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Cost-Effectiveness of Recombinant Tissue Plasminogen Activator 3–4.5 Hours after Onset of Acute Ischemic Stroke in Patient Subgroups

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Abstract

Background—The ECASS III study showed that recombinant tissue plasminogen activator (rtPA) given 3–4.5 hours after acute ischemic stroke (AIS) led to improvement in patient disability versus placebo.

Objective—To evaluate the long-term incremental cost-effectiveness of rtPA given 3–4.5 hours after AIS onset versus no treatment based on patient clinical and demographic factors.

Methods—We developed a disease-based decision analytic model to project lifetime outcomes of patients post-AIS from the payer perspective. Clinical data were derived from the ECASS III trial, longitudinal cohort studies, and health state preference studies. Cost data were based on Medicare reimbursement and other published sources. We performed probabilistic sensitivity analyses to evaluate uncertainty in the analysis.

Results—rtPA in a hypothetical cohort of 100 patients resulted in a gain of 7 years of life (95% credible range [CR], 0.05–17) and 24 quality-adjusted life-years (QALYs) (95% CR, 1–60), and a difference in cost of \$149,500 (95% CR, –\$463,700 – \$610,000) compared with placebo. The incremental cost-effectiveness ratio for all patients was \$6,300 per QALY gained; for patients <65 years old, cost saving; 65 years old, \$35,800/QALY; for patients with baseline NIHSS 0–9, \$16,300/QALY; 10–19, \$37,500/QALY; 20, \$2,400/QALY. The majority of other subgroups such as gender, history of stroke, and history of hypertension were cost-saving to cost-effective with the exceptions of diabetes and atrial fibrillation.

Conclusion—The results indicate that rtPA in the 3- to 4.5-hour therapeutic window provides improvement in long-term patient outcomes in most patient subgroups and is a good economic value versus no treatment.

Keywords

Cerebrovascular disorders; Stroke; Cost effectiveness; Outcome studies; Quality of life; Thrombolytic therapy

INTRODUCTION

Background

Stroke remains a significant public health problem, with approximately 795,000 new or recurrent stroke cases and 133,000 stroke deaths occurring each year in the United States.¹ It is estimated that \$74 billion were spent in 2010 on stroke-related medical costs and disability.² The burden of disease from stroke is expected to increase over the coming decades due to the aging of the population and the limited control of stroke risk factors.³

Thrombolysis is effective in reducing disability due to acute ischemic stroke (AIS).^{4–7} rtPA (alteplase, Activase®) was approved as thrombolytic therapy by the US Food and Drug Administration for treating AIS 15 years ago but is underutilized,^{8–10} due in part to restrictions on the time window.^{11–13} Specifically, rtPA is currently indicated for use within 3 hours after the onset of symptoms based on data from the National Institute of Neurological Disorders and Stroke (NINDS) trial.⁴ However, recent results from the European Cooperative Acute Stroke Study (ECASS III) trial suggest that the therapeutic window may be safely extended to 4.5 hours.⁵ When given within 3–4.5 hours of stroke-symptom onset, a 7.2% reduction in 90-day disability compared with placebo was noted in ECASS III.⁵ The AHA/ASA recently advised in favor of extending the window for rtPA use in eligible patients with AIS.¹⁴

Importance

Prior cost-effectiveness analyses (CEA) have reported that rtPA use 0–3 hours after onset of AIS is cost-saving,^{15–18} and one recent study reported that use in the 3- to 4.5-hour timeframe was cost-effective for all patients on average,¹⁹ but no study has evaluated economic outcomes in patient subgroups.

Goals of This Investigation

The objective of this study was to estimate the average clinical and economic impact of thrombolysis by intravenous therapy with rtPA for AIS within 3–4.5 hours of stroke-symptom onset compared with no rtPA for patient subgroups.

METHODS

Study design

Model structure—A decision analytic model was developed to examine the cost-effectiveness of rtPA versus no rtPA from a payer perspective using a lifetime horizon. We created a decision tree to simulate treatment and 90-day outcomes in a hypothetical cohort of patients presenting to the hospital with AIS (Figure 1a). The simulated patient population was similar in age (mean = 66 years) to that of the ECASS III clinical trial population.⁵ Patients could be disabled, non-disabled, or die, with or without experiencing symptomatic intracranial hemorrhage (sICH).

Patients surviving to 90 days then entered a Markov model to simulate long-term clinical outcomes such as disability, recurrent stroke, and death over the patients' remaining years of life (Figure 1b). We defined non-disabled as modified Rankin scores (mRS) of 0–1 and disabled as mRS scores 2–5. The mRS scale describes 6 grades of disability post-stroke (grade 5 denotes severe disability, grade 0 denotes no symptoms at all) and captures the full spectrum of limitations in activity and social participation.²⁰ We evaluated the validity of grouping mRS rankings compared with using separate mRS scores by comparing the weighted values for costs, quality of life (patient preferences), and mortality using data from a previous study.²¹ We found that grouping mRS scores led to similar results for rtPA versus

no rtPA; in other words, the distribution of mRS scores within the non-disabled and within the disabled categories were similar, on average, between rtPA and no rtPA, thus justifying our simplified modeling approach.

Patients remained in the health states experienced at the end of the initial 90-day period in the long-term model until either (1) nonstroke death or (2) a stroke recurrence moved them to a worse health state or stroke death. Patients in the model transitioned between the health states of non-disabled (mRS 0–1), disabled (mRS 2–5), and dead, as indicated by the arrows in Figure 1b. The model was programmed in Microsoft Excel.

Data collection

Clinical input parameters—Clinical parameters are shown in Tables 1 and 2. These estimates were derived from randomized trial data and published clinical studies. We used standard sources (MEDLINE, EMBASE) to search for data to support the model inputs using a variety of keywords such as *stroke*, *thrombolysis*, *tissue plasminogen activator*, and *cost-effectiveness*.

The probabilities of 90-day disability status and death from the placebo arm of the ECASS III trial were used to estimate baseline risks for the no-rtPA group (Table 1). We then multiplied the no-rtPA risks (ie, baseline rates) by the treatment relative risk (RR) estimates derived from the trial to calculate probabilities for the rtPA group.⁵ We conservatively assumed there was no mortality difference between no-rtPA and rtPA groups in our base-case analysis based on the non-statistically significant decrease in mortality with rtPA treatment versus no-rtPA observed in the ECASS III study (7.7% vs 8.4%; $P = .68$).

The ECASS III study reported several definitions of sICH, including the NINDS definition, and previous cost-effectiveness studies have used the NINDS definition in their analyses. We also used the NINDS sICH definition, as it was more conservative (an absolute increase in sICH of 4.4%) than the definition used in the ECASS III study (an absolute increase in sICH of 2.2%).⁵ We evaluated the impact of using the ECASS III definition in a scenario analysis.

The long-term clinical parameters are shown in Table 2. Annual death rates for non-disabled patients were derived from US life table age- and sex-adjusted mortality rates.²² Disabled patients were assumed to have a higher risk of death based on recent studies indicating these patients have significantly increased mortality. However, there is some uncertainty in the magnitude of the increased risk. Hong and Saver²³ recently used estimates ranging from a 1.5-fold increase in mortality for mRS 0 patients up to a 6.5-fold increase for mRS 5 patients based on the results of two cohort studies in Europe.^{24, 25} In contrast, Fagan et al estimated a 2.7-fold increase for all stroke survivors, but no difference between non-disabled and disabled patients.¹⁶ One of the most commonly used mortality estimates is from Samsa et al, who assumed no increase in mRS 0–1 patients and up to a 2.4-fold increase in mRS 5 patients (an average of approximately 1.5 for mRS 2–5 patients based on ECASS III outcomes).²¹ Given the uncertainty in this parameter, we calculated a weighted average (from Samsa) of 1.52-fold risk for disabled patients and explored a range from 1.22–1.82 in sensitivity analyses (1.10 [1.00–1.20] for non-disabled).

We assumed recurrent stroke rates were equal across all levels of disability based on previous studies.^{16, 26} Annual rates of stroke recurrence were based on a systematic review of 59 controlled trials of medical secondary stroke prevention therapies published from 1960 to 2009.²⁷ The control arms of the trials were used to estimate annual event rates over time, and we used the most recent decade (2000s) annual event rate for the current study. We assumed patients did not receive rtPA for recurrent strokes. Patients alive after a recurrent

stroke defaulted in equal proportions to the same or worse Rankin categories than prior to the recurrent stroke, similar to the methods employed in previous studies.^{16, 28} Deaths from recurrent stroke were based on estimates used in a cost-effectiveness of rtPA analysis conducted by Fagan and colleagues shortly after the release of the NINDS trial results.¹⁶

We applied quality of life scores (utilities or patient preferences) for each mRS score (0–5) from Stahl and colleagues²⁸ to arrive at weighted utilities for the non-disabled (Rankin 0–1) and disabled (Rankin 2–5) health states, based on the mRS outcomes of the ECASS III study. We derived sensitivity analysis estimates for utilities from Fagan and Samsa.^{16, 21} We verified that the weighted utilities for the corresponding health states were essentially equivalent in the no-rtPA and rtPA arms, thus justifying our simplified model structure. We applied a disutility of –0.38 for 2 weeks if sICH occurred.²⁹

Cost input parameters—Costs known to contribute the majority of direct medical costs or potentially differ across treatment groups were derived from a variety of sources in the literature. We did not include indirect costs such as productivity losses or caregiver time, as the analysis was conducted from the payer perspective. Inpatient costs for AIS were obtained from Reed and colleagues.^{30, 31} Reed et al analyzed data from HBSI EXPLORE which contains comprehensive administrative data for all patients admitted to more than 150 community hospitals located throughout the United States.³¹ Estimated mean costs included all inpatient services for stroke patients (identified via ICD-9 codes), stratified by discharge status. Following Earnshaw and colleagues, we used Reed et al's costs for patients discharged to home or home health services as a proxy for non-disabled and costs for patients discharged to skilled nursing facilities for disabled.³⁰ sICH inpatient costs were derived in a similar fashion.

We explicitly added the cost of rtPA to inpatient costs for patients in the rtPA treatment strategy. The total cost of rtPA, administration, and additional monitoring time was estimated from 2011 national Medicare reimbursement rates calculated as the difference in reimbursement for acute care of stroke patients with and without administration of rtPA (MS DRG 61 minus 64).^{30, 32} We conservatively used the higher reimbursement rates of DRGs for major complication or comorbidity.

The long-term annual health costs in the years following a stroke were based on a methodology previously described by Earnshaw et al and Fagan et al^{16, 30} Briefly, yearly direct costs, excluding the first 90 days, were stratified by disability status.³³ Recurrent strokes were assigned the cost of an incident acute stroke. All costs were inflated to 2011 dollars using the Medical Consumer Price Index (Table 2).³⁴

Outcome measures

We calculated life-years (LYs), quality-adjusted life-years (QALYs), and direct medical costs over patients' lifetimes, and calculated incremental differences between the rtPA and no-rtPA strategies. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in costs divided by the difference in QALYs. All costs and outcomes were discounted at 3% per year.³⁵

Primary data analysis

Base-case Analysis and Model Validation—We compared rtPA with no rtPA for patients presenting 3–4.5 hours after AIS onset in our base-case analysis. This analysis addresses the question faced by clinicians and payers about whether to provide rtPA to this patient population. We also performed an analysis to estimate outcomes for rtPA versus no

rtPA among patients arriving within 0–3 hours of symptoms based on data from the NINDS trial⁴ in order to validate the model against previously published studies.

Subgroup analyses—We conducted analyses of clinical and economic outcomes in patient subgroups based on the ECASS III subgroup analyses reported by Bluhmki and colleagues (Table 1).³⁶ Bluhmki et al further evaluated the efficacy and safety of rtPA from the ECASS III trial data according to predefined (time from onset of symptoms, baseline National Institutes of Health stroke scale [NIHSS], age, sex) and post hoc subgroups (diabetes, previous stroke, hypertension, atrial fibrillation, smoking status, and previous chronic use of antiplatelet drugs). We used the rtPA efficacy and safety estimates for the outcomes of mRS and sICH at 90 days by subgroups reported in this analysis.³⁶ We used reported placebo arm mortality estimates for each subgroup and assumed no mortality difference between treatment groups, similar to the base case analysis. We also evaluated sICH rates across each subgroup while holding all other base case parameters constant.

Sensitivity analyses

Scenario analyses—We conducted a scenario analysis in which we assumed an absolute 0.7% increase in overall 90-day mortality in the rtPA group to explore the impact of increased sICH mortality on model outcomes.

Uncertainty analyses—We performed a series of sensitivity analyses to examine the influence of uncertainties in the model inputs and to judge the robustness of the findings.^{35, 37} Single-variable (one-way) sensitivity analyses were performed with the value of each input varied over a plausible range (ranges specified in Tables 1–2) and the impact on incremental costs and QALYs examined. The results of the sensitivity analyses are presented in the form of tornado diagrams.

We also performed probabilistic sensitivity analysis (PSA).^{37, 38} All model parameters were allowed to take a range of values described by the specified distributions that represent the uncertainty in their estimation. This allows for the effects of joint uncertainty across all parameters in the model. Monte Carlo simulation was used to select values at random from the distributions, and by repeating this process 10,000 times, 95% credible ranges were estimated.^{39, 40} We created a cost-effectiveness acceptability curve based on the results of the probabilistic simulation to demonstrate the probability of rtPA being cost effective versus no rtPA at the price society is willing to pay for a QALY.^{41, 42}

RESULTS

Main results

Base case analysis and model validation—The lifetime cost effectiveness of rtPA treatment in the 3- to 4.5-hour window versus no rtPA in patients with AIS is summarized in Table 3. Treatment with rtPA between 3–4.5 hours of symptom onset increased life expectancy by an average of 0.07 year per patient, QALYs by 0.24, and costs by \$1,495. The incremental cost per QALY gained was \$6,300.

The model validation results for 0–3 hours were as follows: \$3,723 saved per patient, 0.14 life years gained, and 0.51 QALYs gained.

Patient subgroups—The incremental cost-effectiveness ratio for key patient subgroups were as follows: patients <65 years old, cost saving; ≥65 years old, \$35,800/QALY; for patients with baseline NIHSS 0–9, \$16,300/QALY; 10–19, \$37,500/QALY; ≥20, \$2,400/QALY (Table 4). Patients with a history of diabetes or atrial fibrillation did not have an

improvement in outcomes and treatment with rtPA at 3–4.5 hours and thus rtPA was not cost-effective in these subgroups. Subgroup analyses of sICH rates showed little impact on the incremental cost per QALY gained (range, \$5026/QALY to \$5768/QALY).

Sensitivity analyses

Scenario analysis—When we conservatively assumed an overall increased risk of mortality due to sICH, the difference in life expectancy changed from 0.07 to –0.01 per patient, the difference in QALYs changed from 0.24 to 0.19, and the difference in costs changed from \$1,495 to \$739 as a result of fewer patients living past 90 days to accrue both lifetime costs and life expectancy in the treatment group.

One-way sensitivity analyses—The tornado diagrams in Figure 2 display the results of all one-way sensitivity analyses for the incremental QALYs (Figure 2a) and costs (Figure 2b). Model inputs at the top of the tornado diagrams have the largest impact on the results. Incremental costs and QALYs were influenced by similar inputs. The analyses were most sensitive to the relative risk of disability (or of being non-disabled); secondarily, QALYs were sensitive to health state utilities, and costs were sensitive to health state costs and the cost of rtPA.

Probabilistic sensitivity analyses (PSA)—Results of the PSA showed that rtPA treatment increased both life-years [0.07; 95% credible range (CR), 0.0005 to 0.17] and QALYs (0.24; 95% CR, 0.01 to 0.60) per patient. The incremental cost per patient was \$1,495 (95% CR, –\$4,637 to \$6,100). The cost-effectiveness acceptability curve illustrates the estimated 88.4% probability that rtPA was cost-effective at a \$50,000/QALY threshold, and a 93.8% probability of being cost-effective at a \$100,000/QALY threshold (Figure 3).

DISCUSSION

Overview

We evaluated the long-term clinical and economic outcomes associated with the use of rtPA to treat patients with AIS 3–4.5 hours after onset using a disease-based decision-analytic model. The results of this analysis suggest that use of rtPA in this therapeutic window increases average life expectancy and QALYs in a cost-effective manner. Specifically, our analyses indicated there is over a 90% probability that rtPA 3–4.5 hours after AIS onset is cost-effective using commonly accepted cost-effectiveness thresholds. From a practice perspective, for every 100 patients treated with rtPA within 3–4.5 hours of symptom onset, 7 years of life or 24 years of quality-adjusted life would be gained at a cost of \$149,500.

This is the first study to evaluate the cost-effectiveness of rtPA at 3–4.5 hours post-AIS for unique subgroups. Consistent with the efficacy and safety outcomes presented by Bluhmki and colleagues,³⁶ our study found a clear pattern in favor of rtPA for the majority of subgroups. rtPA was especially cost saving or cost-effective among younger patients and patients without comorbidities such as hypertension and diabetes. rtPA was cost-effective in the ≥65 age group but the ICER in this group was lower than the <65 age group (cost-saving) because of the lower life expectancy in the older age group. Bluhmki and colleagues observed improved mRS at 90 days post AIS among patients treated with rtPA compared to placebo in both age groups (statistically significant only in <65 group), improved mortality in the <65 group (although not statistically significant), and a significant difference in mortality risk between the two age groups.³⁶ The ≥65 group also had a higher likelihood of developing sICH than the <65 group. Interestingly, patients with a higher NIHSS score had a more favorable cost-effectiveness than those with lower NIHSS scores. This finding is a result of the large benefit in mRS improvement observed in high NIHSS group; however,

given the relatively small size of this subgroup ($N < 100$), these results should be interpreted with caution.³⁶

Even with these mostly encouraging findings, results of these subgroup cost-effectiveness analyses should be interpreted with some caution since the efficacy and safety end points used from the Bluhmki et al study were not powered for the subgroup analyses.

Implications

Our findings support the inclusion of rtPA use 3–4.5 hours post-AIS in clinical guidelines and reimbursement policies. Furthermore, treatment in the majority of patient subgroups was either cost saving or cost-effective, and use of rtPA should be based on assessment of clinical factors in patients in this expanded therapeutic window. Efforts to ensure that eligible patients have the opportunity to receive rtPA should be enhanced through the use of educational activities and establishment of primary stroke centers.

Comparison to previous studies

The results of our scenario analysis of the cost-effectiveness of rtPA within 0–3 hours are similar to US and non-US rtPA cost studies in the literature, supporting the validity of our analysis in the 3- to 4.5-hour timeframe.^{15–18, 43} Using efficacy data from the NINDS trial as well as medical literature, Fagan and colleagues estimated in a 1998 publication that rtPA within 3 hours of symptom onset results in a net cost savings to the health care system.¹⁶ Other studies conducted in Canada,⁴³ the United Kingdom,^{15, 18} Denmark,⁴⁴ and Australia⁴⁵ report rtPA to be a cost-effective, and in many cases a cost-saving/dominant strategy for treating eligible patients with AIS.

One recent study has been published on the cost-effectiveness of rtPA in the 3- to 4.5-hour timeframe.¹⁹ Although both the Tung study and our study found rtPA treatment within 3–4.5 hours to be cost-effective, the primary explanation for the differences in our findings (\$22,000/QALY vs \$6,300/QALY) is the estimated cost of rtPA. We based our cost on Medicare reimbursement rates, for a total acquisition, administration, and monitoring cost of \$6,083. We additionally accounted for the cost of sICH. In contrast, Tung et al estimated the cost of rtPA (\$9,400) from a study that compared the cost of hospitalization for patients who received rtPA versus those who did not using observational retrospective data.⁴⁶ It is possible that inherent differences in the patient groups (confounding) led to their estimated rtPA treatment cost of \$9,400 per patient, as the source of the additional cost beyond drug, administration, monitoring, and adverse effect (sICH) costs is not clear.

Limitations

There are several limitations of our study worth noting. We developed a decision model based on certain necessary assumptions and populated the model with data from numerous published studies including clinical trials. The results and conclusions are therefore specific to those assumptions and data. However, our sensitivity analyses suggest our results are robust to uncertainty in the model parameters. More specifically, the literature is inconsistent in defining the increase in mortality following stroke, particularly in disabled patients. We used conservative estimates of this increase, and indeed higher disabled patient mortality tended to favor cost-saving versus cost-effective results because patients with disability have shorter life expectancy and thus lower costs. Furthermore, we assumed no difference in mortality between rtPA and no-rtPA patients, a reflection of the clinical trial findings. We modeled a scenario in which overall mortality with rtPA was increased through sICH, which still indicated an overall improvement in QALYs. Our patient subgroup analysis is limited by smaller sample sizes of the clinical data. Lastly, generalizing trial results to real-world effectiveness is challenging and many of the model inputs were based

on a single European clinical trial. Future research based on real-world use of rtPA within a 3- to 4.5-hour window will be useful for refining these results.

Conclusion

In summary, rtPA in the 3- to 4.5-hour window post-AIS appears to be cost-effective in the majority of patient subgroups, and efforts should be made to increase the proportion of patients who may safely benefit from the treatment. When clinically appropriate, patients should be treated as early as possible because both efficacy and cost-effectiveness may be greater. Further research is needed to study implications of extended rtPA use in real-world settings and to improve upon the delivery of rtPA when patients are eligible and protocols are in place.

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References

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation*. 2010; 121:e46–e215. [PubMed: 20019324]
2. American Heart Association. [Accessed March 4, 2011] Heart Disease and Stroke [online]. Available at: <http://www.heart.org/HEARTORG/>
3. Elkins JS, Johnston SC. Thirty-year projections for deaths from ischemic stroke in the United States. *Stroke*. 2003; 34:2109–2112. [PubMed: 12881608]
4. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995; 333:1581–1587. [PubMed: 7477192]
5. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008; 359:1317–1329. [PubMed: 18815396]
6. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995; 274:1017–1025. [PubMed: 7563451]
7. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998; 352:1245–1251. [PubMed: 9788453]
8. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. *Arch Neurol*. 2001; 58:2009–2013. [PubMed: 11735774]
9. Reeves MJ, Arora S, Broderick JP, et al. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. *Stroke*. 2005; 36:1232–1240. [PubMed: 15890989]
10. Use of a registry to improve acute stroke care--seven states, 2005–2009. *MMWR Morb Mortal Wkly Rep*. 2011; 60:206–210. [PubMed: 21346707]
11. Alberts MJ. Hyperacute stroke therapy with tissue plasminogen activator. *Am J Cardiol*. 1997; 80:29D–34D. discussion 35D–39D.
12. Fonarow GC, Smith EE, Saver JL, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation*. 2011; 123:750–758. [PubMed: 21311083]
13. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA*. 2000; 283:1151–1158. [PubMed: 10703777]

14. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke*. 2009; 40:2945–2948. [PubMed: 19478221]
15. Chambers MG, Koch P, Hutton J. Development of a decision-analytic model of stroke care in the United States and Europe. *Value Health*. 2002; 5:82–97. [PubMed: 11918824]
16. Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology*. 1998; 50:883–890. [PubMed: 9566367]
17. Mar J, Begiristain JM, Arrazola A. Cost-effectiveness analysis of thrombolytic treatment for stroke. *Cerebrovasc Dis*. 2005; 20:193–200. [PubMed: 16088115]
18. Sandercock P, Berge E, Dennis M, et al. Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs. *Stroke*. 2004; 35:1490–1497. [PubMed: 15105519]
19. Tung CE, Win SS, Lansberg MG. Cost-effectiveness of tissue-type plasminogen activator in the 3- to 4.5-hour time window for acute ischemic stroke. *Stroke*. 2011; 42:2257–2262. [PubMed: 21719767]
20. Wilson JT, Hareendran A, Hendry A, et al. Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. *Stroke*. 2005; 36:777–781. [PubMed: 15718510]
21. Samsa GP, Reutter RA, Parmigiani G, 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. [PubMed: 10210244]
22. [Accessed March 13, 2011] National Vital Statistics Report. United States Life Tables. 2006. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr58/nvsr58_21.pdf
23. Hong KS, Saver JL. Years of disability-adjusted life gained as a result of thrombolytic therapy for acute ischemic stroke. *Stroke*. 2010; 41:471–477. [PubMed: 20133917]
24. Eriksson M, Norrving B, Terent A, Stegmayr B. Functional outcome 3 months after stroke predicts long-term survival. *Cerebrovasc Dis*. 2008; 25:423–429. [PubMed: 18349536]
25. Slot KB, Berge E, Dorman P, Lewis S, Dennis M, Sandercock P. Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. *BMJ*. 2008; 336:376–379. [PubMed: 18230644]
26. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet*. 1989; 1:1215–1220. [PubMed: 2566778]
27. Hong KS, Yegiaian S, Lee M, Lee J, Saver JL. Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. *Circulation*. 2011; 123:2111–2119. [PubMed: 21536995]
28. 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. [PubMed: 12954888]
29. Christensen MC, Broderick J, Vincent C, Morris S, Steiner T. Global differences in patient characteristics, case management and outcomes in intracerebral hemorrhage: the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial. *Cerebrovasc Dis*. 2009; 28:55–64. [PubMed: 19468216]
30. 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. [PubMed: 19286581]
31. Reed SD, Blough DK, Meyer K, Jarvik JG. Inpatient costs, length of stay, and mortality for cerebrovascular events in community hospitals. *Neurology*. 2001; 57:305–314. [PubMed: 11468317]
32. Ingenix, I. [Accessed January 3, 2011] Billing and Payment Reference [online]. Available at: <http://www.shoppingenix.com/Category/100112/>
33. Caro JJ, Huybrechts KF. Stroke treatment economic model (STEM): predicting long-term costs from functional status. *Stroke*. 1999; 30:2574–2579. [PubMed: 10582980]
34. [Accessed January 3, 2011] <http://www.bls.gov/data/#calculators>

35. Manning, WG.; Fryback, DG.; Weinstein, M. Reflecting uncertainty in cost-effectiveness analysis. In: Gold, MR.; Siegel, JE.; Russell, LB.; Weinstein, M., editors. *Cost Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.
36. Bluhmki E, Chamorro A, Dávalos A, Machnig T, Sauce C, Wahlgren N, et al. Stroke treatment with alteplase given 3.0–4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurol*. 2009; 8:1095–1102. [PubMed: 19850525]
37. Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000; 17:479–500. [PubMed: 10977389]
38. Critchfield GC, Willard KE, Connelly DP. Probabilistic sensitivity analysis methods for general decision models. *Comput Biomed Res*. 1986; 19:254–265. [PubMed: 3709122]
39. Briggs AH, Gray AM. Power and sample size calculations for stochastic cost-effectiveness analysis. *Med Decis Making*. 1998; 18:S81–92. [PubMed: 9566469]
40. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making*. 1985; 5:157–177. [PubMed: 3831638]
41. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. *Annu Rev Public Health*. 2002; 23:377–401. [PubMed: 11910068]
42. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ*. 2001; 10:779–787. [PubMed: 11747057]
43. Sinclair SE, Frighetto L, Loewen PS, et al. Cost-Utility analysis of tissue plasminogen activator therapy for acute ischaemic stroke: a Canadian healthcare perspective. *Pharmacoeconomics*. 2001; 19:927–936. [PubMed: 11700779]
44. Ehlers L, Andersen G, Clausen LB, Bech M, Kjolby M. Cost-effectiveness of intravenous thrombolysis with alteplase within a 3-hour window after acute ischemic stroke. *Stroke*. 2007; 38:85–89. [PubMed: 17122430]
45. Moodie ML, Carter R, Mihalopoulos C, et al. Trial application of a Model of Resource Utilization, Costs, and Outcomes for Stroke (MORUCOS) to assist priority setting in stroke. *Stroke*. 2004; 35:1041–1046. [PubMed: 15031457]
46. Young KC, Benesch CG, Jahromi BS. Cost-effectiveness of multimodal CT for evaluating acute stroke. *Neurology*. 2010; 75:1678–1685. [PubMed: 20926786]

Figure 1a.

Figure 1b.

Figure 1.

Figure 1a. Short-term decision model representing trial outcomes. Patients could be non-disabled (mRS 0–1), disabled (mRS 2–5), experience sICH (not shown), or die during the first 90 days after AIS. The primary analysis evaluated patients in the 3- to 4.5-hour therapeutic window; separate scenario analyses were conducted for patients in the 0- to 3- and 0- to 4.5-hour therapeutic windows.

Figure 1b. Long-term model used to simulate lifetime patient outcomes. Three distinct health states were tracked, and patients could transition between them as indicated by the arrows.

Figure 2a.

Figure 2b.

Figure 2.

Figure 2a. One-way sensitivity analyses for incremental QALYs. The widths of the horizontal bars represent the change in results when each parameter was varied over the ranges specified in Tables 1–3. Blue represents results for low range of input and red the upper range of input.

Figure 2b. One-way sensitivity analyses for incremental costs. The widths of the horizontal bars represent the change in results when each parameter was varied over the ranges specified in Tables 1–3. Blue represents results for low range of input and red the upper range of input.

Figure 3.

Probabilistic sensitivity analyses of the ICER of rtPA versus no rtPA among patients arriving within 3–4.5 hours of AIS onset. Treatment with rtPA was cost-effective (greater QALYs at higher cost) in 91.2% of simulations if society is willing to pay \$50,000/QALY, and in 94.8% of simulations if society is willing to pay \$100,000/QALY.

Table 1

Clinical inputs – 90-day outcomes of rtPA within 3–4.5 hours of onset

Analysis (Reference)	non-rtPA Group (probability, Pr)		rtPA Group (relative risk, RR)*	
	Pr non-disabled	Pr sICH	RR non-disabled	RR sICH
Base Case (Hacke, 2008⁵)	0.45	0.035	1.16	2.27
Sensitivity Range	(0.36–0.54)	(0.028–0.042)	(1.01–1.34)	(1.23–4.18)
Subgroup Analyses (Bluhmki, 2009³⁶)				
<i>Age (years)</i>				
<65	0.45	0.06	1.26	0.75
65	0.45	0.02	1.07	5.28
<i>Sex</i>				
Male	0.42	0.03	1.25	2.73
Female	0.50	0.04	1.05	1.48
<i>NIHSS at baseline</i>				
0–9	0.67	0.02	1.08	2.95
10–19	0.31	0.06	1.11	2.05
20	0.08	0.04	2.11	2.81
<i>Time to treatment initiation (min)</i>				
181–210	0.40	0.05	1.42	1.58
211–240	0.47	0.04	1.03	1.89
241–270	0.43	0.03	1.30	2.98
<i>Previous diabetes</i>				
No	0.44	0.03	1.21	2.40
Yes	0.49	0.04	0.92	1.80
<i>History of stroke</i>				
No	0.47	0.03	1.09	2.68
Yes	0.33	0.05	1.88	0.00
<i>Hypertension</i>				
No	0.44	0.05	1.29	1.42
Yes	0.46	0.02	1.08	3.39
<i>Atrial flutter or fibrillation</i>				

Analysis (Reference)	non-rtPA Group (probability, Pr)		rtPA Group (relative risk, RR)*	
	Pr non-disabled	Pr sICH	Pr death	RR non-disabled
No	0.47	0.03	0.07	1.20
Yes	0.35	0.07	0.15	0.76
<i>Smoking history</i>				
Non-smoker	0.48	0.03	0.07	1.13
Current smoker	0.39	0.03	0.13	1.35
Ex-smoker	0.47	0.06	0.06	1.03
<i>Previous chronic use of antiplatelets</i>				
No	0.46	0.03	0.08	1.14
Yes	0.44	0.04	0.10	1.20
				2.22

* The model assumes no mortality difference between rtPA and non-rtPA patients, therefore the rtPA relative risk of death is 1.00 in all analyses.

Abbreviation: rtPA = recombinant tissue plasminogen activator; sICH = symptomatic intracranial hemorrhage; NIHSS = National Institutes of Health stroke scale

Table 2

Clinical inputs (long-term transition probabilities and utilities) and cost inputs

Clinical inputs	Base case probability (range)	Reference
Yearly mortality rates (non-disabled)	US life tables	CDC ²²
Mortality hazard ratio for patients w/out disability	1.10 (1.00–1.20)	Samsa, 1999 ²¹
Mortality hazard ratio for patients with disability (mRS 2–5)	1.52 (1.22–1.82)	
Annual stroke recurrence rate	0.05 (0.04–0.06)	Hong, 2011 ²⁷
Probability of death from recurrent stroke	0.19 (0.10–0.30)	Fagan, 1998 ¹⁶
Utilities by mRS		Stahl, 2003 ²⁸
mRS 0–1 non-disabled	0.84 (0.77–0.92)	Fagan, 1998 ¹⁶
mRS 2–5 disabled	0.53 (0.31–0.74)	
Disutility for 2 weeks due to sICH	–0.38 (–0.46 to –0.30)	Christensen, 2009 ²⁹
Cost inputs	Base case costs in 2011 US dollars (range)	Reference
Total cost of rtPA (drug, administration, monitoring)	\$6,083 (\$4,866–\$7,300)	Medicare
Inpatient costs, non-disabled	\$7,503 (\$6,003–\$9,004)	Reed, 2001 ³¹
Inpatient costs, disabled	\$11,397 (\$9,117–\$13,676)	
Inpatient costs, death	\$13,324 (\$10,659–\$15,989)	
sICH care, non-disabled	\$1,073 (\$858–\$1,287)	
sICH care, disabled	\$2,529 (\$2,023–\$3,035)	
Annual health costs, non-disabled	\$5,289 (\$4,231–\$6,347)	Earnshaw, 2009 ³⁰
Annual health costs, disabled	\$13,548 (\$10,838–\$16,258)	Earnshaw, 2009 ³⁰ ; Samsa, 1999 ²¹

Abbreviations: CDC = Centers for Disease Control; mRS = modified Rankin scale; sICH = symptomatic intracranial hemorrhage; rtPA = recombinant tissue plasminogen activator; sICH = symptomatic intracranial hemorrhage; USD = US dollars; WAC, wholesale acquisition cost.

Table 3

Cost-effectiveness of rtPA within 3–4.5 hours of symptom onset compared with no treatment in patients with acute ischemic stroke

Treatment	Costs	Life Years	QALYs	Incremental cost/QALY
No rtPA	\$110,367	9.69	6.45	--
rtPA 3–4.5 hours	\$111,861	9.76	6.69	--
Difference, rtPA vs No rtPA	\$1,495	0.07	0.24	\$6,300

Abbreviation: rtPA = recombinant tissue plasminogen activator; QALY = quality-adjusted life year

Table 4

Results of patient subgroup and scenario analyses

Scenario	rtPA Incremental Cost	rtPA Incremental QALYs	ICER
Base case analysis	\$1,495	0.24	\$6,255
ECASS III subgroup analyses			
Age (years)			
<65	−\$1,518	0.39	cost saving
65	\$3,981	0.11	\$35,813
Sex			
Male	−\$714	0.35	cost saving
Female	\$4,709	0.07	\$63,960
NIHSS at baseline			
0–9	\$2,796	0.17	\$16,322
10–19	\$4,050	0.11	\$37,462
20	\$685	0.28	\$2,432
Time to treatment initiation (minutes)			
181–210	−\$4,816	0.56	cost saving
211–240	\$5,162	0.05	\$102,314
241–270	−\$2,274	0.43	cost saving
Previous diabetes			
No	\$242	0.30	\$799
Yes	\$8,792	−0.14	dominated
History of stroke			
No	\$3,378	0.14	\$23,768
Yes	−\$12,640	0.97	cost saving
Hypertension			
No	−\$2,243	0.43	cost saving
Yes	\$3,851	0.12	\$32,677
Atrial flutter or fibrillation			
No	\$230	0.30	\$758
Yes	\$11,405	−0.27	dominated
Smoking history			
Non-smoker	\$2,069	0.21	\$9,882
Current smoker	−\$2,575	0.45	cost saving
Ex-smoker	\$5,277	0.04	\$118,464
Previous chronic use of antiplatelet drugs			
No	\$2,091	0.21	\$10,040
Yes	\$487	0.29	\$1,674
0–3 hours-only therapy window	−\$3,723	0.51	cost saving
Absolute mortality increase (0.7%) due to sICH		0.19	\$3,924
Cost of rtPA from Tung et al.	\$4,812	0.24	\$20,137

Abbreviations: rtPA = recombinant tissue plasminogen activator; ICER=incremental cost-effectiveness; NIHSS= National Institutes of Health stroke scale