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 efficacy1 and cost-effectiveness2 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.3 Endovascular techniques such as mechanical thrombectomy and intra-arterial thrombolysis4,5 have been developed to directly target occluded vessels and restore blood flow in an attempt to limit infarct size and improve patient outcomes.3 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,8 additional data on costs, recanalization rates, complication rates, and outcomes have become available.3,9,10 Furthermore, recent evidence supporting expanding the IV tPA treatment window to 4.5 hours11 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
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 management and applied existing data on clinical outcomes to establish a decision tree, selecting inputs from best available sources, Markov modeling, and discounting of future costs and utilities.12

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.15 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 37184, 36216, 36217, 36218, 75680, 75671 75685, 75685 to 59, and +75774. Physician costs for diagnostic angiography were estimated based on these codes, except for the code for thrombectomy (37184). For the medical strategy, we used reimbursements for cerebral infarction treated with thrombolytic agent (MS-DRG 61 and 63). For the cost of long-term disability, we used estimates of annual medical costs with independent or dependent disability, which have been used in previous cost–utility studies of stroke19 after updating these values to 2009 dollars using inflation rates for medical services.20

**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

---

**Table. Model Inputs**

<table>
<thead>
<tr>
<th></th>
<th>Intervventional Strategy</th>
<th>Medical Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model input outcomes</strong></td>
<td>Baseline Case</td>
<td>Input Distribution</td>
</tr>
<tr>
<td>Recanalization rate</td>
<td>72.9%</td>
<td>95% CI, 61.7%–82.5%; beta; n = 48</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>
</tr>
<tr>
<td>Symptomatic ICH rate without recanalization</td>
<td>15.4%</td>
<td>95% CI, 3.1%–34.4%; beta; n = 13</td>
</tr>
<tr>
<td>Early recanalization rate</td>
<td>17.0%</td>
<td>95% CI, 12.6%–21.9%; beta; n = 179</td>
</tr>
</tbody>
</table>

| Relative risk of death | | |
|------------------------| | |
| Independent | 1.96 | Range, ±20%; triangular | 1.96 | Range, ±20%; triangular | Strauss 1998 |
| Dependent | 3.73 | Range, ±20%; triangular | 3.73 | Range, ±20%; triangular | Strauss 1998 |

| Utilities | | |
|-----------| | |
| Independent | 0.85 | Range, 0.70–1.00; triangular | 0.85 | Range, 0.70–1.00; triangular | Earnshaw 2006 |
| Dependent | 0.27 | Range, 0.22–0.32; triangular | 0.27 | Range, 0.22–0.32; triangular | Earnshaw 2006 |

| Death | 0 | ... | 0 | ... | By convention |

| Costs | | |
|-------| | |
| Initial acute hospitalization without ICH complication | $20,657 | Range, ±50%; triangular | $8408 | Range, ±50%; triangular | MS-DRG 024; MS-DRG 063 + CPT codes |
| Initial acute hospitalization with ICH complication | $29,534 | Triangular | $15,945 | Range, ±50%; triangular | MS-DRG 023; MS-DRG 061 + CPT codes |

| Ongoing costs | | |
|---------------| | |
| Independent | $2,885 | Range, ±20%; triangular | $2885 | Range, ±20%; triangular | Gage, 1995, in 2009 dollars |

| Discount rate | 3% | ... | 3% | ... | By convention |

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 study10 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.15,16,25

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%.3 However, symptomatic hemorrhage rates for a combined IV tPA and mechanical thrombectomy approach16 or a combined IV tPA and IA thrombolysis approach11 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 treat-

Figure 2. Univariate sensitivity analyses for acute large-vessel ischemic stroke varying (A): recanalization rate for the medical strategy (treatment with intravenous [IV] tissue-type plasminogen activator [tPA]), (B): recanalization rate with an interventional strategy (treatment with IV tPA followed by interventional treatment), and (C): early recanalization rate for the medical strategy (treatment with IV tPA) at time of diagnostic angiography. Arrows and dotted lines indicate baseline scenarios. Inputs that result in an incremental cost-effectiveness ratio of less than $50,000-quality-adjusted life year are considered cost-effective (horizontal dashed line).
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 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. In particular, 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.

Acknowledgments
The authors thank Amy Markowitz, JD, for her thoughtful editorial review.
Disclosure

This study was unfunded. M.H.N. has received an unrestricted research grant from Concentric Medical. S.C.J. has received research support from Boston Scientific. A.S.K., M.H.N., and S.C.J. are employed by the University of California, a patent holder of retriever devices for stroke.

References

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, Mai Nguyen-Huynh and S. Claiborne Johnston

Stroke. 2011;42:2013-2018; originally published online June 2, 2011;
doi: 10.1161/STROKEAHA.110.606889

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/7/2013

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/