More than 50% of patients with ischemic stroke remain disabled despite intravenous recombinant tissue-type plasminogen activator (rt-PA) treatment. It has been anticipated that adjunctive endovascular therapies will lead to better clinical outcomes than intravenous rt-PA alone after severe strokes. However, results of the recently published randomized controlled trials (Interventional Management of Stroke [IMS] III, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke [SYNTHESIS], and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR Rescue]) comparing intravenous thrombolysis therapy with endovascular treatment of acute ischemic stroke failed to demonstrate superiority of endovascular treatment to intravenous-only arm unless time to reperfusion exceeded 347 minutes. Two-way sensitivity analysis demonstrated that endovascular treatment was preferred when probability of reperfusion is high and time to reperfusion is small. Probabilistic sensitivity results demonstrated an average gain for endovascular therapy of 0.76 quality-adjusted life years (SD 0.82) compared with the intravenous-only approach.

Results—In our post hoc model with its underlying limitations, endovascular therapy after intravenous rt-PA is the preferred treatment as compared with intravenous rt-PA alone. However, if time to reperfusion exceeds 347 minutes, intravenous rt-PA alone is the recommended strategy. This warrants validation in a randomized, prospective trial among patients with large vessel occlusions. (Stroke. 2014;45:3625-3630.)

Key Words: reperfusion ■ stroke
perform sensitivity analyses. A decision tree model was constructed to compare the 2 strategies of intravenous r-tPA alone (designated as intravenous only) versus endovascular treatment after intravenous r-tPA (designated as endovascular treatment) in acute ischemic stroke (Figure 1). Based on the IMS III data demographics, the base case was a hypothetical 69-year old with an acute ischemic stroke and presence of a large occlusion.

Data Sources

Data for the decision model were derived from the IMS III trial database and the medical literature. IMS III was a multicenter, phase 3, randomized, open-label clinical trial with blinded outcome assessments. The trial tested the approach of intravenous r-tPA followed by endovascular treatment, as compared with standard intravenous r-tPA alone. According to protocol, the treatment timing guidelines were as follows: intravenous r-tPA was started within 3 hours, endovascular treatment started within 5 hours, and completion of the endovascular procedure within 7 hours.

We focused our model on a subgroup of IMS III trial patients with baseline large vessel occlusion, as time to reperfusion has been shown as an important predictor of outcome in this subgroup. We maintained prespecified definitions from IMS III trial for successful angiographic reperfusion, namely modified thrombolysis in cerebral infarction grade 2 (2a, 2b, or 3). Of note, post hoc analysis showed similar time associations with outcome using thrombolysis in cerebral infarction grade of 2b/3 versus 2a/2b.3 We used the same definition for time to angiographic reperfusion as used in prior post hoc analyses, defined as time from stroke symptom onset to end of procedure (minutes). The rate of successful reperfusion after endovascular therapy was based on IMS III trial data (Table 1).

In the IMS III trial, among the 434 patients who were randomized to endovascular treatment, a total of 240 subjects had complete occlusions of proximal large vessels (ICAT, M1, and M2) on baseline digital subtraction angiograms. Among this 240-subject subcohort, modified Rankin Scale (mRS) scores were available and obtained within the specified window of 90 days in 229 patients (the excluded cases are <5% of our sample and unlikely to affect the results). Among these 229 subjects, 175 subjects (76%) achieved angiographic reperfusion and 54 (24%) did not achieve angiographic reperfusion. The mean time from symptom onset to angiographic reperfusion was 325±51 minutes. In the intravenous treatment arm group, a total of 83 patients had large vessel occlusion, identified on baseline computed tomographic angiogram (CTA) studies. The early reperfusion status of patients in the intravenous-only arm is unknown as follow-up vascular or perfusion studies were not performed.

Table 1. Input Variables

<table>
<thead>
<tr>
<th>Input Variables</th>
<th>Base Case*</th>
<th>Range (Tested in 1-Way and 2-Way Sensitivity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time, min</td>
<td>325</td>
<td>240–380</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>0.76</td>
<td>0.40–1.0</td>
</tr>
</tbody>
</table>

*Source: Broderick et al (Interventional Management of Stroke III data).

Outcome Measures

Patients undergoing endovascular treatment were stratified based on reperfusion status. Outcomes for both groups, with or without successful reperfusion, were measured with mRS at 3 months. The mRS scores for the intravenous-only arm were based on a subset of IMS III subjects with available baseline CTA demonstrating large vessel occlusions. These proportions were all determined directly from the IMS III trial raw data. In the decision analytic model, effectiveness was measured in quality-adjusted life years (QALYs). QALY is a commonly used measure that takes into account both the length and the quality of life. Each mRS outcome was considered a separate health state. The utility score for each mRS category is a measure of patient preferences for these varying levels of disability after stroke, and range from 0 to 1, where 0 represents death and 1 represents perfect health.

QALY was calculated in the following manner. Death hazards and utilities were assigned to each mRS outcome level based on previously published data.3 For our base case 69-year old, we calculated an average annual mortality rate using life table data reported by the National Center for Health Statistics14 and the declining exponential approximation of life expectancy method.15,16 Based on a life expectancy of 15.6 years, the average annual mortality rate is calculated using the declining exponential approximation of life expectancy as (1/15.6) or 0.064. Life expectancy for each mRS outcome was then calculated as the (base population mortality rate, eg, 0.064)×(death hazard rate for each mRS category). QALYs were calculated by multiplying the appropriate average life expectancy times the utility estimate for each mRS level (Table 2).

Decision Model Assumptions

Our analysis focused on patients with acute ischemic stroke because of large vessel occlusion defined as ICAT, middle cerebral artery (M1 or M2) occlusion as seen on baseline CTA or digital subtraction angiogram study.

Major simplifying assumptions for the analyses were:

- Treatment with intravenous r-tPA is initiated before consideration of endovascular therapy.

Table 2. Output Variables

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>Death Hazard*</th>
<th>Utilities</th>
<th>QALY†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (no symptoms)</td>
<td>1</td>
<td>0.80</td>
<td>12.48</td>
</tr>
<tr>
<td>1 (no disability, despite symptoms)</td>
<td>1</td>
<td>0.80</td>
<td>12.48</td>
</tr>
<tr>
<td>2 (slight disability)</td>
<td>1.11</td>
<td>0.65</td>
<td>9.16</td>
</tr>
<tr>
<td>3 (moderate disability)</td>
<td>1.27</td>
<td>0.50</td>
<td>6.15</td>
</tr>
<tr>
<td>4 (moderate to severe disability)</td>
<td>1.71</td>
<td>0.35</td>
<td>3.20</td>
</tr>
<tr>
<td>5 (severe disability)</td>
<td>2.37</td>
<td>0.20</td>
<td>1.32</td>
</tr>
<tr>
<td>6 (death)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; and QALY, quality-adjusted life year.

*Source: Samsa et al.9

†QALY calculations were performed as follows: average annual mortality rate for 69-year-old US population−0.064; QALY=1/(0.064×death hazard (for mRS))×utility (for mRS). Thus, for a 69-year old with a mRS of zero or 1, QALY=1/(0.064×0.80)=12.48; for a 69-year old with a mRS of 2, QALY=1/(0.064×1.11)×0.65=9.16. Small differences in results are because of round-off error.

Figure 1. Decision tree schematic for treatment of acute ischemic stroke. The square represents the decision node describing the 2 strategies: intravenous (IV) only vs endovascular treatment. The circle represents the chance node for patients with endovascular therapy, which can result in angiographic reperfusion or lack of reperfusion. Both treatments can result in range of modified Rankin Scale (mRS) functional outcomes, represented as rectangular terminal nodes. ICAT indicates internal carotid artery terminus.
Treatment options include continuation of intravenous therapy only or addition of endovascular therapy.

Patients remain in constant health utility after the stroke.

We focused on patients with moderate to severe stroke at the onset with large vessel occlusion because this was the specialized subcohort studied in prior analyses as most likely to be considered for endovascular therapy. It is common practice to treat only proximal, vessel occlusions with endovascular therapies because of issues of both accessibility of the thrombus and the presumption that intravenous r-tPA is likely to effectively recanalize smaller thrombi. Therefore, we assumed that cases with more distal occlusions (anterior cerebral artery or distal middle cerebral artery branches, such as M3 and M4) would not be treated with endovascular therapy. Basilar occlusions were excluded from this decision model because of limited data from the primary trial to model the probability of specific outcomes after this specific type of occlusion.

We assumed that intravenous r-tPA was started within 3 hours of symptom onset in both groups; this is consistent with the IMS III trial design.

The IMS III trial had similar safety findings in the endovascular therapy and intravenous alone groups for mortality at 90 days and with symptomatic intracerebral hemorrhage. The SYNTHESIS and MR Rescue trials also demonstrated that primary direct risk of endovascular treatment and intravenous r-tPA is comparable.

Data Analysis

One-way sensitivity analyses for time to reperfusion, and 2-way sensitivity analyses for time to reperfusion and rate of reperfusion success, were performed. We also performed a probabilistic sensitivity analysis using second-order Monte Carlo simulations with 10000 iterations to address uncertainty in the total time to angiographic reperfusion for the endovascular approach.

Results

Base Case

Base case parameter values are listed in Tables 1 and 2. In our base case (69-year old with moderate stroke and large vessel occlusion, receiving intravenous r-tPA within 3 hours of symptom onset), the endovascular approach was the preferred course. This option yielded a higher expected utility of 6.38 QALYs compared with 5.42 QALYs for the intravenous-only strategy.

Deterministic Sensitivity Analysis

As shown in Figure 2, a 1-way sensitivity analysis examining total time to reperfusion, endovascular treatment was superior to intravenous-only treatment unless time to reperfusion in the endovascular strategy exceeded a threshold of 347 minutes (base case value 325 minutes). Figure 3 depicts a 2-way sensitivity analysis examining both time to reperfusion and the probability of reperfusion, to explore the impact of newer endovascular devices and variations in associated time to reperfusion. Several scenarios are shown. The base case values are within the region in which endovascular treatment is preferred. The 3 additional scenarios demonstrate that intravenous therapy alone would be preferred with first-generation...
devices if stroke care systems or patient-specific factors result in longer times to reperfusion. However, even with somewhat longer times to reperfusion, endovascular therapy would be preferred if newer devices lead to higher rates of reperfusion (scenario 3). However, it is important to note that there is a ceiling effect for reperfusion rates and hence rapid treatment with earlier reperfusion is a critical factor.

We also performed a 1-way sensitivity analysis examining procedure-related mortality for endovascular treatment. The distribution of functional outcomes (mRS) including death already incorporates procedure-related mortality and morbidity. Therefore, this sensitivity analysis only explored the question, what if procedure-related mortality was higher? Endovascular treatment remained superior unless the additional risk of procedure-related mortality exceeded 0.15.

Probabilistic Sensitivity Analysis
Second-order Monte Carlo analyses were performed with 10000 simulations to address uncertainty associated with time to reperfusion in the endovascular arm. As in the base case analysis, the endovascular approach was preferred, 6.18 QALYs compared with 5.42 QALYs for the intravenous-only approach. The average gain for endovascular therapy was 0.76 QALYs (SD 0.82). As shown in Figure 4, the distribution ranged from a loss of 1.96 QALYs to a gain of 2.40 QALYs. For 10000 patients with acute stroke with large proximal vessel occlusion, 78% would be expected to benefit from endovascular treatment, whereas 22% would be expected do better with intravenous-only therapy. To explore the impact of reducing variation in time to reperfusion, we performed additional Monte Carlo simulations using a smaller SD of 30 minutes instead of 51 minutes, using the same mean time of 325 minutes. In this scenario, the average gain associated with endovascular therapy was slightly greater (0.84 QALYs) with a smaller SD of 0.53. More strikingly, as shown in Figure 5, for 10000 patients with acute stroke with large vessel occlusion, 91% would be expected to benefit from endovascular treatment, whereas only 9% would be expected to do better with intravenous-only therapy.

Discussion
We used empirical data from the IMS III trial and data from the medical literature to explore the role of 2 specific variables, time to reperfusion and rate of reperfusion, for the subgroup of patients with moderate and severe ischemic stroke with large vessel occlusions.

We found that the addition of endovascular treatment is preferred; however, if time to reperfusion is extended beyond a certain threshold (347 minutes), intravenous r-tPA alone is the preferred treatment. Although post hoc subgroup analysis of a neutral primary trial needs to be regarded with caution, our findings are consistent with prior analysis of the IMS pilot trials as well as the IMS III trial, which demonstrated that a 30-minute delay leads to a 10% relative reduction in the probability of a good outcome. This effect of time to reperfusion on clinical outcome has also been demonstrated in other studies.
Our results demonstrating superiority of endovascular treatment may seem at odds with the overall results of the primary IMS III trial. However, it is important to note that our analysis targeted a subgroup of patients with large vessel occlusion. It also considered the effect of endovascular therapy on mRS distributions, as opposed to dichotomized effects. The minimum threshold of 10% effect size postulated in the IMS III trial is not considered here; instead, we show the threshold of minimal superiority based on QALYs without consideration of statistical significance. Our findings are, however, consistent with a prespecified secondary analysis of the IMS III trial of those with proximal vessel occlusions (defined differently as ICAT, M1, basilar) at initial presentation on CTA; this analysis showed a positive direction of effect (difference in mRS distributions) for endovascular therapy (generalized Wilcoxon test \( P = 0.11 \)).

Probabilistic sensitivity analysis examining uncertainty in time to reperfusion demonstrated a nonstatistically significant trend toward better outcomes with the endovascular approach. This result needs to be considered carefully, as the analysis was not able to incorporate any other sources of parameter uncertainty and we made a simplifying assumption that results of intravenous treatment alone were not affected by variations in time to reperfusion in the endovascular arm. It may well be that time to reperfusion is a surrogate for other system-related variables that might influence outcomes of intravenous treatment. If so, the probabilistic sensitivity analysis we performed may be overly conservative by varying outcomes in the endovascular arm (as a function of time to reperfusion) while not assessing similar variation in outcomes in the intravenous-only arm of the analysis. As a result, we explored a hypothetical scenario in which the SD around time to reperfusion was smaller, perhaps as a result of a larger or more select study population.

In the reperfusion cohort of IMS III, the mean total time to reperfusion was 325 minutes with a SD of 51 minutes. In our hypothetical model with a reduced SD, a higher and statistically significant percentage of patients were shown to benefit from endovascular treatment. Measures that potentially could reduce the variation in time to reperfusion including standardization of processes of care across study sites would be worth considering in the design of future clinical trials. A better understanding and quantification of factors (eg, patient or stroke care system specific) that affect time to reperfusion and reperfusion rates (eg, device related) will be critically important to the information gained from future trials.

Lack of newer neurothrombectomy device availability in IMS III has been suggested as a limitation and a possible explanation for the trial’s futility. More recent trials using second-generation endovascular devices have demonstrated higher rates of recanalization and reperfusion (80%–95%). We explored hypothetical scenarios to understand the interplay of time to reperfusion and rates of reperfusion because they are potentially modifiable factors for future endovascular trials. Our analysis shows that higher rates of reperfusion might allow for a slight increase in the time by which angiographic reperfusion must be achieved. For example, an 85% rate of reperfusion would allow for reperfusion to occur for ≤356 minutes before intravenous r-tPA becomes the superior strategy.

**Limitations**

Our study had several important limitations, including the need to make several simplifying modeling assumptions. In addition, our analysis was based on data derived from a post hoc analysis of a subpopulation of the primary trial, possibly limiting the generalizability of our results to broader populations. Another limitation is that the raw data distributions of mRS scores for the intravenous-only arm (with ICAT, M1, and M2 occlusion) suggested that they were time independent and hence the model did not explore the impact of time on this treatment strategy. This simplifying assumption could potentially bias the results as described above. We realize that the lack of time dependency in this intravenous-only treatment group could be related to a small sample size. There may be biological plausibility for the finding of time independence in this subgroup with presumed large clot burden that were less responsive to intravenous r-tPA, although we know that the probability of intravenous r-tPA alone resulting in angiographic reperfusion with large vessel occlusion is estimated to be 40%. Another caveat is that both treatment arms received intravenous r-tPA and some patients may have recanalized in the time between the baseline CTA demonstrating vessel occlusion and follow-up angiogram as a result of intravenous r-tPA. It is difficult to estimate the exact proportion of patients with reperfusion in the intravenous group because of lack of follow-up imaging. A post hoc analysis of IMS III data showed early arterial recanalization after intravenous r-tPA treatment in 25% of patients. Faster reperfusion times and better endovascular devices may also have small inherent risks, which were not considered in this analysis. Outcomes (distributions of mRS scores) after higher reperfusion rates were assumed to be the same as those observed in the IMS III trial.

**Conclusions**

In our post hoc model of patients with large vessel occlusion, endovascular therapy after intravenous r-tPA is preferred to intravenous r-tPA alone. However, if time to reperfusion exceeds 347 minutes, intravenous r-tPA alone is the preferred strategy. Higher rates of reperfusion might allow for an increase in the time by which angiographic reperfusion must be achieved. Our results are based on QALY gain without consideration of statistical significance. These post hoc analyses need to be validated in a randomized, prospective trial to determine whether the endovascular approach will indeed be superior to intravenous r-tPA among patients with large vessel occlusions.

**Disclosures**

This work is in partial fulfillment of the Master of Science degree in Clinical and Translational Research, University of Cincinnati, American Roentgen Ray Society (Dr Vagal); PI, Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trial, Genentech; Neurology PI, THERAPY (Assess Penumbra System in Treatment of Acute Stroke), Penumbra; DSMB member, Biogen (Dr Khatri); research monies to Department of Neurology from Genentech for PRISMS Trial; travel to Australian stroke conference, Boehringer Ingelheim, study medication for Interventional Management of Stroke (IMS) III, Genentech (Dr Broderick), National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke U01 NS052220, Genentech (Dr Yeatts), Pfizer Educational Group,
Informed Medical Decisions Foundation, and NIH/National Center for Research Resource UL1 TR000077-05 (Dr Eckman). The other author reports no conflicts.

References


