Targeting Recombinant Tissue-Type Plasminogen Activator in Acute Ischemic Stroke Based on Risk of Intracranial Hemorrhage or Poor Functional Outcome
An Analysis of the Third International Stroke Trial

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Background and Purpose—Intravenous recombinant tissue-type plasminogen activator (rtPA), despite a risk of early symptomatic intracranial hemorrhage (sICH), is of net clinical benefit to acute stroke patients. We tested if predictive models could identify patients least likely to be harmed by sICH or those who gained no net benefit.

Methods—We used the Third International Stroke Trial (IST-3) trial data set, an international, multicenter, open treatment randomized trial of 0.9 mg/kg rtPA versus control in 3035 patients with acute ischemic stroke. We compared the discrimination and calibration of previously developed predictive models for ICH and poststroke poor outcome and developed a new model using variables selected by systematic review. We calculated the absolute and relative risk reduction of death or dependency with rtPA in patients at a low, medium, or high predicted risk of sICH or poor functional outcome.

Results—Prediction models for sICH or poor outcome (Hemorrhage After Thrombolysis [HAT]; Sugar, Early Infarct Signs, Dense Artery, Age, National Institutes of Health [NIH] Stroke Scale [SEDAN]; Glucose Race Age Sex Pressure Stroke Severity [GRASPS]; Stroke Thrombolytic Predictive Instrument; Dense Artery, Rankin Score, Age, Glucose, Onset to Treatment Time, NIHSS [DRAGON]; Totedal Health Risk in Vascular Events [THRIVE]; our new model; and a model with National Institutes of Health Stroke Scale and age) had similar area under receiver operator characteristic curves (AUROCC) to predict sICH (P for difference >0.05). The simplest model (with covariates National Institutes of Health Stroke Scale and age) predicted both sICH (AUROCC, 0.63; 95% CI, 0.58–0.68) and poststroke poor functional outcome (AUROCC, 0.80; 95% CI, 0.77–0.82) similarly to complex models. There was no evidence that the effect of rtPA in patients at high predicted risk of sICH or poor functional outcome after stroke was less than in those at lower risk.

Conclusions—There is a clinically relevant net positive effect of rtPA in patients with acute stroke at a high predicted risk of sICH or poor functional outcome.


Key Words: prognosis randomized controlled trial stroke thrombolytic therapy
each model. In other words, we sought to assess whether the benefits and harms of thrombolysis vary in groups with different predicted prognosis.

**Methods**

**Ethics Statement**

The study was approved by the Multicenter Research Ethics Committee, Scotland (reference MREC/99/0/78) and by local ethical committees. Patients or a valid proxy gave written consent to participate. This trial was registered (ISRCTN25765518).

**IST-3 Study Design and Participants**

The details of the IST-3 study protocol, statistical analysis plan, and primary outcomes have been published previously. In brief, ischemic stroke patients (with no upper age limit) who could start recombinant tissue-type plasminogen activator (rtPA) treatment <6 hours of symptom onset, and in whom the randomizing clinician was substantially uncertain about the risks and benefits of rtPA, were randomized 1:1 to standard care with an infusion of 0.9 mg/kg rtPA or standard care without rtPA.

**Measurement of Baseline Variables and Clinical Outcomes**

For these analyses, we used baseline clinical variables that had been measured and recorded by the treating clinician before randomization, nonblinded information collected postrandomization, and findings from the brain scans that had been read by an expert panel blinded to clinical details and allocated treatment.

The trial event adjudication committee defined symptomatic post-rtPA ICH (sICH) as a clinically significant deterioration or death within the first 7 days of treatment with evidence of either significant brain parenchymal hemorrhage (local or distant from the infarct) or significant hemorrhagic transformation of an infarct on brain imaging. In addition, we extracted the variable any significant radiological post-rtPA ICH by 7 days, measured by a blinded neuroradiology rater either on routine brain imaging 24 to 48 hours postrandomization or any scans performed in case of clinical deterioration (equivalent to parenchymal hemorrhage type 2 measured in previous trials of intravenous rtPA). The primary measure of clinical outcome was the Oxford Handicap Scale (OHS) measured at 6 months after randomization. We defined poor functional outcome as an OHS of 3 to 6 (dead or dependent). We performed a post hoc sensitivity analysis using a definition of poor functional outcome of OHS 5 to 6 (dead or dependent for all cares).

**Table 1. Baseline Clinical Variables and Symptomatic Intracranial Hemorrhage (sICH) in Patients Randomized to Recombinant Tissue-Type Plasminogen Activator in Third International Stroke Trial (IST-3), With Univariate Associations**

<table>
<thead>
<tr>
<th>Demographic factors</th>
<th>All (n=1515)</th>
<th>sICH (n=104)</th>
<th>No sICH (n=1411)</th>
<th>OR 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>81 (72–86)</td>
<td>81 (74–86)</td>
<td>81 (72–86)</td>
<td>1.01</td>
<td>0.99–1.03</td>
</tr>
<tr>
<td>Male sex, n, %</td>
<td>733, 48%</td>
<td>60, 58%</td>
<td>673, 48%</td>
<td>1.50</td>
<td>1.00–2.24</td>
</tr>
<tr>
<td>Weight, kg, median (IQR)</td>
<td>70 (62–80)</td>
<td>70 (65–80)</td>
<td>70 (62–80)</td>
<td>1.01</td>
<td>0.99–1.02</td>
</tr>
<tr>
<td>Stroke risk factors, n, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>473, 31%</td>
<td>29, 28%</td>
<td>444, 31%</td>
<td>0.84</td>
<td>0.54–1.31</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>184, 12%</td>
<td>17, 16%</td>
<td>167, 12%</td>
<td>1.45</td>
<td>0.84–2.50</td>
</tr>
<tr>
<td>Previous stroke or transient ischemic attack†</td>
<td>354, 23%</td>
<td>34, 33%</td>
<td>320, 23%</td>
<td>1.65</td>
<td>1.08–2.53</td>
</tr>
<tr>
<td>Previous hypertension*</td>
<td>975, 64%</td>
<td>64, 62%</td>
<td>911, 65%</td>
<td>0.90</td>
<td>0.59–1.36</td>
</tr>
<tr>
<td>Treatment, n, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking antiplatelets‡</td>
<td>775, 51%</td>
<td>70, 67%</td>
<td>705, 50%</td>
<td>2.05</td>
<td>1.34–3.13</td>
</tr>
<tr>
<td>Taking &gt;1 antiplatelet§</td>
<td>80, 5%</td>
<td>10, 10%</td>
<td>70, 5%</td>
<td>2.21</td>
<td>1.10–4.46</td>
</tr>
<tr>
<td>Taking warfarin or heparin║</td>
<td>50, 3%</td>
<td>1, 1%</td>
<td>49, 3%</td>
<td>0.29</td>
<td>0.04–2.11</td>
</tr>
<tr>
<td>Stroke characteristics, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>11 (6–18)</td>
<td>15 (10–21)</td>
<td>11 (6–17)</td>
<td>1.06</td>
<td>1.04–1.09</td>
</tr>
<tr>
<td>Blood glucose, mg/dL¶</td>
<td>126 (108–144)</td>
<td>126 (108–162)</td>
<td>126 (108–144)</td>
<td>1.00</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>156 (140–170)</td>
<td>160 (146–175)</td>
<td>155 (139–170)</td>
<td>1.01</td>
<td>1.00–1.02</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg#</td>
<td>80 (71–91)</td>
<td>82 (73–90)</td>
<td>80 (71–91)</td>
<td>1.00</td>
<td>0.99–1.02</td>
</tr>
<tr>
<td>Delay to treatment, h</td>
<td>4 (3–5)</td>
<td>4 (3–5)</td>
<td>4 (3–5)</td>
<td>0.91</td>
<td>0.77–1.07</td>
</tr>
<tr>
<td>Imaging, n, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visible acute lesion on imaging</td>
<td>628, 41%</td>
<td>56, 54%</td>
<td>572, 41%</td>
<td>1.71</td>
<td>1.15–2.55</td>
</tr>
<tr>
<td>Presence of leukoaraiosis**</td>
<td>765, 50%</td>
<td>57, 55%</td>
<td>708, 50%</td>
<td>1.25</td>
<td>0.83–1.87</td>
</tr>
<tr>
<td>Hyperdense artery**</td>
<td>376, 25%</td>
<td>40, 38%</td>
<td>336, 24%</td>
<td>2.05</td>
<td>1.35–3.11</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; IQR, interquartile range; IST-3, Third International Stroke Trial; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*2 missing values.
†3 missing values.
‡4 missing values.
§148 missing values.
║149 missing values.
¶142 missing values.
#12 missing values.
**8 missing values.
Identification of Previously Developed Prediction Models

We identified published clinical prediction scores by systematically searching the literature for models that aimed to predict post-rtPA sICH or poor functional outcome after rtPA. We hypothesized that a simple model containing only the variables National Institutes of Health Stroke Scale (NIHSS) and age would predict both sICH and poor functional outcome as well as the other scores.

Development of a New Predictive Model for sICH

We developed a new model to predict sICH in patients randomized to rtPA from IST-3. We created a binary logistic regression model with variables significantly associated with post-rtPA ICH in a systematic review. We tested model assumptions of linearity and additivity and the effect of missing data. We internally validated the model with 150 bootstrap replicates and shrinkage of estimated regression coefficients to correct for overfitting.

Calibration, Discrimination, and Classification of Predictive Models for sICH and Poor Functional Outcome

We tested model performance in rtPA-treated patients for the outcomes sICH, any significant radiological post-rtPA ICH, and poor functional outcome. We measured discrimination with the area under receiver operator characteristic curve (AUROCC), which we compared nonparametrically. An AUROCC=1 indicates perfect discrimination, and AUROCC=0.5 indicates no better discrimination than chance. To test model calibration, we calculated the calibration slope and intercept by fitting a logistic regression model with predicted risk as the only predictor (where a slope=1 and intercept=0 indicates a perfectly calibrated model) and compared the proportions of patients classified as low, medium, and high risk with each model.

The choice of risk thresholds is controversial. In the absence of generally agreed thresholds, we used the mean of risk thresholds from previous studies to define low, medium, and high risk of post-rtPA ICH and poor functional outcome. The means of the published thresholds for ICH were ≤3%, 3% to 8%, and >8%, and for poor functional outcome were ≤35%, 35% to 50%, and >50%. In a secondary analysis, we examined thresholds for a very high risk of sICH (>20%) and very high risk of poor functional outcome (>70%).

Effect of rtPA in Patients at High, Intermediate, and Low Risk of ICH

We investigated the interaction between rtPA treatment and predictions of sICH or poor functional outcome on an absolute risk scale, by calculating the difference in the proportion of patients with poor functional outcome between patients treated with and without rtPA in groups of patients at low, medium, and high risk. Where possible, we recalibrated the intercept of prediction models to the IST-3 data set. To support this analysis, we looked for interactions on a relative scale between treatment and predicted risk as a continuous variable, using ordinal logistic regression with the whole OHS as the dependent variable, after examining the proportional odds assumption.

We performed sensitivity analyses excluding those few patients randomized to rtPA who did not receive any, examining only those patients where the time to randomization was <4.5 hours and only those treated after 4.5 hours, and in addition made further adjustment for delay to treatment as a continuous variable. Post hoc we repeated this analysis in patients randomized <3 hours after stroke onset.

We used R version 2.13.1 for statistical analysis. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Results

In patients treated with rtPA, 6.8% (104 of 1515) had a sICH <7 days of randomization; another 2% (31) had a radiological hemorrhage by 7 days with no detectable clinical deterioration. The median time from randomization to sICH was 1 day (interquartile range, 1–2). By 6 months, patients who had a sICH were independent in activities of daily living (8 of 104; 8%) compared with rtPA-treated patients who did not have a sICH (546 of 1411; 39%).

Patients who had an sICH (Table 1) were significantly (P<0.05) more likely to have had a history of stroke or transient

Table 2. Discrimination and Calibration of Models to Predict Intracranial Hemorrhage and Poor Functional Outcome After rtPA in IST-3 Data Set

<table>
<thead>
<tr>
<th>Models</th>
<th>Score</th>
<th>AUROCC</th>
<th>95% CI</th>
<th>Intercept</th>
<th>Slope</th>
<th>AUROCC</th>
<th>95% CI</th>
<th>Intercept</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAT</td>
<td>0–5</td>
<td>0.62</td>
<td>0.56–0.68</td>
<td>−0.29</td>
<td>0.39</td>
<td>0.71</td>
<td>0.68–0.73</td>
<td>3.65</td>
<td>0.96</td>
</tr>
<tr>
<td>SEDAN</td>
<td>0–7</td>
<td>0.62</td>
<td>0.56–0.69</td>
<td>−0.46</td>
<td>0.53</td>
<td>0.74</td>
<td>0.71–0.76</td>
<td>3.19</td>
<td>0.99</td>
</tr>
<tr>
<td>SITS</td>
<td>0–11</td>
<td>0.63</td>
<td>0.58–0.69</td>
<td>0.98</td>
<td>0.76</td>
<td>0.66</td>
<td>0.63–0.69</td>
<td>4.45</td>
<td>0.79</td>
</tr>
<tr>
<td>GRASPS</td>
<td>45–101</td>
<td>0.63</td>
<td>0.57–0.68</td>
<td>0.28</td>
<td>0.62</td>
<td>0.77</td>
<td>0.74–0.79</td>
<td>3.76</td>
<td>1.56</td>
</tr>
<tr>
<td>SPAN-100*</td>
<td>0–1</td>
<td>0.56</td>
<td>0.52–0.61</td>
<td>−1.35</td>
<td>0.36</td>
<td>0.66</td>
<td>0.64–0.68</td>
<td>2.19</td>
<td>1.26</td>
</tr>
<tr>
<td>Stroke TPI</td>
<td>GLM</td>
<td>0.64</td>
<td>0.58–0.69</td>
<td>−1.73</td>
<td>0.33</td>
<td>0.80</td>
<td>0.78–0.83</td>
<td>2.49</td>
<td>0.99</td>
</tr>
<tr>
<td>DRAGON</td>
<td>0–10</td>
<td>0.65</td>
<td>0.59–0.70</td>
<td>−3.68</td>
<td>0.47</td>
<td>0.78</td>
<td>0.76–0.81</td>
<td>0.20</td>
<td>0.96</td>
</tr>
<tr>
<td>THRIVE</td>
<td>0–9</td>
<td>0.50</td>
<td>0.45–0.55</td>
<td>−3.53</td>
<td>0.32</td>
<td>0.76</td>
<td>0.74–0.79</td>
<td>0.26</td>
<td>1.07</td>
</tr>
<tr>
<td>NIHSS/age</td>
<td>GLM</td>
<td>0.63</td>
<td>0.58–0.68</td>
<td>−4.46</td>
<td>0.27</td>
<td>0.80</td>
<td>0.77–0.82</td>
<td>0.03</td>
<td>0.84</td>
</tr>
<tr>
<td>IST-3 model</td>
<td>GLM</td>
<td>0.68</td>
<td>0.63–0.74</td>
<td>−0.01</td>
<td>1.32</td>
<td>0.71</td>
<td>0.68–0.74</td>
<td>3.37</td>
<td>1.71</td>
</tr>
</tbody>
</table>

Discrimination is measured by the AUROCC. An AUROCC=1 indicates perfect discrimination, and AUROCC=0.5 indicates no better discrimination than chance. Calibration is measured by the intercept and slope of a calibration curve. A perfectly calibrated model has a slope=1 and intercept=0. AUROCC=100. *AUROCC for SPAN-100 is estimated from logistic regression analysis using the recommended dichotomy SPAN-100 ≥100.
ischemic attack, to have been taking an antiplatelet agent in the
48 hours before randomization, to have had more neurological
impairment or a higher blood glucose at randomization, or to
have had a visible infarct (in any location) or hyperdense artery
on brain imaging. There was no detectable effect of delay to
randomization or delay to treatment on the odds of sICH.

Identification of Previously Developed Prediction
Models
We identified 5 scores to predict post-rtPA ICH and 3 scores
to predict post-rtPA poor functional outcome. We excluded 4
potentially relevant scores: 2 for which we were unable to cal-
culate predicted risks from the published information, and 2
as they required baseline information that was not available in
IST-3 (platelet count and a diagnosis of cancer or renal failure;
Table I in the online-only Data Supplement).

Development of Model to Predict sICH in IST-3
A logistic regression model for the prediction of sICH, devel-
oped in 1515 rtPA-treated patients with variables significantly
associated with ICH from our previous systematic review7
(age, NIHSS, glucose, previous hypertension, atrial fibrilla-
tion, antiplatelets, diabetes mellitus, leukoaraiosis, and visible
infarction), was able to discriminate modestly between
patients with and without sICH (AUROCC corrected for
optimism, 0.65) and was well calibrated in this data set (cali-
boration slope corrected for optimism, 1.12; intercept, 0.32;
Table II in the online-only Data Supplement).

There were no statistically or clinically significant 2-way
interactions between categorical and continuous variables,
and there was no evidence of a nonlinear relationship between
any continuous variables with the odds of sICH. Multiple
imputations for missing data made very little difference to the
magnitude or direction of the estimates.

Calibration and Discrimination of Predictive
Models for sICH and Poor Functional Outcome
All models to predict sICH or poor functional outcome dis-
criminated modestly between patients who did and did not
have a sICH (AUROCC range, 0.56–0.68; Table 2). The
AUROCCs of all models were similar (P>0.05), apart from the
dichotomized Stroke Prognostication Using Age and NIHSS
(SPAN) score, which had significantly worse discrimination
(P<0.05). Each previously developed model discriminated
less well than in previous validation data sets. Models devel-
oped to predict sICH were better calibrated for the sICH out-
come than those models developed to predict post-rtPA poor
functional outcome, though all models (apart from the new
score) overpredicted the risk of sICH. There were no impor-
tant qualitative or quantitative differences in discrimination or
validation for any of the models when the outcome was radio-
logical post-rtPA ICH rather than symptomatic ICH (Table III
in the online-only Data Supplement), or when we examined
only those patients randomized <3 hours of stroke onset. Each
model classified a different proportion of the rtPA-treated
population at high, medium, and low risk of sICH, differences
that are potentially clinically relevant (Figure 1).

All models discriminated moderately well between patients
who did and did not have a poor functional outcome after
stroke (AUROCC range, 0.66–0.80). There were no signif-
cant differences in discrimination between models designed
to predict poor functional outcome post-rtPA (Stroke
Thrombolytic Predictive Instrument; NIHSS/age; Dense
Artery, Rankin Score, Age, Glucose, Onset to Treatment
Time, NIHSS [DRAGON]; new model; Totaled Health Risk
in Vascular Events [THRIVE]; differences all P>0.05), except
the SPAN score that was significantly worse than other mod-
els (P<0.001). All the models were well calibrated for death
or dependence, whether or not they aimed to predict sICH or
poststroke poor functional outcome. A sensitivity analysis
examining a different definition of functional outcome (OHS,
5–6) made no difference to these conclusions.

Although the novel IST-3 score we developed had better
discrimination than previous models to predict sICH, the
absolute difference in the AUROCC between it and other
models was small and likely because of model overfitting, and
therefore we do not think it will perform better than the previ-
ously developed models in external validation.

Effect of rtPA in Patients at High, Intermediate, and
Low Risk of ICH
In the 3035 patients in IST-3, we observed that the absolute
risk reduction in poor functional outcome with rtPA treatment
was greater both among patients at higher predicted risk of sICH (Figure 2) and among patients at higher risk of poor functional outcome (Figure 3). With the more statistically efficient ordinal logistic regression to measure treatment effect, there was no evidence of significant interactions between rtPA with continuous predicted risk of sICH or poor functional outcome on a relative scale. These conclusions were not changed by excluding patients who were randomized but not treated with rtPA, patients who were randomized >3 or >4.5 hours after stroke, making adjustment for delay to treatment as a continuous variable, or when examining higher thresholds of risk for sICH (>20%) or poor functional outcome (>70%). There was,

**Figure 2.** Net clinical effect of recombinant tissue-type plasminogen activator (rtPA) among groups of patients at different risks of symptomatic intracranial hemorrhage. Absolute risk reduction (ARR) observed across 3 categories of predicted risk of symptomatic intracranial hemorrhage. Circle size proportional to number of patients, horizontal line indicates 95% CI. A positive ARR indicates a reduced risk of death or dependency in the treated group, whereas a negative ARR suggests an excess risk in the rtPA-treated group. No patients were classified as medium risk by the SEDAN score. GRASPS indicates Glucose Race Age Sex Pressure Stroke Severity; HAT, Hemorrhage After Thrombolysis; IST-3, Third International Stroke Trial; NIHSS, National Institutes of Health Stroke Scale; SEDAN, Sugar, Early Infarct Signs, Dense Artery, NIH Stroke Score; SITS, Safe Implementation of Treatments in Stroke; and TPI, thrombolytic predictive instrument.

**Figure 3.** Net clinical effect of recombinant tissue-type plasminogen activator (rtPA) among groups at different risks of poor functional outcome. Absolute risk reduction (ARR) observed across 3 categories of predicted risk of poor functional outcome. Circle size proportional to number of patients, horizontal line indicates 95% CI. A positive ARR indicates a reduced risk of death or dependency in the treated group, whereas a negative ARR suggests an excess risk in the rtPA-treated group. DRAGON indicates Dense Artery, Rankin Score, Age, Glucose, Onset to Treatment Time, NIHSS; IST-3, Third International Stroke Trial; NIHSS, National Institutes of Health Stroke Scale; SEDAN, Sugar, Early Infarct Signs, Dense Artery, Age, NIH Stroke Score; SITS, Safe Implementation of Treatments in Stroke; and TPI, thrombolytic predictive instrument.
Discussion

The clinical effect of rtPA in patients at a higher predicted risk of sICH or poor functional outcome was at least as good as, and possibly more than, in patients with a lower risk. We found prediction scores discriminated only modestly well between patients who did and did not have a sICH, though discriminated moderately well between patients who did and did not have a poor functional outcome.

Our analyses suggest that clinical prediction scores are unlikely to play a role in selecting individual ischemic stroke patients for rtPA in routine practice. Patients (or their families) who want to know the probability of poor functional outcome or sICH could choose any 1 of these scores, accepting the uncertainty in absolute predicted risks for an individual. A simple score constructed with the fewest, most easily measured clinical variables (eg, NIHSS and age) would be the easiest to implement.

Our approach had several strengths. We selected comparator models from a systematic review and measured the performance of models to predict important clinical outcomes in a large data set. IST-3 is broadly representative of current clinical practice as it included many elderly patients and patients with severe stroke, and the rate of sICH was similar to that seen in clinical practice and previous clinical trials of rtPA.9 This wider range of patients with differing prognoses from previous cohorts is a strength of the analysis. We developed a new prediction model for ICH minimizing data-dependent biases and maximizing the use of predictive information. Despite this, we were unable to make very much better prediction compared with previously published models. We, therefore, did not validate this model in a new data set.

There were no differences in our conclusions after sensitivity analyses were restricted to patients treated <4.5 hours after stroke (the time threshold of the current European Union license for rtPA). IST-3 had few missing baseline or outcome data (though glucose was not collected in the first 282 patients randomized), had a wide range in potentially predictive variables because of its wide inclusion criteria, and randomly allocated rtPA; so our conclusions about the use of scores to predict response to treatment are robust. Our conclusions are supported by recent work with observational data comparing treated and untreated acute stroke patients with several relative contraindications to rtPA (high glucose levels, extensive CT findings, etc).10

We can, however, identify limitations. IST-3 was an unblinded trial, though steps were taken to minimize bias. Overall, IST-3 was a neutral trial in that there was no statistically significant difference in the dichotomous primary outcome—the proportion of patients dead or dependent after treatment with rtPA (OHS, 0–2; adjusted odds ratio, 1.13; 95% CI, 0.95–1.35). However, the key secondary outcome, assessed by the more statistically efficient ordinal regression analysis, showed clear evidence of a favorable shift in disability scores at both 6 and 18 months,6,11 and the effect of rtPA in IST-3 was similar to previous trials, after accounting for time to randomization.1 We tested the predictions of models constructed with easily measured baseline clinical and simple imaging variables. Future improvements in prediction are only likely if variables that we did not measure, such as advanced imaging methods, genotyping, or blood biomarkers related to the pathophysiology of post-rtPA ICH, better predict response to treatment.

Conclusions

Clinical prediction models were unable to identify patients least likely to be harmed by sICH or those who gained no net benefit from rtPA. These data suggest that intravenous rtPA has an absolute beneficial effect in patients at a high predicted risk of sICH or poor functional outcome.

Sources of Funding

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Disclosures

R.I. Lindley has received payment in his role as conference scientific committee member and for occasional lectures from Boehringer Ingelheim; has attended national stroke meetings organized and funded by Boehringer Ingelheim; and is not a member of any industry advisory boards. P. Sandercock has received lecture fees (paid to the Division of Clinical Neurosciences, University of Edinburgh) and travel expenses from Boehringer Ingelheim for occasional lectures given at international conferences, and was a member of the Independent Data and Safety Monitoring Board (DSMB) of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial funded by Boehringer Ingelheim and received attendance fees and travel expenses for attending DSMB meetings (paid to the Division of Clinical Neurosciences, University of Edinburgh). J. Wardlaw received reimbursement for reading CT scans for European Cooperative Acute Stroke Study III (ECASS III) from Boehringer Ingelheim in the form of funding to her department (the Division of Clinical Neurosciences, University of Edinburgh); has attended meetings held by Boehringer Ingelheim as an unpaid independent external adviser during the licensing of rt-PA, but was refunded for travel expenses and the time away from work; has attended and spoken at national and international stroke meetings organized and funded by Boehringer Ingelheim for which she received honoraria and travel expenses. The other authors have no conflicts to report.

References


Targeting Recombinant Tissue-Type Plasminogen Activator in Acute Ischemic Stroke Based on Risk of Intracranial Hemorrhage or Poor Functional Outcome: An Analysis of the Third International Stroke Trial
William N. Whiteley, Douglas Thompson, Gordon Murray, Geoff Cohen, Richard I. Lindley, Joanna Wardlaw and Peter Sandercock
on behalf of the IST-3 Collaborative Group

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SUPPLEMENTAL MATERIAL

Targeting rtPA in acute ischemic stroke based on risk of intracranial hemorrhage or poor functional outcome: an analysis of the IST-3 trial

Authorship statement

WW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Whiteley, Thompson, Wardlaw, Cohen, Lindley, Murray, Sandercock

Acquisition of data: Whiteley, Wardlaw, Lindley, Sandercock

Analysis and interpretation of data: Whiteley, Thompson, Wardlaw, Cohen, Lindley, Murray, Sandercock

Drafting of the manuscript: Whiteley, Thompson

Critical revision of the manuscript for important intellectual content: Wardlaw, Cohen, Lindley, Murray, Sandercock

Statistical analysis: Thompson, Whiteley, Cohen, Murray

Obtained funding: Sandercock, Lindley, Wardlaw

Study supervision: Whiteley, Wardlaw, Murray, Sandercock
Systematic search for relevant models.

We searched the medical literature from inception to 25th January 2013 for studies which had developed multivariate models for the prediction of intracranial hemorrhage or poor functional outcome after treatment of acute ischemic stroke patients with rtPA. Models were eligible for inclusion if they were developed with a cohort of acute ischemic stroke patients, all of whom had been treated with rtPA, and reported a prediction model either as a score, or a model with constant and weighting for each of the covariates.

We identified studies with an electronic search strategy, reference lists of relevant studies, forward searches from relevant studies with Google Scholar and from our own files. We reviewed titles and abstracts of potentially relevant studies, and extracted models in duplicate from relevant studies.

The literature search identified 797 publications. Of these, 11 studies were relevant, which reported the development of 12 models.

Medline electronic search strategy

1 Cerebrovascular disorders/
2 exp Brain ischemia/
3 Carotid artery diseases/ or Carotid artery thrombosis/
4 stroke/ or exp brain infarction/
5 exp Hypoxia-ischemia, brain/
6 Cerebral arterial diseases/ or Intracranial arterial diseases/
7 exp "Intracranial embolism and thrombosis"/
8 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or transient isch?emic attack$ or tia$).tw.
9 (brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation).tw.
10 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$).tw.
11 9 and 10
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11
13 Thrombolytic therapy/
14 Fibrinolysis/
15 exp plasminogen activators/
16 Fibrinolytic agents/ or Plasmin/ or Plasminogen/
17 (thrombol$ or fibrinoly$ or clot lysis).tw.
18 (plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA).tw.
19 (alteplase).tw.
20 exp "intracranial embolism and thrombosis"/dt or Thromboembolism/dt
21 Thrombosis/dt [Drug Therapy]
22 or/13-21
23 12 and 22
24 randomized controlled trial.pt.
25 randomized controlled trials/
26 controlled clinical trial.pt.
27 controlled clinical trials/
28 random allocation/
29 double-blind method/
30 single-blind method/
31 single-blind method/
32 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
33 placebos/
34 placebo$.tw.
35 random$.tw.
36 research design/
37 clinical trial phase ii.pt.
38 clinical trial phase iii.pt.
39 clinical trial phase iv.pt.
40 multicenter study.pt.
Scores identified by systematic review not assessed in the analysis


Supplementary table I Results of a systematic literature search for models applicable to the IST-3 dataset.

<table>
<thead>
<tr>
<th>Models to predict post rtPA ICH</th>
<th>Models to predict post rtPA poor outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>HAT1</td>
<td>SEDAN1</td>
</tr>
<tr>
<td>NIH5 score</td>
<td>sICH ≥4 NIH5</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>0</td>
</tr>
<tr>
<td>15-19</td>
<td>1</td>
</tr>
<tr>
<td>≥20</td>
<td>2</td>
</tr>
<tr>
<td>Glucose level</td>
<td>&gt;200 or DM</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td>216</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;75</td>
</tr>
<tr>
<td>≥75</td>
<td>1</td>
</tr>
<tr>
<td>CT appearance of</td>
<td>None</td>
</tr>
<tr>
<td>infarct</td>
<td>&lt;1/3 MCA</td>
</tr>
<tr>
<td>≥1/3 MCA</td>
<td>2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>&lt;145</td>
<td></td>
</tr>
<tr>
<td>&gt;145</td>
<td></td>
</tr>
<tr>
<td>Prior hypertension</td>
<td>None</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Use of antiplatelets</td>
<td>Aspirin</td>
</tr>
<tr>
<td>+ clopidogrel</td>
<td>3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>&lt;75</td>
</tr>
<tr>
<td>≥75</td>
<td>1</td>
</tr>
<tr>
<td>Delay to rtPA (mins)</td>
<td>&lt;180</td>
</tr>
<tr>
<td>≥180</td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Asian</td>
</tr>
<tr>
<td>Prior disability</td>
<td>None</td>
</tr>
<tr>
<td>Prestroke mRS</td>
<td>1</td>
</tr>
<tr>
<td>AUROCC in development</td>
<td>0.68 (0.56-0.81)</td>
</tr>
<tr>
<td>AUROCC in external test</td>
<td>0.88 (0.77-0.99)</td>
</tr>
<tr>
<td>AUROCC in external test</td>
<td>0.72 (0.58-0.86)</td>
</tr>
</tbody>
</table>

Per point: 0.077

Total score: 0.125
AUROCC: area under receiver operating characteristic curve; DM: diabetes mellitus; DRAGON: Dense artery, Rankin score, Age, Glucose, Onset to treatment time, NIHSS score; GRASPS: Glucose Race Age Sex Pressure Stroke Severity score; mRS: modified Rankin score; HAT: haemorrhage after thrombolysis score; NIHSS: National Institutes of Health Stroke Scale; NINDS: National Institutes of Neurological Disorders and Stroke; OR: odds ratio; sICH: symptomatic intracranial haemorrhage; SITS: Safe Implementation of Treatments in Stroke; SPAN: Stroke prognostication using age and NIHSS; THRIVE: Totalled Health Risk in Vascular Events
SUPPLEMENTARY TABLE I REFERENCES


Supplementary table II Prediction model for symptomatic ICH in patients treated with rtPA in IST-3. AUROCC=0.65 after correction for optimism (N=1,361).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
<th>β-coefficient (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.00</td>
<td>0.98 to 1.02</td>
<td>0.0004 (0.0096)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.05</td>
<td>1.02 to 1.08</td>
<td>0.0456 (0.0144)</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>1.00</td>
<td>1.00 to 1.01</td>
<td>0.0040 (0.0021)</td>
</tr>
<tr>
<td>Prior Hypertension</td>
<td>0.96</td>
<td>0.65 to 1.41</td>
<td>-0.0418 (0.1964)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.74</td>
<td>0.50 to 1.09</td>
<td>-0.3061 (0.2007)</td>
</tr>
<tr>
<td>Visible infarct on CT</td>
<td>1.20</td>
<td>0.83 to 1.75</td>
<td>0.1861 (0.1907)</td>
</tr>
<tr>
<td>Anti-platelet</td>
<td>1.62</td>
<td>1.12 to 2.37</td>
<td>0.4853 (0.1917)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.07</td>
<td>0.67 to 1.70</td>
<td>0.0645 (0.2367)</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>1.16</td>
<td>0.79 to 1.69</td>
<td>0.1465 (0.1935)</td>
</tr>
<tr>
<td>Intercept</td>
<td>-</td>
<td>-</td>
<td>-4.2071 (0.7977)</td>
</tr>
</tbody>
</table>
Supplementary table III. Metrics of model performance when predicting sICH outcome defined as ‘parenchymal haemorrhage’ by each of the nine models identified through systematic review and the model developed in rt-PA treated IST3 patients.

<table>
<thead>
<tr>
<th>Model</th>
<th>Score</th>
<th>n/N</th>
<th>$R^2$ (%)</th>
<th>AUROCC</th>
<th>AUROCC 95% CI</th>
<th>Calibration</th>
<th>Intercept</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAT</td>
<td>0 to 5</td>
<td>116/1365</td>
<td>3.70</td>
<td>0.63</td>
<td>0.58 to 0.69</td>
<td>0.08</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>SEDAN</td>
<td>0 to 7</td>
<td>116/1365</td>
<td>4.02</td>
<td>0.63</td>
<td>0.58 to 0.68</td>
<td>-0.14</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>SITS</td>
<td>0 to 11</td>
<td>114/1357</td>
<td>2.84</td>
<td>0.60</td>
<td>0.55 to 0.65</td>
<td>1.31</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>GRASPS</td>
<td>45 to 101</td>
<td>116/1365</td>
<td>3.21</td>
<td>0.63</td>
<td>0.58 to 0.68</td>
<td>0.60</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>SPAN-100$^1$</td>
<td>0 to 1</td>
<td>133/1507</td>
<td>1.10</td>
<td>0.56</td>
<td>0.51 to 0.60</td>
<td>-1.04</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>STROKE TPI</td>
<td>GLM</td>
<td>116/1365</td>
<td>3.97</td>
<td>0.64</td>
<td>0.59 to 0.69</td>
<td>-1.37</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>DRAGON</td>
<td>0 to 10</td>
<td>116/1363</td>
<td>5.18</td>
<td>0.66</td>
<td>0.61 to 0.70</td>
<td>-3.35</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>THRIVE</td>
<td>0 to 9</td>
<td>132/1504</td>
<td>2.63</td>
<td>0.62</td>
<td>0.57 to 0.67</td>
<td>-3.21</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>NIHSS/age</td>
<td>GLM</td>
<td>133/1507</td>
<td>3.96</td>
<td>0.64</td>
<td>0.59 to 0.69</td>
<td>-4.11</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>IST3 model</td>
<td>GLM</td>
<td>115/1361</td>
<td>5.37</td>
<td>0.66</td>
<td>0.61 to 0.71</td>
<td>0.33</td>
<td>1.11</td>
<td></td>
</tr>
</tbody>
</table>