A Cost–Utility Analysis of Mechanical Thrombectomy as an Adjunct to Intravenous Tissue-Type Plasminogen Activator for Acute Large-Vessel Ischemic Stroke

Anthony S. Kim, MD; Mai Nguyen-Huynh, MD, MAS; S. Claiborne Johnston, MD, PhD

Background and Purpose—Mechanical thrombectomy has the potential to improve recanalization rates and outcomes for patients with ischemic stroke, but potential gains could be offset by procedural complications and costs. We evaluated the cost and utility of combined intravenous (IV) tissue-type plasminogen activator (tPA) and mechanical thrombectomy compared to IV tPA alone for acute large-vessel ischemic stroke.

Methods—We constructed a decision tree for a hypothetical 68-year-old with a large-vessel ischemic stroke who is eligible for IV tPA. The interventional strategy was IV tPA, a cerebral angiogram, and mechanical thrombectomy and thrombolysis if indicated. Recanalization, hemorrhage complications, and outcomes for the interventional strategy were from the Multi-MERCI study. The medical strategy was IV tPA using inputs from a comprehensive systematic review. Costs were estimated from Medicare reimbursements. We modeled lifetime costs and utilities for disability using a Markov model and Monte-Carlo multivariable sensitivity analysis.

Results—For the baseline scenario, the recanalization rate was 72.9% for the interventional strategy and 46.2% for the medical strategy. For the interventional strategy, the symptomatic hemorrhage rate was 8.6% with recanalization and 15.4% without. For the medical strategy, the corresponding rates were 3.6% and 13.3%, respectively. The interventional strategy was cost-effective in 97.6% of simulations (incremental cost-effectiveness ratio $16 001/quality-adjusted life year; 95% CI, $2736–$39 232).

Conclusions—Based on observational data, the combination of IV tPA and mechanical thrombectomy for large-vessel ischemic stroke appears to be cost-effective compared to IV tPA alone. These findings require additional validation with randomized trial data. (Stroke. 2011;42:2013-2018.)

Key Words: acute stroke ■ cost-utility analysis ■ economics ■ endovascular treatment ■ interventional neuroradiology ■ thrombolysis ■ thrombolytic prescription

For acute ischemic stroke, intravenous (IV) tissue-type plasminogen activator (tPA) has demonstrated efficacy and cost-effectiveness when administered to eligible patients. However, the prognosis for patients with strokes from proximal large-vessel occlusion remains disappointing, in part because IV tPA alone is often unable to achieve recanalization. Endovascular techniques such as mechanical thrombectomy and intra-arterial thrombolysis have been developed to directly target occluded vessels and restore blood flow in an attempt to limit infarct size and improve patient outcomes. However, in the absence of direct evidence of clinical efficacy and acceptable costs, the precise role of these interventional approaches, particularly for patients already treated with IV tPA, has not been established.

Previous cost-effectiveness analyses have largely focused on patients who were otherwise ineligible for standard IV tPA protocols because of initial concerns about bleeding risks. Although randomized trials directly comparing IV tPA to combination IV tPA and interventional treatment are ongoing, additional data on costs, recanalization rates, complication rates, and outcomes have become available. Furthermore, recent evidence supporting expanding the IV tPA treatment window to 4.5 hours has increased the overlap of treatment windows for IV tPA and interventional treatments. Therefore, some centers have expanded the use of interventional strategies for patients already treated with IV tPA despite the current lack of randomized clinical trial data on efficacy or on cost-effectiveness.

We developed a decision model to evaluate a medical strategy of IV tPA alone compared to an interventional strategy of IV tPA followed by interventional therapy for acute large-vessel ischemic stroke based on currently available data. Our goals were to assess whether the incremental

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costs, risks, and efficacy of an interventional strategy could justify its use over IV tPA alone and, more importantly, to assess the sensitivity of these assessments to current uncertainties in key risk, cost, and efficacy inputs.

Materials and Methods
We used established methods for cost-utility analysis, including establishing a decision tree, selecting inputs from best available sources, Markov modeling, and discounting of future costs and utilities.12

Model Overview
For patients with large-vessel ischemic stroke, acute interventions lead to short-term costs and utilities, whereas subsequent disability after the acute period impacts long-term costs and utilities. To capture these impacts, we developed a decision tree for acute management and applied existing data on clinical outcomes to distribute a theoretical cohort of patients into 1 of 3 initial health states: independent, with no or mild disability corresponding to a modified Rankin score of 0 to 2; dependent, with moderate to severe disability corresponding to a modified Rankin score of 3 to 5; or death (Figure 1). We used a Markov model to calculate the annual costs of subsequent medical care and mortality risk based on disability status over the remaining years of life. Costs were assessed from a societal perspective. We applied a 3% discount rate to future costs and utilities. Estimates of the total lifetime costs and utilities.12

Figure 1. Decision tree to compare the incremental cost-effectiveness of an interventional strategy (intravenous [IV] tissue-type plasminogen activator [tPA] and interventional treatment) compared to a medical strategy (IV tPA alone) for large-vessel ischemic stroke. Values along the right margin refer to the proportion of patients with each outcome based on the Multi-MERCI study and include the risks of morbidity and death from procedural complications related to diagnostic cerebral angiography. mRS indicates modified Rankin scale; sICH, symptomatic intracerebral hemorrhage.

Model Inputs and Outcomes
The baseline scenario included a 68-year-old with an acute large-vessel ischemic stroke who was eligible for IV tPA (the mean age of patients in Multi-MERCI and CLOTBUST).10,15 Major inputs are summarized in the Table.

For the interventional strategy, the recanalization rate after IV tPA assessed at the initial angiogram was based on middle cerebral artery recanalization rates observed within 1 hour after IV tPA infusion by transcranial Doppler ultrasound.16 Cerebral angiogram complication rates were derived from a series of 7619 patients with atherosclerotic risk factors who received diagnostic cerebral angiograms,13 and we assumed that any complication from cerebral angiography resulted in moderate disability or death. Recanalization rates after mechanical thrombectomy were based on thrombolysis in myocardial infarction II or III flow17 achieved among the 48 patients who were pretreated with either full-dose or partial-dose IV tPA in the Multi-MERCI study, an international, multicenter, prospective, single-arm trial of mechanical thrombectomy for large-vessel stroke within 8 hours of symptom onset (Table).10 Symptomatic intracerebral hemorrhage rates for patients who had achieved recanalization on the initial angiogram were based on patients with large-vessel occlusion who achieved recanalization after IV tPA as assessed by transcranial Doppler ultrasound in the CLOTBUST study.13 Symptomatic intracerebral hemorrhage rates for those patients requiring interventional therapy were based on patient-level data from the Multi-MERCI study.10 For the medical strategy, the overall recanalization rate after IV tPA was based on a comprehensive meta-analysis analyzing recanalization for acute ischemic stroke.1 Symptomatic hemorrhage rates conditional on recanalization were derived from the CLOTBUST study.15

For both strategies, the proportion of patients without intracranial hemorrhage with each initial clinical outcome conditional on recanalization status was based on 90-day modified Rankin scores from Multi-MERCI subjects without intracranial hemorrhage. Because clinical outcome data for patients with symptomatic hemorrhage conditional on recanalization status were limited, we used pooled outcomes for all patients with a symptomatic intracerebral hemorrhage from the Multi-MERCI study (Table). Outcomes for patients...
in the intervention arm who had achieved recanalization at the initial angiogram include the risk of additional morbidity and death from any procedural complications of the cerebral angiogram itself as described above.

### Costs

We used reimbursement data from the Centers for Medicare and Medicaid Services, which provide an estimate of what society pays for these interventions in the United States in terms of initial procedural and hospitalization costs.18 For the interventional strategy, we used national average reimbursement payments for urban hospitals for acute ischemic stroke with mechanical thrombectomy (Medicare Severity-Diagnosis Related Group [MS-DRG] 23 and 24). Physician payments were estimated based on Medicare national average payments from for Current Procedural Terminology codes (Medicare Severity-Diagnosis Related Group).

### Utilities

Utilities were measured in QALYs, which combine information on mortality and long-term morbidity. By convention, we assigned a utility of 0 for death and 1 for perfect health. We used median utility for mild strokes (0.85) and an average for moderate and major strokes (0.27) as baseline utilities for independent and dependent health states.19,21 For estimating annual mortality, we multiplied age-specific all-cause mortality rates from the 2006 United States Centers for Disease Control and Prevention life tables22 by the relative risk of death for persons with independent (1.96) and dependent functional status (3.73) after neurological injury.23

### Sensitivity Analysis

To account for input uncertainty, we constructed input distributions that incorporated the variance of source data in the univariate and multivariable sensitivity analyses. For univariate sensitivity analyses, we varied inputs throughout plausible ranges while holding all other variables constant to evaluate how robust the model was to variation in key inputs and assumptions. Ranges were selected to include previous published values in clinical studies and meta-analysis, or 80% to 120% of the baseline values for inputs related to outcomes (Table), between 50% and 150% for inputs related to costs, and between 45% and 90% for age.

For the multivariable sensitivity analysis, we used a beta distribution for inputs based on a proportion (such as recanalization rates, symptomatic intracerebral hemorrhage rates) with parametrically-defined input distributions around point estimates that were based on variation and sample size. We then used probabilistic Monte Carlo simulation to vary the inputs listed in the table simultaneously over a total of 10,000 iterations to develop a 95% confidence ellipse nonparametrically. As a prespecified conservative scenario, we considered a 95% confidence region that excluded an incremental cost-effectiveness ratio of <$50,000 per QALY as strong evidence of cost-effectiveness, although a $100,000/QALY criterion has been used in other contexts to justify the adoption of new medical strategies.24 All analyses were performed using TreeAge Pro 2009 Suite (version 1.02; TreeAge Software, Williamstown, MA).

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**Table. Model Inputs**

<table>
<thead>
<tr>
<th>Source</th>
<th>Baseline Case</th>
<th>Input Distribution</th>
<th>Baseline Case</th>
<th>Input Distribution</th>
<th>Baseline Case</th>
<th>Input Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model input outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recanalization rate</td>
<td>72.9%</td>
<td>95% CI, 61.7%–82.5%; beta; n = 48</td>
<td>46.2%</td>
<td>95% CI, 42.4%–50.0%; beta; n = 474</td>
<td>Multi-MERCI: Rha 2007</td>
<td></td>
</tr>
<tr>
<td>Symptomatic ICH rate with recanalization</td>
<td>8.6%</td>
<td>95% CI, 2.5%–17.6%; beta; n = 35</td>
<td>3.6%</td>
<td>95% CI, 1.8%–5.9%; beta; n = 222</td>
<td>Multi-MERCI: Saqqur 2008</td>
<td></td>
</tr>
<tr>
<td>Symptomatic ICH rate without recanalization</td>
<td>15.4%</td>
<td>95% CI, 3.1%–34.4%; beta; n = 13</td>
<td>13.3%</td>
<td>95% CI, 8.8%–18.3%; beta; n = 135</td>
<td>Multi-MERCI: Saqqur 2008</td>
<td></td>
</tr>
<tr>
<td>Early recanalization rate</td>
<td>17.0%</td>
<td>95% CI, 12.6%–21.9%; beta; n = 179</td>
<td>...</td>
<td>...</td>
<td>Ribo 2006</td>
<td></td>
</tr>
<tr>
<td><strong>Relative risk of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent</td>
<td>1.96</td>
<td>Range, ±20%; triangular</td>
<td>1.96</td>
<td>Range, ±20%; triangular</td>
<td>Strauss 1998</td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>3.73</td>
<td>Range, ±20%; triangular</td>
<td>3.73</td>
<td>Range, ±20%; triangular</td>
<td>Strauss 1998</td>
<td></td>
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<tr>
<td><strong>Utilities</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Independent</td>
<td>0.85</td>
<td>Range, 0.70–1.00; triangular</td>
<td>0.85</td>
<td>Range, 0.70–1.00; triangular</td>
<td>Earnshaw 2006</td>
<td></td>
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<tr>
<td>Dependent</td>
<td>0.27</td>
<td>Range, 0.22–0.32; triangular</td>
<td>0.27</td>
<td>Range, 0.22–0.32; triangular</td>
<td>Earnshaw 2006</td>
<td></td>
</tr>
<tr>
<td><strong>Costs</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial acute hospitalization without ICH complication</td>
<td>$20,657</td>
<td>Range, ±50%; triangular</td>
<td>$8408</td>
<td>Range, ±50%; triangular</td>
<td>MS-DRG 024; MS-DRG 063 = CPT codes</td>
<td></td>
</tr>
<tr>
<td>Initial acute hospitalization with ICH complication</td>
<td>$29,534</td>
<td>Triangular</td>
<td>$15,945</td>
<td>Range, ±50%; triangular</td>
<td>MS-DRG 023; MS-DRG 061 = CPT codes</td>
<td></td>
</tr>
<tr>
<td><strong>Ongoing costs</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent</td>
<td>$2,885</td>
<td>Range, ±20%; triangular</td>
<td>$2885</td>
<td>Range, ±20%; triangular</td>
<td>Gage, 1995, in 2009 dollars</td>
<td></td>
</tr>
<tr>
<td><strong>Discount rate</strong></td>
<td>3%</td>
<td>...</td>
<td>...</td>
<td>3%</td>
<td>...</td>
<td>By convention</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; CPT, Current Procedural Terminology; ICH, intracerebral hemorrhage; MS-DRG, Medicare Severity-Diagnosis Related Group.
Results

The incremental cost of the interventional strategy was $10,840 (95% CI, $1924–$20,366) and the incremental effectiveness was 0.68 QALY (95% CI, 0.32–1.03 QALY). This strategy was preferred over the medical strategy with an incremental cost-effectiveness ratio of $16,001 per QALY (95% CI, $2736–$39,232 per QALY) and appeared to be cost-effective.

In the univariate sensitivity analysis, the interventional strategy remained cost-effective for patients up to age 84. Univariate sensitivity analysis demonstrated that 3 other variables were influential in our model: an IV tPA recanalization rate >62% (Figure 2A); an interventional recanalization rate <52% (Figure 2B); and a symptomatic hemorrhage rate for patients with successful thrombectomy of >27% (Figure 3B). Interestingly, other symptomatic intracerebral hemorrhage rates and the rate of early recanalization at the initial angiogram had little impact (Figures 3B–D, 2C). The interventional strategy remained cost-effective provided that procedural and hospitalization costs were <$47,600. In the multivariable analysis, 97.6% of 10,000 simulated iterations were cost-effective (Figure 4) and the 95% confidence ellipse was mostly contained within the cost-effective region.

Discussion

Our principal finding is that an interventional strategy consisting of IV tPA followed by angiography and directed interventional treatment for acute large-vessel ischemic stroke is cost-effective when compared to IV tPA alone. This finding is based on currently available data on inputs across a broad range of plausible values for recanalization rates, symptomatic hemorrhage rates, and procedural costs.

Because ischemic stroke can result in long-term disability, the recurring costs and disutilities from disability often exceed initial treatment or acute hospitalization costs. Therefore, treatment strategies that offer modestly improved outcomes are often cost-effective from a societal perspective. The main question when assessing these 2 treatment strategies is whether potential benefits from a more aggressive approach are offset by attendant procedural risks or secondary symptomatic intracerebral hemorrhages.

In our model, the comparative effectiveness of the interventional strategy was largely driven by higher recanalization rates. With the 72.9% recanalization rate reported in the Multi-MERCI study as our baseline, the recanalization rate for IV tPA alone would have to be >62% to be preferred over the interventional strategy. However, IV tPA recanalization rates >50% have not been reported. In contrast, despite initial concerns about causing undue intracerebral hemorrhages in patients who have already received IV tPA, our model was relatively insensitive to the rate of symptomatic intracerebral hemorrhage. The prognosis for persistent large-vessel occlusion is already quite sobering, with a reported mortality rate of >40%. However, symptomatic hemorrhage rates for a combined IV tPA and mechanical thrombectomy approach or a combined IV tPA and IA thrombolysis approach appear to be comparable to IV tPA alone. In our model, the symptomatic intracerebral hemorrhage rate became an important factor only for patients who had achieved recanalization after interventional treatment, but not in other scenarios, consistent with the notion that hemorrhages may be markers of stroke severity rather than a principal cause of worsened outcomes. A symptomatic hemorrhage rate >27% would be required before the interventional strategy would no longer be cost-effective. This value is greater than the 9% to 11% range, which was reported in a meta-analysis of multiple recanalization methods, the 8.6% to 15.4% range seen in patients pretreated with IV tPA in the Multi-MERCI study, and the 11% reported in the RECANALISE study.

Previous cost-effectiveness studies have focused on interventional approaches for patients who were ineligible for
IV-tPA. For instance, an analysis of the cost-effectiveness of first-generation mechanical thrombectomy devices for patients with acute large-vessel ischemic stroke from 3 to 8 hours after symptom onset reported an incremental cost-effectiveness ratio of $12 120 per QALY, and a second analysis reported an incremental cost-effectiveness ratio of $9386 per QALY for newer-generation devices. Our results are consistent with these estimates and include a more relevant baseline treatment scenario, particularly given data supporting the safety of using IV tPA before interventional treatment and given the overlap between IV tPA and interventional treatment time windows.

Our study should be interpreted in the context of certain limitations. First, the decision model is subject to the validity of our assumptions and the availability and reliability of model inputs. Recanalization is a complex process that depends on study subjects, the timing of the evaluation, the vessel involved, and the modality used to assess recanalization. Recanalization as assessed by ultrasound may not directly correspond to recanalization by cerebral angiography. Our model did not specifically account for differences in prognosis and recanalization rates based on the site of large-vessel occlusion. There is also uncertainty in model inputs drawn from studies with small sample sizes and potential heterogeneity from disparate data sources, particularly for inputs derived from observational rather than experimental data, although we attempted to account for this uncertainty with our sensitivity analyses. For example, CLOTBUST and Multi-MERCI used different definitions of symptomatic intracranial hemorrhage. In our study, we allowed for combinations of mechanical thrombectomy as well as angioplasty and intra-arterial thrombolysis to be applied to reflect innovations in current practice at the expense of heterogeneity of the intervention. Furthermore, the interaction between time to treatment and treatment modality are not directly accounted for in our model. However, our model does incorporate major key inputs, tests the robustness of outcomes in rigorous multivariable sensitivity analysis estimates, and incorporates the impact of long-term morbidity and mortality.

Interventional treatment strategies with adjunctive mechanical thrombectomy or intra-arterial thrombolysis appear to have an acceptable cost-effectiveness profile compared to IV tPA alone for large-vessel stroke based on currently available data. Efficacy data from randomized clinical trials will provide additional information to establish the precise role for these interventional approaches within the context of expanded eligibility of IV tPA.

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