Cost-Effectiveness of Patient Selection Using Penumbral-Based MRI for Intravenous Thrombolysis

Stephanie R. Earnshaw, PhD; Dan Jackson, MSc; Ray Farkouh, PhD; Lee Schwamm, MD

Background and Purpose—Better selection of patients for intravenous recombinant tissue plasminogen activator (IV tPA) treatment may improve clinical outcomes. We examined the cost-effectiveness of adding penumbral-based MRI to usual computed tomography (CT)-based methods to identify patients for IV tPA treatment.

Methods—A decision-analytic model estimated the lifetime costs and outcomes associated with penumbral-based MRI selection in a patient population similar to that enrolled in the IV tPA clinical trials. Inputs were obtained from published literature, clinical trial data, claims databases, and expert opinion. Outcomes included cost per life-year saved and cost per quality-adjusted life-year (QALY) gained. Costs and outcomes were discounted at 3% annually. Sensitivity analyses were conducted.

Results—The addition of penumbral-based MRI selection increased total cost by $103 over the patient’s remaining lifetime. Penumbral-based MRI selection resulted in favorable outcomes (modified Rankin Scale ≤1) more often than CT-based selection (36.66% versus 35.06%) with an incremental cost per life year of $1840 and an incremental cost per QALY of $1004. Multivariate sensitivity analysis predicted cost-effectiveness (≤$50 000 per QALY) in 99.7% of simulation runs.

Conclusions—Selecting ischemic stroke patients for IV tPA treatment using penumbral-based MRI after routine CT may increase overall acute care costs, but the benefit is large enough to make this highly cost-effective. This economic analysis lends further support to the consideration of a paradigm shift in acute stroke evaluation. (Stroke. 2009;40:1710-1720.)

Key Words: ischemic stroke ■ MRI ■ cost-effectiveness analysis ■ economics ■ stroke management

Stroke is the leading cause of serious, long-term disability and the third leading cause of death in the United States (US).1 The vast majority of stroke events are ischemic in nature, with intracerebral and subarachnoid hemorrhages making up the remainder of stroke events.2

Even though stroke is a highly prevalent disease, effective treatment is limited. Treatments for ischemic stroke focus on restoring or improving perfusion to the ischemic area. Current treatment for most patients with acute ischemic stroke is limited to management of symptoms, antiplatelet therapy, secondary stroke prevention, and rehabilitation.3 Less than 5% of cases of stroke can be treated by thrombolysis with intravenous recombinant tissue plasminogen activator (IV tPA).4 In absence of contraindications, IV tPA treatment is to be administered when (1) National Institute of Neurological Disorders and Stroke (NINDS) criteria have been met; (2) hemorrhage has been excluded through interpretation of computed tomography (CT) scans; and (3) treatment can be administered within 3 hours after onset of stroke symptoms as it has proven effective only in these patients.5,5 Treating within 3 hours after the onset of stroke symptoms is a difficult criterion to meet because the median time from stroke onset to arrival in an emergency department is between 3 and 6 hours, according to a study of more than 48 unique reports of prehospital delay time for patients with stroke, transient ischemic attack, or stroke-like symptoms.6 It has been noted that in the US, up to 20% of all stroke patients should be able to receive this treatment. However, Barber and colleagues7 estimated that the actual percentage of patients treated is much lower, mainly because of delays between onset of stroke symptoms and a patient’s admission to a hospital. As a result, a substantial number of potentially eligible ischemic stroke patients are unable to be treated with IV tPA.

MRI has proven to be a useful diagnostic tool for stroke.8–10 Several studies have suggested that the use of multi-parametric MRI protocols using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) before IV tPA treatment can identify patients who may benefit from IV tPA within and beyond 3 hours after onset of stroke symptoms.11–18 These studies suggested that the use of MRI as a selection tool may potentially improve the safety and efficacy profile for IV tPA treatment. In particular, a treatment benefit in terms of improvement in functional outcome and an improved safety profile in terms of reduction in mortality and symptomatic intracerebral hemorrhage (SICH) has been shown.11–18 However, the use of MRI is costly, both in terms of time and money. The delays associated with use of MRI must be outweighed by the benefits of safer delivery or an extended

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time window for treatment. Thus, the objective of our study was to examine the potential cost-effectiveness, albeit using limited data, of selecting patients for thrombolysis by adding penumbral-based MRI to usual care methods of unenhanced CT compared with current usual care of unenhanced CT only.

Subjects and Methods

Overview
A decision-analytic model was developed to examine the cost-effectiveness of using penumbral-based MRI selection (ie, MRI and the penumbral hypothesis following unenhanced CT and patient history) to select acute ischemic stroke patients for treatment with IV tPA up to 6 hours after symptom onset when compared with the current usual care of CT-based selection (ie, unenhanced CT alone, patient history, and treatment with IV tPA within the currently indicated 3-hour time window restriction). The model simulated treatment and outcomes for a cohort of patients presenting to the emergency department with acute stroke symptoms.

Model Structure
The model (Figure 1) was programmed in Microsoft Excel. The model calculates the following outcomes: costs (initial hospitalization, long-term medical, and total), percentage of ischemic stroke patients treated, the 90-day modified Rankin Scale (mRS); life-years;
quality-adjusted life-years (QALYs); incremental cost per life-year gained; incremental cost per QALY gained, incremental cost to improve the clinical outcome by 1 mRS grade, and incremental cost to avoid one major disability (mRS ≥4).

Patients enter the model at stroke onset, after which time they proceed to the emergency department. Patient history is obtained, and patients are assumed to get standard acute stroke workup and an unenhanced head CT scan. At this time, interpretation of the CT scan is assumed to identify hemorrhage with 100% accuracy. Patients with hemorrhagic stroke are assumed to be treated according to standard clinical practice. Patients without evidence of hemorrhage or large-territory ischemic infarction are candidates for IV tPA if they have no contradictions such as active internal bleeding, uncontrolled hypertension, or risk factors related to bleeding. Patients in the usual care arm are treated with IV tPA as appropriate based on the evidence thus far. Patients in the penumbral-based MRI arm are screened for eligibility for MRI. These patients then are screened for IV tPA eligibility based on MRI with penumbral imaging. A subset of patients may not proceed to MRI because of recognized contraindications or claustrophobia. Patients who are eligible for an MRI incur the diagnostic scanning. On MRI scanning, scans are interpreted for presence of penumbra (ie, perfusion lesion volume greater than diffusion lesion volume by ≥20%). Patients in whom penumbra is present may be treated in the model with IV tPA up to 6 hours after onset of stroke. All other patients in the decision tree are assumed to receive usual care. Usual care is assumed to be IV tPA as currently indicated under FDA labeling (if diagnosis is completed within 3 hours from onset of stroke). Other standard treatments such as antplatelet therapy or MERCI if diagnosis is completed more than 3 hours from the onset of stroke. Patients who are not candidates for MRI, who are not able to get an MRI because of its lack of availability, or in whom penumbra is not present are treated according to usual clinical practice. IV tPA treated patients are administered 0.9 mg/kg body weight, 10% as bolus, remainder as 1-hour infusion per FDA labeling. The model assumes all patients are admitted to a hospital where IV tPA can be administered. Thus, patients are not transferred to another facility for treatment (ie, no “drip and ship” or “ship and drip”). Patient outcome is “observed,” and a certain percentage of patients will experience a SICH.

Because it is routine to assess stroke outcome at 90 days in both observational studies and clinical trials,19 outcome was measured at 90 days for each treatment arm. A 90-day modified Rankin Scale (mRS) of 0 to 6 within the model is assumed to be a patient’s steady state mRS. Ninety day mRS was selected as this is the common measurement of functional outcome across major thrombolyis clinical trials. A patient’s functional outcome is expected to continue to improve over the course of the first 12 months or more after stroke, as the National Institute of Neurological Disorders and Stroke tPA trial (NINDS) showed improvements in the mRS at 3, 6, 9, and 12 months.20 In addition, Samsa et al interviewed a panel of experts who noted that functional outcome will continue to improve over the course of the first 12 months after stroke, but “the steady state for the mRS would typically occur within 3 to 6 months.”21 Thus, by using and carrying forward 90-day mRS, it is believed that the results of this analysis will be conservative as patient functional outcome will most likely improve beyond that time point.

Costs and outcomes are estimated for each outcome state at 90 days from onset of stroke symptoms and then estimated annually for the remainder of a patient’s lifetime. Costs were reported in 2007 US dollars, and all costs and outcomes were discounted at 3% per annum.22

Input Parameters
Input parameters were drawn from clinical trial data and published clinical studies12,14 and included the following elements.

Patient Characteristics
Patients in the model were assumed to have a mean age of 68 years, as observed in the pooled analysis of ATLANTIS, ECASS, and NINDS trials and in Schellinger et al.13 The majority of the patients were assumed to be white and non-Hispanic: baseline National Institute of Health Stroke Scale scores ranged from 11 to 14. Median time from symptom onset to treatment was 131 minutes for patients treated less than 3 hours and 240 minutes for patients treated more than 3 hours.12 Patient history that deemed a patient as ineligible for IV tPA treatment included contraindications as outlined by the package insert: active internal bleeding, uncontrolled hypertension, and early rapid improvement. The model assumed that 43.2% of patients would have contraindications for IV tPA.20 This was based on a study of 9 US clinics that reported the percentage of patients arriving at the hospital less than 3 hours after stroke onset. Average patient weight was assumed to be 70 kilograms.

Imaging Assumptions
The model was based on a number of assumptions around imaging performed via CT scanning and MRI. These assumptions include, but are not limited to, the following:

- All patients undergoing diagnostics produce interpretable scan images;
- Interpretation of the CT scan in combination with patient history is assumed to diagnose hemorrhage stroke with 100% probability;
- CT scan cannot detect disturbances in blood flow;
- All patients undergo CT scan first, even those who undergo MRI;
- MRI and CT scan are available 24 hours a day for 7 days a week for stroke patients; and
- Patients are assumed not to have contraindications for MRI or CT scanning.

Using data adapted from Darby et al,21 the model assumed that approximately 62% of patients had a mismatch, defined as PWI–DWI by ≥20%. In this study to identify patterns that might be clinically useful in examination and treatment of acute stroke, patients with nonhemorrhage stroke but with no preexisting non-ischemic neurological deficits or history of prior stroke that would hamper interpretation of clinical and radiological data were imaged within 24 hours of onset of stroke. In this study, 61.7% of the patterns examined demonstrated persistent penumbra.

Clinical Efficacy
Data on treatment efficacy was programmed into the model for the following patients: treated with usual care within 3 hours from onset of stroke (usual care ≤3), selected with CT scan and treated with IV tPA within 3 hours from onset of stroke (CT tPA ≤3), selected with MRI and treated with IV tPA within 3 hours from onset of stroke (MRI tPA ≤3), and selected with MRI and treated with IV tPA more than 3 hours but less than 6 hours from onset of stroke (MRI tPA >3). For usual care ≤3, usual care >3, and CT tPA ≤3, clinical efficacy was defined as mRS at day 90 and was derived from a pooled analysis of the IV tPA clinical trials.19

Schellinger et al recently performed a clinical study in which 1210 patients were selected for IV tPA treatment via CT or MRI. Specifically, CT-selected patients and patients in whom penumbra could not be detected could be treated with IV tPA within 3 hours of onset of stroke symptoms, as indicated for tPA treatment. However, patients selected via MRI who had evidence of penumbra could not be treated beyond 3 hours. Odds ratios were calculated via forward stepwise logistic regression models. Compared with CT, the odds ratio of favorable outcome (defined as mRS ≤1) for patients being treated >3 hours based on MRI was 1.467 (95% confidence interval: 1.017 to 2.117; P = 0.04), and for patients being treated <3 hours based on MRI was 1.136 (95% confidence interval: 0.841 to 1.534; P = 0.05). These data were used to derive the percentage of patients with mRS at day 90 for MRI tPA ≤3 and MRI tPA >3. Although the maximum time from symptom onset to treatment for patients in the MRI tPA >3 group in Schellinger et al was 1032 minutes (17.2 hours), benefit for this group of patients was restricted to patients treated within a 3- to 6-hour time window from onset of stroke symptoms, because the median time from symptom onset to treatment for patients in the MRI tPA >3 group was 240 minutes. The distribution of patients’ mRS at day 90 is presented in Table 1.
Table 1. Distribution of 90-Day mRS for Usual Care ≤3, Usual Care >3, CT tPA ≤3, MRI tPA ≤3, MRI tPA >3, and Incidence of SICH

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Usual Care ≤3 Hours (Plausible Range)</th>
<th>Usual Care &gt;3 Hours (Plausible Range)</th>
<th>CT tPA ≤3 Hours (Plausible Range)</th>
<th>MRI tPA ≤3 Hours (Plausible Range)</th>
<th>MRI tPA &gt;3 Hours (Plausible Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (90-day disease severity by mRS score)</td>
<td>mRS 0 13.8% 13.2% 19.4% 22.0% 28.4%</td>
<td>mRS 1 15.4% 20.9% 22.9% 26.0% 11.0%</td>
<td>mRS 2 10.8% 12.1% 7.3% 6.6% 7.7%</td>
<td>mRS 3 15.1% 14.8% 14.0% 12.6% 14.7%</td>
<td>mRS 4 20.0% 19.4% 11.7% 10.5% 12.3%</td>
</tr>
<tr>
<td>Incidence of SICH</td>
<td>0.65% (0.0061, 0.0068)</td>
<td>1.31% (0.012, 0.014)</td>
<td>4.8% (0.047, 0.0484)</td>
<td>2.50% (0.024, 0.026)</td>
<td>3.90% (0.037, 0.042)</td>
</tr>
<tr>
<td>Mortality caused by SICH</td>
<td>46.7% (0.404, 0.530)</td>
<td>46.7% (0.404, 0.530)</td>
<td>62.2% (0.611, 0.634)</td>
<td>62.2% (0.611, 0.634)</td>
<td>62.2% (0.611, 0.634)</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; ICH, intracranial hemorrhage; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; SICH, symptomatic intracerebral hemorrhage; tPA, tissue plasminogen activator.

number of SICHs occurring in patients treated within the various time windows. As a result, the percentage of patients experiencing a SICH was obtained from Hacke et al.19 To estimate the SICH experienced in the MRI tPA ≤3 and the MRI tPA >3 groups, we estimated the relative differences in SICH for MRI tPA ≤3 and MRI tPA >3 compared with CT tPA ≤3 in Schellinger et al.12 These data are applied to the incidence of SICH in the CT tPA ≤3 group in Hacke et al19 as SICH incidence reported in Schellinger et al12 and Hacke et al19 are similar. Mortality in patients with SICH was assumed to be 46.7% in patients treated with usual care and 62.2% in patients treated with IV tPA.19 This percentage was assumed to be constant, regardless of selection modality. Incidence and mortality for SICH is presented in Table 1.

Timing Data
Successful treatment of acute stroke is dependent on timely administration of proper treatment, and treatment with IV tPA is time dependent.19 As a result, the model considers time since onset of stroke symptoms as a factor for determining treatment eligibility. Time from stroke symptom onset to arrival at an emergency department and time from emergency department to completion of patient history and interpretation of CT scan were estimated from the Genentech Stroke Presentation Survey (GSPS)24 and Smith et al.25 GSPS was a large multi-center study designed to investigate the patient delays in seeking care after stroke, as well as delays in diagnostic studies within the emergency department. Means and standard deviations from these studies were obtained and are presented in Table 2.

For patients who received MRI, an additional 45 minutes was assumed to be added to the total time from onset of stroke symptoms to completion of typical diagnostics (ie, obtaining patient history and performance and interpretation of a CT scan). The time to perform and interpret MRI findings was examined in sensitivity analysis, as this is an important parameter because of the availability of MRI and because efficient stroke centers may be able to perform and interpret these scans in less time.

Based on the total mean time and standard deviations, a gamma distribution was used to estimate the percentage of patients eligible for treatment within each of the treatment time windows considered by the model.

Costs
Costs for hospitalization of the index event and posthospitalization costs for patients with various levels of mRS were estimated from the published literature. Hospitalization costs for the index event were obtained from Reed et al.32 Reed et al performed an analysis of community hospitals within the US to estimate inpatient length of stay, costs, and mortality for patients reported as having an ischemic cerebral infarction, a transient ischemic attack, an intracerebral hemorrhage, or subarachnoid hemorrhage. These costs include all costs incurred while in the hospital, such as general ward, intensive care unit, procedures, laboratory services, imaging services (assumed to be standard CT scan), and other standard hospital costs. Total inpatient costs were obtained by stroke type and discharge status. Patients with minor disability (ie, mRS 0 to 3) were assumed to incur the cost observed by patients discharged to home or home health services. Patients with major disability (ie, mRS 4 to 5) were assumed to be discharged to a skilled nursing facility.23

Because inpatient costs from Reed et al were obtained from community hospitals, it was assumed that these costs did not include costs associated with the administration and interpretation of MRI to select patients for IV tPA treatment. Such costs were obtained from standard US costing sources using current procedural codes and Medicare reimbursement schedules, which are reimbursable costs that consider physician work, practice expense, and malpractice.28,29 The model assumed that MRI capability existed for all patients and that MRI could be performed 24 hours, 7 days a week at no additional cost to the facility. The costs of additional MRI machines and MRI personnel such as standby technicians to provide this uninterrupted coverage was not added to this analysis as these costs are difficult to estimate. Instead, the cost of a single MRI acquisition was examined as part of the sensitivity analysis.

The additional cost incurred by patients attributable to the occurrence of SICH was estimated similar to the approach taken by Fagan et al.30 Specifically, the difference in cost per hospital day for ICH patients, when compared with ischemic stroke patients, was estimated from Reed et al32 and multiplied by to the average length of stay expected for ischemic stroke patients. For patients with a day 90 mRS between 0 and 3, costs per day were estimated for patients discharged to home. For patients with a day 90 mRS of 4 or 5, costs per day were estimated for patients discharged to a skilled nursing facility. This additional cost was applied to the base inpatient costs of treating ischemic stroke patients who experienced an SICH. All hospitalization costs were inflated to 2007 US dollars using the Medical Consumer Price Index.38

Annual costs posthospitalization were obtained from the published literature. Specifically, Caro and Haybrehcs31 estimated a lifetime cost of $46,000 patients with minor disability and $125,000 for major disability after stroke. These costs assumed a remaining lifetime of 15 years for both patient types. Thus, annual cost posthospitalization were estimated at $3067 for patients considered to have minor impairment and $8334 for patients considered to have major impairment recorded at 90 days after stroke. Samsa et al31 estimated cost multipliers for annual costs by mRS after stroke.
Table 2. Base-Case Values and Ranges of Plausible Values

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Base-Case Value</th>
<th>Plausible Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of stroke that is ischemic</td>
<td>87.0%</td>
<td>±20%</td>
<td>2</td>
</tr>
<tr>
<td>Percentage of ischemic stroke within 3 hours with IV tPA contraindications</td>
<td>43.2%</td>
<td>0.422–0.4419</td>
<td>26</td>
</tr>
<tr>
<td>Percentage of ischemic stroke in which penumbra is present</td>
<td>61.7%</td>
<td>0.592–0.645</td>
<td>23, 27</td>
</tr>
<tr>
<td>Timing data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke onset to ED (in minutes)</td>
<td>324.0</td>
<td>290.7–357.3</td>
<td>24</td>
</tr>
<tr>
<td>ED to treatment pre-MRI (in minutes)</td>
<td>97.0</td>
<td>85.7–108.3</td>
<td>25</td>
</tr>
<tr>
<td>Perform and interpret MRI (in minutes)</td>
<td>45.0</td>
<td>±15 minutes</td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI (in US $)</td>
<td>$821.62</td>
<td>±20%</td>
<td>28 (CPT code 70552), 29</td>
</tr>
<tr>
<td>IV tPA 0.9 mg/kg (in US $)</td>
<td>$3152.30</td>
<td>±20%</td>
<td>19, 30</td>
</tr>
<tr>
<td>Administration of IV tPA (in US $)</td>
<td>$292.57</td>
<td>±20%</td>
<td>28 (CPT code 37195), 5, 29</td>
</tr>
<tr>
<td>Physician time to monitor IV tPA treatment (in US $)</td>
<td>$587.92</td>
<td>±20%</td>
<td>28 (CPT codes 99291 and 99292), 29, 31</td>
</tr>
<tr>
<td>Inpatient costs: patients with 90-day mRS 0–3 (in US $)</td>
<td>$6693</td>
<td>±20%</td>
<td>32</td>
</tr>
<tr>
<td>Inpatient costs: patients with 90-day mRS 4–5 (in US $)</td>
<td>$10 166</td>
<td>±20%</td>
<td>32</td>
</tr>
<tr>
<td>Inpatient costs: patients with 90-day mRS 6 (death) (in US $)</td>
<td>$11 885</td>
<td>±20%</td>
<td>32</td>
</tr>
<tr>
<td>Additional cost of SICH in patients with 90-day mRS 0–3 (in US $)</td>
<td>$957</td>
<td>±20%</td>
<td>32</td>
</tr>
<tr>
<td>Additional cost of SICH in patients with 90-day mRS 4–5 or 6 (death) (in US $)</td>
<td>$2256</td>
<td>±20%</td>
<td>32</td>
</tr>
<tr>
<td>Annual post-hospitalization for patients with 90-day mRS 0–3 (in US $)</td>
<td>$4718</td>
<td>±20%</td>
<td>33</td>
</tr>
<tr>
<td>Annual post-hospitalization for patients with 90-day mRS 4–5 (in US $)</td>
<td>$12 085</td>
<td>±20%</td>
<td>33</td>
</tr>
<tr>
<td>Remaining lifetime cost for ICH (in US $)</td>
<td>$172 763</td>
<td>±20%</td>
<td>34</td>
</tr>
<tr>
<td>Death hazard ratios</td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>mRS 0</td>
<td>1</td>
<td>1.0–1.2</td>
<td></td>
</tr>
<tr>
<td>mRS 1</td>
<td>1</td>
<td>1.0–1.2</td>
<td></td>
</tr>
<tr>
<td>mRS 2</td>
<td>1.11</td>
<td>1.0–1.2</td>
<td></td>
</tr>
<tr>
<td>mRS 3</td>
<td>1.27</td>
<td>1.2–1.4</td>
<td></td>
</tr>
<tr>
<td>mRS 4</td>
<td>1.71</td>
<td>1.3–2.0</td>
<td></td>
</tr>
<tr>
<td>mRS 5</td>
<td>2.37</td>
<td>1.5–4.0</td>
<td></td>
</tr>
<tr>
<td>ICH remaining life expectancy (in years)</td>
<td>6.12</td>
<td>±20%</td>
<td>34</td>
</tr>
<tr>
<td>ICH remaining QALYs (in years)</td>
<td>2.80</td>
<td>±20%</td>
<td>34</td>
</tr>
</tbody>
</table>

Utility values* Range† Stahl et al36‡ Gage et al37§ 21, 35, 36, 37

| mRS 0                                                 | 0.80            | ±20%            | 0.90  | 0.85  | 21, 35, 36, 37 |
| mRS 1                                                 | 0.80            | 0.80–0.95       | 0.79  | 0.85  |
| mRS 2                                                 | 0.65            | 0.68–0.90       | 0.68  | 0.85  |
| mRS 3                                                 | 0.50            | 0.45–0.65       | 0.65  | 0.51  |
| mRS 4                                                 | 0.35            | 0.10–0.40       | 0.40  | 0.15  |
| mRS 5                                                 | 0.20            | 0.00–0.32       | 0.32  | 0.15  |
| mRS 6                                                 | 0.00            | 0.00–0.00       | 0.00  | 0.00  |

Discount rate Costs 0.03 ±20% 22  
Outcomes 0.03 ±20% 22

CPT indicates current procedural terminology; ED, emergency department; ICH, intracranial hemorrhage; IV, intravenous; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; QALY, quality-adjusted life-year; SICH, symptomatic intracerebral hemorrhage; tPA, tissue plasminogen activator; US, United States.

*Baseline utility values were obtained from Samsa et al.21
†Plausible range is based on upper and lower bounds on mRS-specific utility values found in the published literature.21,36–37
‡mRS-specific utilities obtained from Stahl et al.36
§mRS-specific utilities obtained from Gage et al.37

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These data were run as a sensitivity analysis with an annual posthospitalization base cost of $3067 for patients with an mRS of 0. IV tPA drug costs were estimated from the wholesale acquisition price30 using a dose of 0.9 mg/kg.5 Average patient weight was assumed to be 70 kg; therefore, a 100-mg vial was used for each dose.30 Costs of administration and physician time for monitoring administration were obtained from the Resource-Based Relative Value Scale.29

All costs shown in Table 2 are reported in 2007 US dollars, inflated using the Medical Consumer Price Index when appropriate, and discounted at 3% per annum.

Mortality
Age- and gender-specific life tables were obtained from the US National Vital Statistics Reports.39 Life expectancy was adjusted by death hazard ratios reported by Samsa et al21 to estimate life expectancy for stroke survivors, stratified by mRS score at 90 days. Life expectancy was allowed to decrease as a function of patient’s age in the model. Death hazard ratios are presented in Table 2. Life years were discounted at 3% per annum.

Utility Weights
Utility weights range from 0.0 to 1.0, where a utility value of 1.0 represents perfect health and a value of 0.0 represents death. These utility values are used to estimate QALYs by multiplying the number of life-years within a particular health state by that health state’s utility weight. Interventions were considered to be cost-effective if the incremental cost per QALY was less than or equal to $50 000.

Utility weights, by mRS group status, were obtained from a study by Samsa et al.21 These all-stroke utility weights are presented in Table 2. Because several studies were performed in which utilities were derived for each of the mRS groups,16,37 we performed a sensitivity analysis around these estimates, given the likelihood that there may be a difference in utility between functional status health states. The model assumed that a mRS of 5 is a better outcome than death (mRS=6).

Sensitivity Analysis
To test the robustness of the model’s assumptions and specific parameters, we examined the effect of changing several parameters in 1-way sensitivity analyses. Parameters analyzed included the clinical efficacy (ie, percentage of patients reporting 90 day mRS and odds ratios of improved outcome for MRI-selected patients), incidence of and mortality attributable to SICH, incidence of ischemic stroke, incidence of IV tPA contraindications, presence of penumbra, timing (ie, from stroke onset to emergency department, from emergency department to treatment, and MRI interpretation), costs, utilities, mortality, and discount rates. The effect of varying individual parameters was examined using plausible ranges of values from the literature (Tables 1 and 2), 95% confidence intervals, or by varying the estimates by up to 20% in each direction.

In addition to 1-way sensitivity analyses, we also performed probabilistic sensitivity analysis (second-order Monte Carlo simulation) in which all parameters were varied simultaneously.30 All the parameters mentioned in the previous paragraph were varied in this analysis. We assumed the baseline percentage of patients reporting 90 day mRS following a Dirichlet distribution. Incidence of ischemic stroke, incidence of IV tPA contraindications, incidence and mortality associated with SICH, presence of penumbra, utilities, and mortality were all varied assuming a beta distribution. The alpha parameters for each beta distribution were approximated by the number of cases and the population complement. We assumed all costs followed a gamma distribution where the shape and scale parameters were estimated via means and standard deviations. The analysis was run 10 000 times to capture stability in the results. A scatter plot was developed to represent uncertainty.

Results
Base-Case Analysis
A summary of results is presented in Table 3. Penumbral-based MRI selection performed after unenhanced CT resulted in a small increase in per-patient diagnostic costs by $423. However, the model showed decreases in the per-patient index event costs, IV tPA (drug, monitoring, and administration) costs, and long-term care costs of $36, $108, and $176, respectively. Overall, the use of MRI produced an increase in costs of $103 over a patient’s remaining lifetime.

Penumbral-based MRI selection resulted in favorable outcome (ie, mRS=1) in 36.66% versus 35.06% of ischemic stroke patients. Death (ie, mRS=6) would be avoided in 0.24% of IV tPA patients. As a result, penumbral-based MRI selection showed an improvement in life-years of 0.05 and in QALYs of 0.10. Penumbral-based MRI selection therefore is cost-effective with an incremental cost per life of $1840 and an incremental cost per QALY of $1004. The incremental cost to improve the clinical outcome by 1 mRS grade is $1963, whereas the incremental cost to avoid a major disability (mRS ≥3) is $12 861.

Sensitivity Analyses
The tornado diagram in Figure 2 illustrates the effect of varying input parameters on the incremental cost-effectiveness ratio (cost per QALY) of penumbral-based MRI selection versus CT-based selection alone. Overall, results were most sensitive to changes in the odds ratio of achieving favorable outcome (ie, mRS=0 or 1). If the odds ratio for MRI tPA =3 was set at its lower bound, the incremental cost per QALY increased to $13 982, whereas setting the odds ratio for MRI tPA ≤3 at its upper bound resulted in cost savings (ie, more efficacious and less costly) when compared
with CT-based selection alone. Similar results occurred when the odds ratio for MRI tPA > 3 was set at its lower bound, the incremental cost per QALY increased to $13 205, whereas setting the odds ratio for MRI tPA > 3 at its upper bound resulted in cost savings when compared with CT-based selection alone.

The incremental cost per QALY was relatively insensitive to changes in other parameters. Changes in the long-term survivor costs, the cost of the MRI, the mRS-specific mortality hazard odds ratios, the percentage of patients where penumbra is present, and the time from onset of stroke symptoms to the time the patient is seen in the emergency department caused changes in the incremental cost per QALY. However, changes were small and were well within the acceptable limits of cost-effectiveness, defined as cost savings or incremental cost per QALY of less than $50 000. The impact of using utility values from other published sources had minimal impact on the incremental cost per QALY.

Additional sensitivity analyses were performed around the model assumptions of MRI availability and ability to reliably identify penumbra. In these analyses, decreasing the availability of MRI to being available during business hours (Monday through Friday, 9 AM to 5 PM) had little to no impact on the results. The 1-time cost of the MRI to account for standby technicians, additional MRI machines, and on-call neurologists could be as high as $10 559 and still be within the acceptable range of being cost-effective (ie, incremental cost per QALY < $50 000). Decreasing the ability to identify whether or not penumbra exists to under 90% increases the incremental cost per QALY by approximately $500.

Results of 10 000 iteration probabilistic sensitivity analysis (Figure 3) showed that in 22.7% of simulation runs, penumbral-based MRI selection had lower costs and greater QALYs gained than CT-based selection alone. Penumbral-based MRI selection was cost-effective in 99.7% of the simulation runs (ie, cost savings or an incremental cost per QALY < $50 000); it remained cost-effective in 97.8% of the runs with an incremental cost per QALY threshold of $10 000.

**Discussion**

Standard imaging practice when treating acute ischemic stroke is to perform unenhanced CT to rule out hemorrhage. A patient’s clinical history, examination, laboratory assessment, and a 3-hour time window are then used to determine the patient’s eligibility for IV tPA treatment. Recent studies...
have been performed to examine the potential effectiveness of the use of MRI and the penumbral hypothesis in selecting patients for IV tPA treatment. This analysis builds on those studies by examining the potential cost-effectiveness of penumbral-based MRI selection compared with CT-based selection alone. Specifically, we developed a decision-analytic model to simulate selection and treatment using penumbral-based MRI plus unenhanced CT compared with selection and treatment using unenhanced CT alone. Data for the model were obtained from the published literature, with clinical efficacy estimated from a pooled analysis of the IV tPA clinical trials and subsequent IV tPA studies in which MRI was used to select patients for treatment and compared outcomes to IV tPA patients using standard unenhanced CT imaging.

Despite the increase in imaging costs and delay in treating patients because of increased time to perform the MRI, penumbral-based MRI selection was shown to decrease mortality and to improve functional outcome (ie, greater percentage of patients achieved mRS of 1 or better). Overall, a slight increase in total costs over a patient’s lifetime indicated that adding penumbral-based MRI selection is highly cost-effective compared with usual CT-based care. Given the improvement in functional outcome and mortality that penumbral-based MRI selection has shown in clinical studies, these results are not surprising considering the results reported by previous cost-effectiveness analyses on the use of IV tPA for treating ischemic stroke. Specifically, several IV tPA cost-effectiveness analyses have shown that improvements in functional outcome and mortality have a great impact on the cost-effectiveness of an acute stroke treatment. Sensitivity analyses showed results to be sensitive to changes in the odds of achieving favorable outcome for the MRI tPA ≤3 and MRI tPA >3 groups compared with the CT tPA ≤3 group. However, within published 95% confidence intervals, penumbral-based MRI selection was still cost-effective. Probabilistic sensitivity analysis showed consistency with favorable results.

To our knowledge, no US analyses to examine the cost-effectiveness of adding penumbral-based MRI selection to routine CT-based selection with associated clinical benefit have been performed. Elhers et al41 performed a cost-effectiveness analysis to assess the use of “thrombolysis treatment with 24-hour in-house neurology coverage and prompt and frequent” MR imaging. This Danish-based analysis reported costs in US dollars. The analysis accounted for the additional cost of MRI and on-call health care professional required to administer thrombolysis 24-hours a day. However, the authors did not account for improvements in functional outcome and SICH that may be associated with better patient selection. In addition, they performed their analysis among only patients in which tPA is indicated (ie, patients diagnosed with ischemic stroke who arrive within 3 hours of symptom onset) and do not account for the impact that the timing from onset of stroke until treatment may have on treatment efficacy. Our analysis examines cost-effectiveness among all stroke patients who arrive at the emergency department and considers the eligibility and clinical benefit of treatment based on arrival times. In addition, clinical efficacy is based on recent clinical studies of Schellinger et al12 and Thomalla et al16 which showed clinical evidence of a potential benefit.

We recognize that this model has a number of limitations. A key limitation of this analysis lies within the estimates of clinical efficacy around which the model was based. Specifically, to our knowledge there are no adequately powered
randomized controlled trials that show that penumbral-based MRI selection is superior to CT-based selection. The efficacy within this model is based on a study by Schellinger et al in which prospective IV tPA databases of 5 European stroke centers were pooled to examine the safety and efficacy of penumbral-based MRI selection "within and beyond the 3-hour time window compared with standard CT-based" selection.

Thomalla et al also performed a prospective study to examine the use of MRI to select patients for treatment with IV tPA within an expanded 6-hour window. They compared their data with data from the pooled IV tPA stroke trials and found results similar to those found by Schellinger et al. As a result, the lack of blinding and the selection of very experienced stroke centers may introduce potential biases. The EPITHET study was a placebo-controlled randomized trial to assess the effects of tPA on lesion growth, reperfusion, and clinical outcome in patients with mismatch 3 to 6 hours after stroke onset. This study showed that patients with mismatch who were treated with tPA had improved favorable outcome (ie, mRS 0 to 1) over patients receiving placebo. However, they note that sample sizes were "too small to assess the effects of" tPA "on clinical outcome in patients who had a mismatch of DWI and PWI." The results were not statistically significant. As a result, a debate over the true benefit of penumbral-based MRI selection exists. Overall, we noted limitations with each of these studies. Thus, we performed sensitivity analyses around the MRI tPA ≤3 and MRI tPA >3 odds ratios of favorable outcome. Penumbral-based MRI selection was found to retain its cost-effectiveness at their 95% confidence intervals. Clearly, further randomized controlled trials are needed to further refine these data, and our model can easily be adapted to incorporate new data as it emerges.

Another key limitation of this analysis is the definition of mismatch. We assumed that a PWI/DWI mismatch of 20% is sufficient to select responders for IV tPA treatment based on the mismatch definition used in Schellinger et al. In fact, there is increasing evidence that a more conservative mismatch definition may be required to select optimal treatment responders. However, there is currently no accepted standard definition of mismatch or the thresholds at which patient selection should occur. As a result, the data to guide IV tPA treatment are limited at this point in time. As the definitions of mismatch improve, it is likely that the utility of PWI/DWI will increase and therefore so will its cost-effectiveness.

Another assumption made within the model relates to the efficacy of IV tPA treatment in patients selected and treated less than 3 hours after onset of stroke symptoms. Overall, the base efficacy for IV tPA in this model is as currently indicated and is based on the clinical trial evidence, which looks at efficacy in 0- to 3-hour and 3- to 6-hour time windows. A recent CT-based study, European Cooperative Acute Stroke Study (ECASS3), reported an unadjusted odds ratio of 1.34 (95% CI: 1.02 to 1.76; \( P = 0.04 \)) and an adjusted odds ratio of 1.42 (95% CI: 1.02 to 1.98; \( P = 0.04 \)) for improved favorable outcome for patients treated with IV tPA compared with placebo within the 3- to 4.5-hour time window. As a result, IV tPA has shown a benefit beyond the 3-hour time window similar to what was seen in the pooled analysis. When considering the ECASS3 results in the model (ie, allowing CT-based selected patients to receive IV tPA up to 4.5 hours), we observed cost-effectiveness of penumbral-based MRI selection compared with CT-based selection similar to that seen in the base case analysis. This result was observed because penumbral-based MRI selection retains improved favorable outcome over CT-based selection within both the 0- to 3-hour and the full 3- to 6-hour time windows, and the difference in costs are minimal. Thus, off-label treatment with IV tPA within the 3- to 4.5-hour time window is expected to minimally impact results. When IV tPA is approved for use up to 4.5 hours after stroke, the cost-effectiveness can be reevaluated.

In the model, we restricted the efficacy of treatment for post–3-hour, MRI-selected, and IV tPA-treated patients, as estimated by Schellinger et al, to a 3- to 6-hour window. The MRI tPA >3 group in Schellinger et al included patients who were treated after 6 hours. However, because the median was 240 (4 hours), and because in the large IV tPA risk-adjusted meta-analysis of Hacke et al (2004) there was a lack of significance of benefit after 5 hours, we felt it more appropriate to limit the time window to 6 hours for achieving efficacy. Rerunning the model to consider MRI tPA >3 (not restricted to <6 hours) group efficacy for all patients selected using MRI improves the results to be cost saving (ie, less costly, more efficacious). Thus, results reported by our model are considered to be conservative from this perspective.

In the base case model, we assumed that the hospital to which the patient is arriving has the ability to perform the suggested imaging and treatment approaches and that no increased costs are required from base case to maintain readiness to perform this imaging. As such, the costs for additional MRI machines and to have standby technicians and neurologists available 24 hours a day, 7 days a week were not considered. Rural community hospitals, where advanced imaging and specialized stroke care physicians are not available 24 hours a day, will observe differences in cost-effectiveness for their patients. The transferring of patients to approved stroke centers for imaging and treatment was not considered in this analysis. When considering the availability of MRI imaging and changes to key parameters that would be affected if transferring a patient to a stroke center were necessary, such as time to treatment, showed that the model results had little sensitivity to variations. We modeled the additional implementation costs such as purchasing additional MRI machines and 24-hour coverage of technicians and neurologists and found that it could be as high as $10,559 per patient and still be cost-effective. It should be noted that these costs are difficult to estimate and vary greatly from hospital to hospital. Thus, further and individualized analyses are necessary to examine the impact that penumbral-based MRI selection may have in patients arriving at hospitals without ample stroke care.

Other important assumptions around MRI interpretability were made. The model assumed that all MRI scans are interpretable and that there is no difference between MRI machines, software, or radiologist interpretations. Further, the model assumed that imaging experts interpret scans and identify penumbra with 100% accuracy and that interpreta-
tion of perfusion MRI is as generalizable as interpreting CT. Finally, the model assumed that the penumbral hypothesis is valid and that patients with penumbra are better candidates for IV tPA. Despite these assumptions, our results and examination of the sensitivity of parameters related to MRI availability and interpretability show that MRI selection may still be cost-effective. It will be important to perform additional studies to further support these results.

We recognize that this model is built with a number of limitations, most notably the limited data around the definition of mismatch, quantification of clinical efficacy, potential efficacy of IV tPA within the 3- to 4.5-hour time window, and implementation issues. However, MRI has proven to be a useful tool for diagnosing acute ischemic stroke. MRI protocols using PWI/DWI provide a definitive diagnosis of acute stroke including location and circulation affected in >90% of patients, and much research has been focused around the potential to better select ischemic stroke patients for treatment. As a result, understanding the potential cost-effectiveness of this diagnostic approach at this early stage is important and provides us with guidance of whether the use of this technology has the potential to be good value for money. This study suggests that adding penumbral-based MRI selection for IV tPA treatment in patients presenting with acute ischemic stroke may be cost-effective compared with usual care with CT-based selection. Extensive sensitivity analysis shows results to be robust to changes in input parameters. While definitions around mismatch and the penumbral hypothesis are still being refined, it is important for stroke clinicians to become familiar with this technology. As further studies in this area become available to support the added value of penumbral-based MRI selection in acute stroke treatment, policy-makers and institutional decision-makers should consider the positive economic effect that the use of MRI may provide in the selection of patients for IV tPA treatment.

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Cost-Effectiveness of Patient Selection Using Penumbral-Based MRI for Intravenous Thrombolysis
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