Cost-Effectiveness of Recombinant Tissue-Type Plasminogen Activator Within 3 Hours of Acute Ischemic Stroke

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Background and Purpose—Despite the availability of results from multiple newer clinical trials and changing healthcare costs, the cost-effectiveness of recombinant tissue-type plasminogen activator (r-tPA) for treatment of acute ischemic stroke within 0 to 3 hours of symptom onset was last evaluated in 1998 for the United States. Using current evidence, we evaluate the long-term cost-effectiveness of r-tPA administered 0 to 3 hours after acute ischemic stroke onset versus no r-tPA.

Methods—A disease-based decision model to project lifetime outcomes of patients after acute ischemic stroke by r-tPA treatment status from the US payer perspective was developed. Model inputs were derived from a recent meta-analysis of r-tPA trials, cohort studies, and health state preference studies. Cost data, inflated to 2013 dollars, were based on drug wholesale acquisition cost and the literature. To compare r-tPA to no r-tPA, we calculated incremental total direct costs, incremental quality-adjusted life years, and incremental cost-effectiveness ratios. We performed 1-way and probabilistic sensitivity analyses to evaluate uncertainty in the results.

Results—r-tPA resulted in a gain of 0.39 quality-adjusted life years (95% confidence range, 0.16–0.66) on average per patient and a lifetime cost-saving of $25,000 (95% confidence range, −$42,500 to −$11,000) compared with no r-tPA. In probabilistic sensitivity analyses, r-tPA was dominant compared with no r-tPA in 100% of simulations. The model was sensitive to inputs for r-tPA efficacy, healthcare costs for disabled patients, mortality rates for disabled and nondisabled patients, and quality of life estimates.

Conclusions—Our analysis supports earlier economic evaluations that r-tPA is a cost-effective method to treat stroke. Appropriate use of r-tPA should be prioritized nationally. (Stroke. 2014;45:3032-3039.)

Key Words: cerebrovascular disorders ■ cost-effectiveness ■ quality of life ■ thrombolytic drugs ■ stroke

Stroke is a significant public health problem and one of the most costly diseases in the United States. Each year, ≈800,000 Americans experience a new or recurrent stroke and 134,000 deaths occur as a result of stroke.1–3 An estimated $74 billion were spent in 2010 on stroke-related medical costs and disability.4 The burden of disease from stroke is expected to increase over the coming decades because of the aging of the population and the limited control of stroke risk factors.5 The American Heart Association projects that the direct medical costs of stroke will increase 238% from 2010 to 2030.6

Intravenous recombinant tissue-type plasminogen activator (r-tPA) is a beneficial treatment for reducing the disability of acute ischemic stroke (AIS).7–11 r-tPA, a thrombolytic agent, was approved by the US Food and Drug Administration to treat AIS over 15 years ago but is underutilized.12,13 It is approved for use within 3 hours after the onset of stroke symptoms in the United States7 and is recommended for a selected spectrum of patients within 4.5 hours after symptom onset by the American Heart Association/American Stroke Association.14

Prior economic evaluations in the United States and Europe report that administration of r-tPA within 0 to 3 hours of symptom onset is cost-saving.15–17 Our recent economic analysis of r-tPA for patients treated 3 to 4.5 hours after symptom onset found r-tPA to be highly cost-effective compared with no r-tPA.18 However, despite new clinical data, the most recent US-based economic evaluation for r-tPA in the primary treatment window (0–3 hours) was published in 1998.15

Several recent studies provide a stronger evidence base for conducting an updated economic evaluation of r-tPA in the 0- to 3-hour time frame. Specifically, Wardlaw et al11 conducted a meta-analysis of r-tPA trials that included ≈1800 patients treated within 0 to 3 hours, a 5-fold increase compared with the original 333 patients in the National Institute of Neurological Disorders and Stroke (NINDS) study on which the original economic evaluation was based.15 The majority of the additional patients were from the Third International Stroke Trial (IST-3), a pragmatic international, multicenter, randomized, open-treatment trial conducted to better establish...
the benefits and harms of r-tPA in patients who did not exactly meet the license criteria in Europe and to refine the duration of the therapeutic time window.19

The objective of this study was to use the most recent data on efficacy, safety, and costs to estimate the cost-effectiveness, from the US payer perspective, of r-tPA for AIS within 0 to 3 hours of symptom onset compared with no r-tPA.

Methods

Approach

We developed a decision analytic model adapted from our prior evaluation of r-tPA within 3 to 4.5 hours of AIS19 to examine the long-term cost-effectiveness of r-tPA within 0 to 3 hours versus no r-tPA. The analysis was conducted from a US third-party payer perspective using a lifetime horizon. All costs were inflated to 2013 dollars using the Medical Consumer Price Index.20 and long-term costs and outcomes were discounted at 3% per year.21 The model was programmed in Microsoft Excel.

Model Structure

A decision tree was used to simulate 3-month outcomes in a hypothetical cohort of patients presenting with AIS and randomly assigned to r-tPA or no r-tPA (Figure 1A). The 3-month outcomes were disabled, nondisabled, or death, with or without experiencing symptomatic intracranial hemorrhage (sICH).

Following methods from 2 of our previously published stroke economic evaluations,1,12 patients with modified Rankin scores (mRS) of 0 to 1, 2 to 5, and 6 at 3 months were classified into health states of nondisabled, disabled, or dead, respectively.22 We then derived group-weighted parameters from mRS-specific ones. We evaluated the validity of grouping mRS rankings by comparing this approach with using individual mRS health states and found that the distribution of mRS scores within the nondisabled and within the disabled categories were similar, on average, between r-tPA and no r-tPA. Thus grouping mRS scores led to similar results versus modeling individual mRS scores, justifying our simplified approach.

Hypothetical patients surviving 3 months in the short-term model entered a Markov model to simulate the long-term clinical outcomes of recurrent stroke, transition to disability, and death over the patients’ remaining years of life (Figure 1B). In the model, patients remained in the health states experienced at the end of the initial 3-month period (nondisabled or disabled) until either nonstroke death or a stroke recurrence moved them to a worse health state or stroke-related death. Patients transitioned between health states as indicated by the arrows in Figure 1B.

Model Parameters

Model parameters for the base case and sensitivity analyses are shown in Table 1. These estimates were derived from literature reviews for our prior published studies15,18,22 and an updated literature search (2011–2013) using standard sources (MEDLINE, EMBASE) and keywords such as stroke, thrombolysis, tissue plasminogen activator, cost, outcomes, trials, and cost-effectiveness.

Short-Term Clinical Events

Of the 12 trials included in the Wardlaw meta-analysis (n=1779), 6 reported on treatment with r-tPA in the 0- to 3-hour time frame versus no r-tPA.11 The meta-analysis control group results were used to estimate the probabilities of 3-month disability status, death, and sICH for the no-r-tPA group and r-tPA groups (Table 1). These baseline rates were then multiplied by treatment relative risk estimates we derived from the meta-analysis results for the r-tPA group. Compared with no r-tPA, r-tPA was associated with a relative risk of 1.38 for no disability and 6.45 for sICH. Although Wardlaw et al11 did not report on the average age of trial participants, original reports indicate that the trials included subjects 18 to 80 years except the IST-3 trial with no maximum age. The median age of trial participants was ≈68 years, and we assumed this age for our modeled cohort. We assumed no mortality difference between the 2 groups in our base-case analysis based on estimates for r-tPA versus no-r-tPA in the meta-analysis (2.5% versus 2.6%; P=0.6).

There were several definitions of sICH used in the trials included in the Wardlaw meta-analysis,11 and results varied based on the definition. For example, the European Cooperative Acute Stroke Study (ECASS) III study reported several definitions of sICH, including the NINDS definition (absolute increase in sICH of 4.4% with r-tPA versus no r-tPA) and the ECASS III study definition (absolute increase in sICH of 2.2% with r-tPA versus no r-tPA).3 Estimate conservatively the benefit of r-tPA versus no r-tPA, we chose the sICH rate from the Wardlaw meta-analysis. This data source is consistent with our efficacy estimate and more complete as the meta-analysis rate reflects 7 days of follow-up for sICH versus, for example, only 3 days in the NINDS definition.

Long-Term Clinical Events

Annual baseline mortality was derived from US life table age- and sex-adjusted mortality rates.23 Both nondisabled and disabled patients were assumed to have a higher mortality risk than the general population based on numerous studies.26,33,34 The 1998 economic evaluation of r-tPA within the 0- to 3-hour time frame used a 2.7-fold increase for all stroke survivors and assumed no difference by disability status.15 Sandercoc et al15 and Ehlers et al12 assumed similar assumptions in their evaluations of r-tPA but used a 2.5-fold increase based on data from the Perth Community Stroke Study.36 Hong and Saver37 used estimates ranging from a 1.5-fold increase in mortality for mRS 0 patients up to a 6.5-fold increase for mRS 5 patients based on 2 European studies.38,39 Samsa et al13 assumed no increased risk in mRS 0 to 1 patients and up to a 2.4-fold increase in mRS 5 patients (an average of ≈1.5 for mRS 2–5 patients). We conservatively assumed
The annual stroke recurrence rate was based on a review of medical secondary stroke prevention trials. This rate was similar to those used in other recent economic evaluations of r-tPA. Based on 2 additional studies and our prior work, we assumed that the stroke recurrence rate was equal regardless of disability status. We assumed patients did not receive r-tPA for recurrent strokes. Nondisabled patients surviving a recurrent stroke had an equal probability of being nondisabled or disabled after recurrent stroke, similar to prior studies, and based on data from the Northern Manhattan Stroke Study. The mortality rate for a recurrent stroke was based on the NINDS trial and other population based estimates.

Quality of Life
Three recent stroke-based economic evaluations used estimates from Gage et al for the utility scores of mild and moderate to severe stroke health states. Using Gage et al’s utility scores that were derived from atrial fibrillation patients (average age of 70 years), we calculated a weighted average for the disabled group (0.47). Utility scores for mild disability (assumed equivalent to mRS 2) and moderate-severe (assumed equivalent to mRS 3–5) were weighted by the proportions of patients who had those mRS scores in the meta-analysis to estimate an average utility for our disabled group (0.47). Additionally, we could not assume that mild stroke in the Gage study was equivalent to mRS 0 to 1 (nondisabled group) because their reported utilities were for mild stroke (0.76) and thus low compared with utility estimates for mRS 0 to 1 (nondisabled) from other r-tPA studies. We thus applied utilities for mRS 0 to 1 (nondisabled group) from other r-tPA studies to arrive at a weighted utility (0.84) for the nondisabled health state that was more consistent with other r-tPA economic evaluations. If we had used a similar method to derive utility weights for disabled patients (mRS 2 to 5) from Stahl et al instead of Gage et al, we would arrive at a less conservative utility of 0.52. We applied a disutility of −0.38 for the first 90 days if sICH occurred.

Cost Input Parameters
Direct medical costs were derived from a variety of literature sources. The payer perspective we assumed includes only direct healthcare costs typically incurred by healthcare payers (eg, drug reimbursement, inpatient, and outpatient care) and not indirect costs such as productivity loss or caregiver time.

Acute care hospital costs by disability status were obtained from a study by Earnshaw et al, who adapted total inpatient costs derived from Reed et al’s analysis of US community hospital data. In the Reed analysis, total inpatient costs included general ward, intensive care unit, procedures, laboratory services, imaging, and other standard hospital costs. Earnshaw used the total inpatient hospital costs for patients subsequently discharged to home or home health services as a proxy for the nondisabled group and costs for patients discharged to skilled nursing facilities as a proxy for the disabled group. Recurrent strokes were assigned the cost of an incident AIS. sICH inpatient costs were estimated in a similar fashion as stroke costs. The cost of r-tPA was based on Wholesale Acquisition Cost. This cost is similar to the difference in the Centers for Medicare and Medicaid Services reimbursement for acute care of stroke patients with and without administration of r-tPA (ie, Diagnostic-Related Groups 61 minus 64).

Long-term annual health costs in the years after a stroke for disabled patients were derived from costs used in 3 recent stroke economic evaluations. Annual direct costs for mild disability (assumed equivalent to mRS 2) and moderate-severe (assumed equivalent to mRS 3–5) were weighted, as described above for utility scores, to estimate an average annual cost for our disabled group (mRS 2–5). Long-term annual costs for nondisabled patients were based on a previously described methodology because the sources for the cost of disabled patients with stroke did not include nondisabled. Briefly, yearly direct costs, excluding the first 90 days, were stratified by disability status. Because we used a grouped mRS health state approach (ie, disabled and nondisabled) as opposed to previous studies that modeled individual mRS health states, we weighted each health state’s long-term cost by the proportions of patients who had

Table 1. Clinical and Cost Model Inputs

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<th>Probabilistic References</th>
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<tr>
<td>Disabled</td>
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QALY indicates quality-adjusted life year; r-tPA, recombinant tissue-type plasminogen activator; and sICH, symptomatic intracranial hemorrhage. *Sensitivity range equivalent to ±20%.

a 1.1-fold increase for nondisabled patients, which is only slightly higher than Samsa but accounts for some increased risk as observed in cohort studies. We assumed a conservative 2.5-fold increase for disabled patients based on review of other r-tPA studies and a large stroke registry-based study of the influence of 3-month stroke disability status on long-term survival (hazard ratio: 1.7 for mRS 3, 2.5 for mRS 4, and 3.8 mRS 5 compared with mRS 0–2).
The model was most sensitive to the following inputs: efficacy of r-tPA in reducing disability, annual healthcare costs for disabled patients, annual mortality rates for disabled and nondisabled patients, and quality of life estimates. Compared with no treatment, r-tPA reduced costs and increased QALYs under all 1-way sensitivity analysis scenarios.

### Probabilistic Sensitivity Analyses

PSA results were consistent with our base case findings of increased QALYs (0.39; 95% credible range, 0.16–0.66) per patient over no treatment and decreased costs −$25,000 (95% credible range, −$42,500 to −$11,000). Results of the PSA for the distribution of the incremental cost-effectiveness ratio results are displayed on the cost-effectiveness plane (Figure 3), and all (except 1 in 10,000) fall in the southeast quadrant of the plane (ie, treatment dominates no treatment). Within our model, this can be interpreted as r-tPA administered within 0 to 3 hours of acute ischemic stroke symptom onset is cost-effective over no treatment essentially 100% of the time.

### Discussion

The results of our analysis suggest that use of r-tPA within 0 to 3 hours of AIS symptom onset provides favorable long-term clinical and economic outcomes compared with no r-tPA. Our findings were robust to a variety of sensitivity analyses. From a policy perspective, 39 years of QALYs would be gained, and over 2.5 million US dollars saved in medical costs for every 100 patients treated with r-tPA within 0 to 3 hours of AIS symptom onset. Our assumptions and results are supported by findings that chronic disability and its long-term impact rather than stroke fatality are the major burden of stroke.56,57

A recent study conducted using data from a large US registry of over 50,000 patients with AIS indicated that faster onset to thrombolytic treatment, in 15 minute increments, was associated with reduced inpatient mortality and SICH.57 Faster onset to treatment time was also associated with higher rates of independent ambulation at discharge and discharge to home. Wardlaw et al11 also concluded that earlier treatment with r-tPA is more favorable, based on an absolute increase of 90 per 1000 individuals alive and independent (mRS 0–2) at 90 days after AIS when treated within 3 hours of symptom onset, compared with 18 per 1000 alive and independent when treated within the 3 to 6 hour time window.11

This was the first study to evaluate the cost-effectiveness of r-tPA at 0 to 3 hours after AIS from the US payer perspective in over 15 years. Results from the 1998 model by Fagan et al15 were similar with respect to r-tPA being dominant versus no r-tPA. QALYs saved for 30 years of the model were 564 per 1000 persons treated with r-tPA, and cost-savings were $=4000 per person treated with r-tPA. Updates to key model inputs, a morality adjustment, and differences in how mRS outcomes were modeled (ie, mRS=0–1, mRS=2–5, or death [mRS=6] in the current study versus individual mRS scores of 0–6 in Fagan et al15) may explain differences in costs saved and QALYs gained. Fagan et al15 used only the NINDS r-tPA Stroke Trial as the source of data for efficacy (13% absolute difference in patients nondisabled) and safety (SICH 10-fold increase with r-tPA). Additional trials of r-tPA have since been published and aggregated in the meta-analysis that we used to

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### Table 2. Costs and QALYs With r-tPA Within 0 to 3 Hours of Acute Ischemic Stroke Symptom Onset Compared With No r-tPA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Costs in US $ (95% CR)</th>
<th>QALYs (95% CR)</th>
<th>ICER</th>
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<td>Base case: 4.29</td>
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<td>Probabilistic: $240,700</td>
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<tr>
<td></td>
<td>to $360,000</td>
<td>to 5.46</td>
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<tr>
<td>No r-tPA</td>
<td>Base case: $312,400</td>
<td>Base case: 3.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probabilistic: $262,600</td>
<td>Probabilistic: 2.85</td>
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</tr>
<tr>
<td></td>
<td>to $391,000</td>
<td>to 5.16</td>
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<tr>
<td>Difference,</td>
<td>Base case: −$25,000</td>
<td>Base case: 0.39 Dominant</td>
<td>0.16</td>
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<td>r-tPA vs no r-tPA</td>
<td>Probabilistic:</td>
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<td></td>
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<tr>
<td></td>
<td>−$42,000 to −$11,000</td>
<td></td>
<td>−0.67</td>
</tr>
</tbody>
</table>

CR indicates credible range; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; and r-tPA, recombinant tissue-type plasminogen activator.

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### Analyses

#### Outcome Measures

We calculated lifetime direct healthcare costs and quality-adjusted life years (QALYs) and incremental differences in costs and QALYs between the r-tPA and no r-tPA arms. The incremental cost-effectiveness ratio was calculated as the difference in costs divided by the difference in QALYs.

#### Sensitivity Analyses

We performed sensitivity analyses to examine the influence of uncertainties in the model inputs and to judge the robustness of the findings.21,48,49 Clinical parameter ranges were obtained from reported literature (when available) and data-derived confidence intervals, and all costs were varied by ±20%. Single-variable (1-way) sensitivity analyses were performed with the value of each input individually varied over ranges shown in Table 1; 1-way sensitivity analysis results are presented as tornado diagrams.49

We also performed probabilistic sensitivity analysis (PSA),56,50 wherein all model parameters were jointly varied over 10,000 Monte Carlo simulations using prespecified statistical distributions, enabling the calculation of 95% credible ranges for model outcomes.51,52 Results of the PSA were plotted on an incremental cost-effectiveness plane.

### Results

#### Primary Analyses

**Base Case Analysis**

The costs, QALYs, and lifetime cost-effectiveness of r-tPA in the 0- to 3-hour window versus no r-tPA in patients with AIS is summarized in Table 2. Lifetime medical costs for the r-tPA group were $287,400 compared with $312,400 in the no r-tPA group. QALYs were 4.29 in the r-tPA group and 3.90 in the no r-tPA group. Treatment with r-tPA increased QALYs by 0.39 and decreased costs by $25,000, thus r-tPA dominated no treatment.

#### Sensitivity Analyses

**One-Way Sensitivity Analyses**

The results of 1-way sensitivity analyses of incremental costs, QALYs, and cost-effectiveness ratio are presented in Figure 2A–2C, respectively. Model parameters at the top of the tornado diagrams have the largest impact on the results. Those outcomes in the trial and then calculated a weighted average for the nondisabled group.

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**Figure 2. A**, One-way sensitivity analyses for incremental costs. The widths of the horizontal bars represent the change in results when each parameter was varied over the ranges specified in Table 1. Blue represents results for low range of input and red the upper range of input. **B**, One-way sensitivity analyses for incremental quality-adjusted life years (QALYs). The widths of the horizontal bars represent the change in results when each parameter was varied over the ranges specified in Table 1. Blue represents results for low range of input and red the upper range of input. **C**, One-way sensitivity analyses for incremental costs per QALYs or incremental cost-effectiveness ratio. The widths of the horizontal bars represent the change in results when each parameter was varied over the ranges specified in Tables 1. Blue represents results for low range of input and red the upper range of input. r-tPA indicates recombinant tissue-type plasminogen activator; and sICH, symptomatic intracranial hemorrhage.
estimate efficacy (9% absolute difference in patients nondisabled) and sICH (6.5-fold increase with r-tPA). Our analysis also included more up-to-date information on medical costs, stroke recurrence, and mortality rates for disabled and non-disabled. Most notably, we estimate the annual cost for being disabled has increased by >60% since the 1998 analysis.

Of note, other fairly recent cost-effectiveness analyses of r-tPA conducted in Canada, the United Kingdom, Denmark, and Australia report r-tPA to be cost-effective and in many cases a cost-saving/dominant strategy for treating eligible AIS patients.

Implications

Our findings support clinical guidelines and reimbursement policies for the use of r-tPA therapy in treating AIS. Yet, r-tPA is underutilized, in part, because of the restricted time window for use and safety concerns with sICH. The 7-day sICH rate reported in the recent Wardlaw meta-analysis was 7.7% in the r-tPA arm versus 1.8% in the placebo arm. Despite this adverse event, the authors indicated that 55 more patients were alive with a favorable outcome (mRS 0–1) at 90 days after AIS for every 1000 patients treated with r-tPA. r-tPA is also underutilized because many US hospitals lack the necessary infrastructure and organization required to triage and treat patients with stroke quickly and efficiently. Efforts such as specialized stroke units, specially trained staff, code stroke systems, telestroke systems, prehospital notification systems, and participation in programs such as the American Heart Association’s Get With The Guidelines-Stroke program may appropriately increase the r-tPA treatment rate and improve safe delivery of r-tPA. These efforts should be strongly considered. However, such efforts commonly require additional equipment, staff, and other resources. Staff, as well as stroke team members, are then faced with an increasing pressure of responding to more stroke codes and are often required to move more rapidly through evaluation, decision, and treatment. As such, the current cost-effectiveness findings could be leveraged in future discussions around the diagnostic related group reimbursement policy for stroke.

Limitations

Our decision model was based on required assumptions, and we populated the model with data from numerous published studies including clinical trials. The results and conclusions are, therefore, specific to those assumptions and data. For example, limited data were available on the long-term costs of stroke survivors, subsequent quality of life after AIS, and disability associated with recurrent stroke. We were also unable to use one data source to estimate quality of life after AIS for disabled and nondisabled. The literature is also inconsistent in defining the increase in mortality after stroke, particularly in disabled patients. The mortality rate for recurrent stroke is also somewhat dated. We collapsed mRS individual states into 0 to 1 (nondisabled) and 2 to 5 (disabled) based on similar distributions between the r-tPA and placebo group, as well as similar results compared with individual scores. However, it should be noted that the distributions of individual mRS states within the nondisabled and disabled states between the r-tPA and placebo groups appeared slightly different. We followed Earnshaw and used acute inpatient costs by subsequent discharge status as a proxy for costs by disability status. As such, these acute costs are subject to the validity of that assumption. However, we attempted to capture this in our sensitivity analyses where we varied both short- and long-term costs. Our model, assumptions, and model inputs are, however, similar to that of other published studies on the cost-effectiveness of r-tPA. In addition, our sensitivity analyses suggest that our results are robust to uncertainty in the model parameters. We used a broad range of values in uncertainty analyses and consistently produced results showing r-tPA to be dominant over no r-tPA. Last, we note that our results are specific to AIS only.

Wardlaw et al noted a difference in AIS outcomes by age (29% alive and independent with r-tPA versus 19% no r-tPA among patients >80 years of age; 50% alive and independent in r-tPA versus 40% no r-tPA among patients ≤80 years), but r-tPA was highly effective in both age groups (P values=0.003 and 0.001, respectively). We were unable to conduct subgroup analyses by these age groups because independence was defined as mRS 0 to 2 instead of the mRS 0 to 1 used in our
analysis. Given that the effect size of r-tPA was similar across the 2 age groups, we expect r-tPA would remain dominant and any differences would be attributable to the fact that older people are more likely to die based on background mortality.

Conclusions

In summary, r-tPA in the 0- to 3-hour window after AIS seems to be cost-saving and increases QALYs compared with no treatment with r-tPA. The generated cost-savings seems to be greater than over a decade ago because of the increasing cost of caring for disabled patients with stroke. Additional research is needed to study implications of r-tPA use in real-world settings and to improve on the delivery of r-tPA when patients are eligible and protocols are in place.

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Cost-Effectiveness of Recombinant Tissue-Type Plasminogen Activator Within 3 Hours of Acute Ischemic Stroke: Current Evidence
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