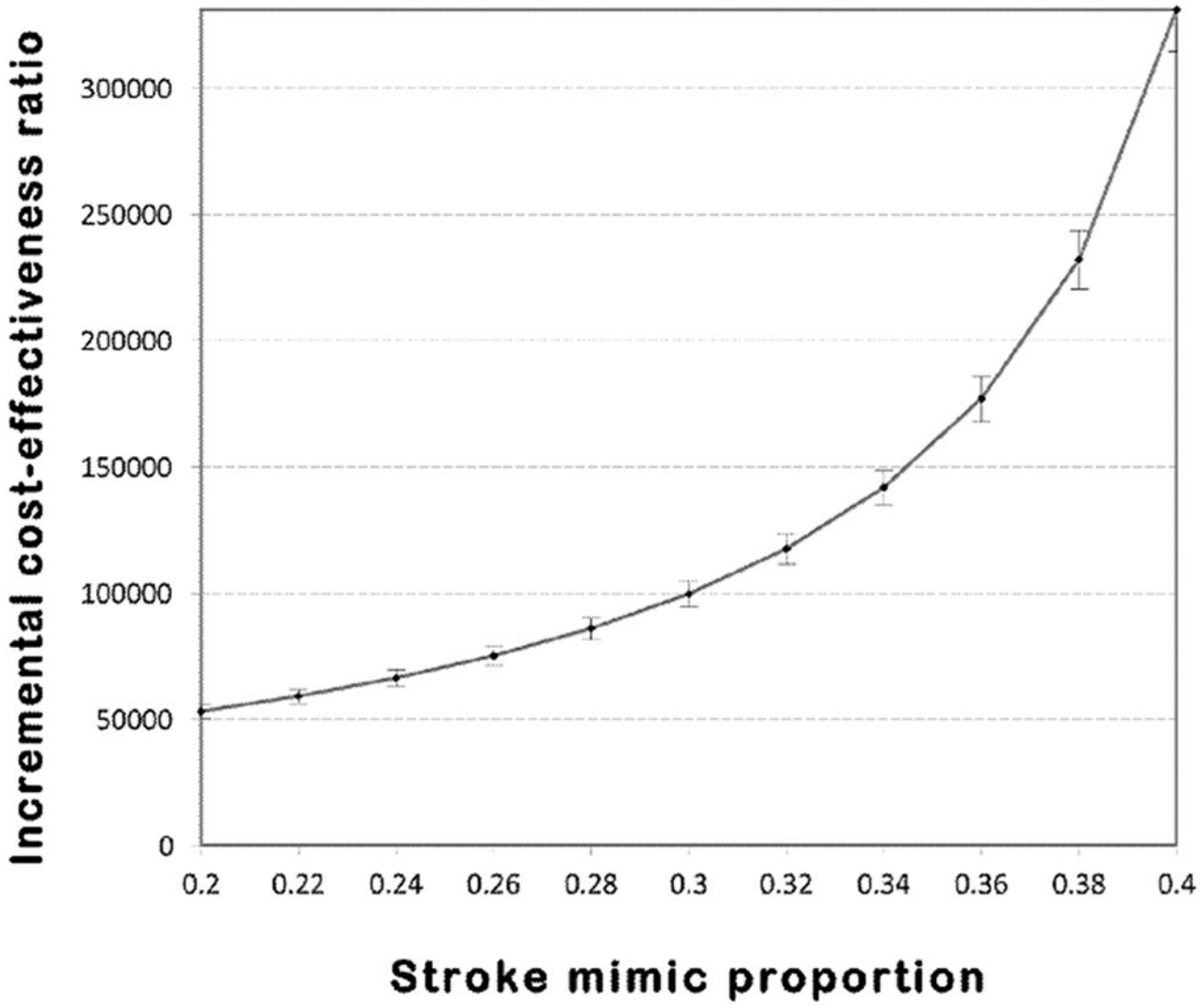

Figure 2. Incremental cost-effectiveness ratio at varying stroke mimic proportions

Incremental cost-effectiveness ratio in the 0-90 minute window with 5% error bars around each point.

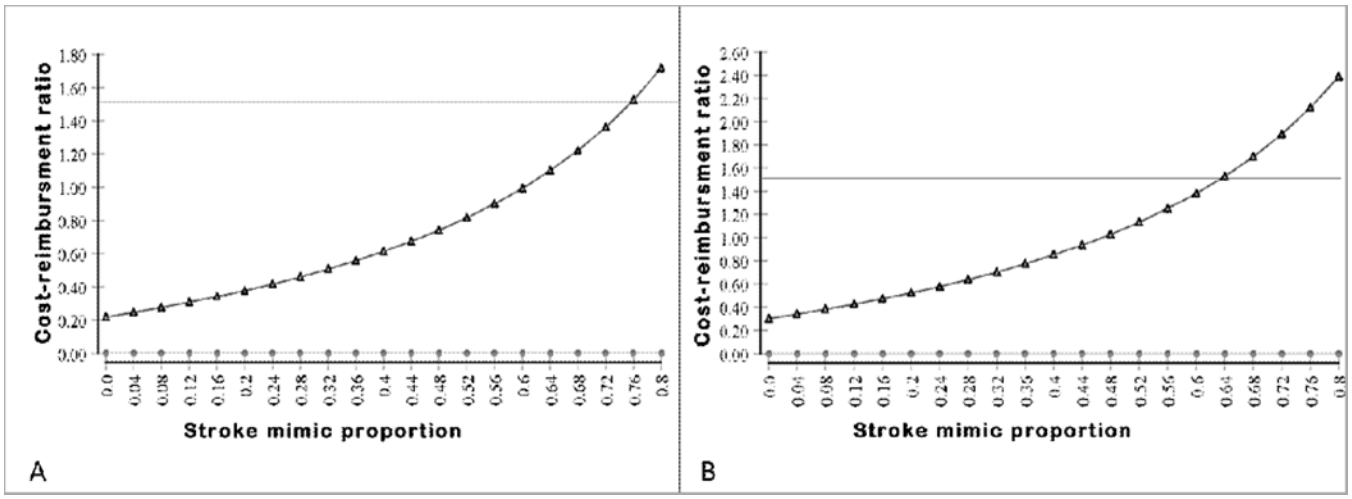

Figure 3. Cost-reimbursement ratio at varying stroke mimic proportions

Cost-reimbursment ratio with (a) 100% reimbursment rate and (b) 72% reimbursment rate where time from symptom onset to treatment time is 91-180 minutes. Strategy of treatment with alteplase represented with triangles; strategy of no treatment represented with circles. Thin gray line where cost-reimbursement ratio is 1.5.

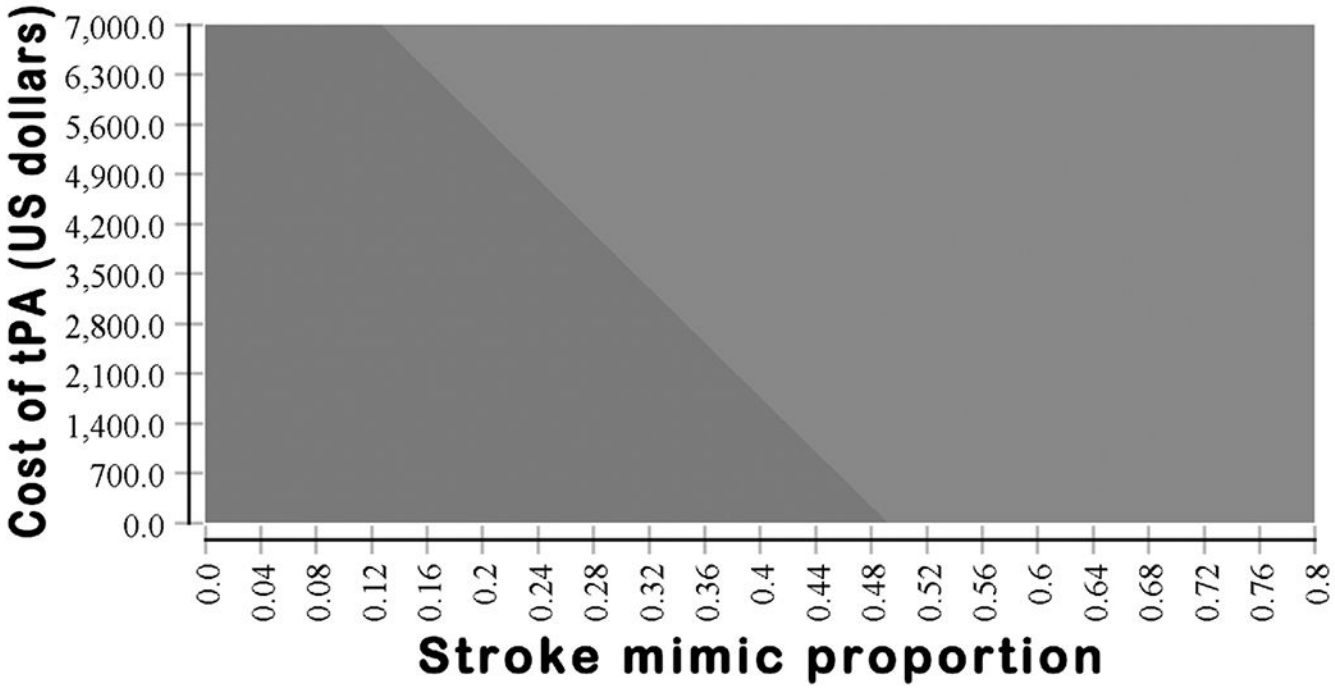

Figure 4. Relationship between alteplase cost and stroke mimic cost-effectiveness thresholds

Two-way cost-effectiveness sensitivity analysis of varying alteplase cost and the proportion of stroke mimics where time from symptom onset to treatment is 91-180 minutes. Light grey represents the strategy of thrombolysis treatment; dark grey represents no treatment.

Table 1.

Model assumptions

	Value	Range	References
Utilities			
QALY mRS 0	0.90	None	1
QALY mRS 1	0.80		1
QALY mRS 2	0.46		1
QALY mRS 3	0.34		1
QALY mRS 4	0.30		1
QALY mRS 5	-0.02		1
QALY mRS 6	0		1
Probabilities			
Symptomatic intracerebral hemorrhage rate for true stroke	7%	5–8%	17
Symptomatic intracerebral hemorrhage rate for stroke mimics	1%	0–2%	4
Angioedema for true stroke	3%	0–5%	18
Angioedema rate for stroke mimics	1%	0–2%	4
Costs, $ *			
Additional cost of 100 mg vial of alteplase	3,127	0–7,000	19,20
Inpatient costs: mRS 0	3,504	+/− 20%	21
Inpatient costs: mRS 1	4,672	+/− 20%	21
Inpatient costs: mRS 2	5,840	+/− 20%	21
Inpatient costs: mRS 3	9,343	+/− 20%	21
Inpatient costs: mRS 4	23,358	+/− 20%	21
Inpatient costs: mRS 5	23,358	+/− 20%	21
Inpatient costs: mRS 6	23,358	+/− 20%	21
Additional cost of symptomatic intracerebral hemorrhage in patients with 90-day, mRS 0–3	1,347	+/− 20%	22, 23
Additional cost of symptomatic intracerebral hemorrhage in patients with 90-day, mRS 4–6	3,176	+/− 20%	22, 23
Additional cost of angioedema	2,112	+/− 20%	
Reimbursements, $ *			
True stroke, treated with thrombolysis (average DRG 559)	14,101	None	24
True stroke, not treated with thrombolysis (average DRGs 064 and 066)	8,160		25
Stroke mimic, treated with thrombolysis (average DRGs 063, 069, 093, 101, 103)	5,852		25
Stroke mimic, not treated with thrombolysis (average DRGs 069, 093, 101, 103)	4,689		25

* Costs and reimbursements were converted to US dollars and adjusted using Consumer Price Index to reflect the value in 2017