THRI VE Score Predicts Ischemic Stroke Outcomes and Thrombolytic Hemorrhage Risk in VISTA

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Background and Purpose—In previous studies, the Totaled Health Risks in Vascular Events (THRI VE) score has shown broad utility, allowing prediction of clinical outcome, death, and risk of hemorrhage after tissue-type plasminogen activator (tPA) treatment, irrespective of the type of acute stroke therapy applied to the patient.

Methods—We used data from the Virtual International Stroke Trials Archive to further validate the THRI VE score in a large cohort of patients receiving tPA or no acute treatment, to confirm the relationship between THRI VE and hemorrhage after tPA, and to compare the THRI VE score with several other available outcome prediction scores.

Results—The THRI VE score strongly predicts clinical outcome (odds ratio, 0.55 for good outcome [95% CI, 0.53–0.57]; P<0.001), mortality (odds ratio, 1.57 [95% confidence interval, 1.50–1.64]; P<0.001), and risk of intracerebral hemorrhage after tPA (odds ratio, 1.34 [95% confidence interval, 1.22–1.46]; P<0.001). The relationship between THRI VE score and outcome is not influenced by the independent relationship of tPA administration and outcome. In receiver operator characteristic curve analysis, the THRI VE score was superior to several other available outcome prediction scores in the prediction of clinical outcome and mortality.

Conclusions—The THRI VE score is a simple-to-use tool to predict clinical outcome, mortality, and risk of hemorrhage after thrombolysis in patients with ischemic stroke. Despite its simplicity, the THRI VE score performs better than several other outcome prediction tools. A free Web calculator for the THRI VE score is available at http://www.thrivescore.org.

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Key Words: cerebral hemorrhage ■ forecasting ■ outcome assessment ■ stroke

Several ischemic stroke outcome prediction scores have been published in the past several years that predict ischemic stroke outcomes (eg, functional outcome, mortality, and risk of hemorrhage after tissue-type plasminogen activator [tPA] administration) in various clinical contexts (tPA administration, endovascular stroke treatment [EST], or no acute stroke treatment).1–11

The Totaled Health Risks in Vascular Events (THRI VE) score was initially developed9 and validated10 in the context of EST. We then found that THRI VE seems to work equally well to predict clinical outcome in patients receiving tPA or no acute stroke treatment using data from the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial.11 In the NINDS trial, THRI VE was also found to predict the risk of symptomatic intracerebral hemorrhage after tPA.11

Here, we further examine the use of THRI VE score using >5000 patients enrolled in clinical trials collected in the Virtual International Stroke Trials Archive (VISTA).12 First, we examine the relationship between THRI VE and functional outcome, mortality, and risk of hemorrhage after tPA. Second, we compare the performance of the THRI VE score to other clinical prediction scores.

Methods

Data Source and Subjects

We obtained demographic, clinical data, 3-month functional outcomes on the modified Rankin Scale (mRS), and 3-month mortality from the VISTA repository of controlled stroke trials results.12 VISTA (http://www.vista.gla.ac.uk) is an anonymized data repository of 34 acute stroke clinical trials.12 All included trials were performed under appropriate institutional review board and regulatory approvals, and only fully anonymized data are held by VISTA. We included acute stroke trials in VISTA with available data on THRI VE components and outcomes, with the exception of the NINDS tPA trial, as we have validated previously the THRI VE score in this data set. Patients were
included for the present analysis if necessary data were available to compute the THRIVE score, if data were available on functional outcome on the mRS at 3 months, or data were available on mortality by 3 months. On the basis of these criteria, data were available from a total of 5419 subjects with mRS data and 5724 subjects with mortality data. Subjects who died within 3 months were coded as a 6 on the 0- to 6-point 3-month mRS.

**Measurements**

To calculate each patient’s THRIVE score, we noted his or her age, initial stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS) score, and the presence or absence of hypertension, diabetes mellitus (DM), or atrial fibrillation (AF). The THRIVE score assigns 1 point for 60 to 79 years of age, 2 points for ≥80 years of age, 2 points for NIHSS score 11 to 20, 4 points for NIHSS score ≥21, and 1 point each for hypertension, DM, and AF.7 Other clinical prediction scores (Houston Intra-Arterial Therapy [HIAT] score, HIAT-2, Hemorrhage After Thrombolysis [HAT], Stroke Prognostification using Age and NIH stroke scale [SPAN-100]) were calculated as follows: HIAT assigns 1 point each for ≥75 years of age, NIHSS ≥18, and glucose ≥150 mg/dL.7 HIAT-2 assigns 2 points for 60 to 79 years of age, 4 points for ≥80 years of age, 1 point for NIHSS score 11 to 20, 2 points for NIHSS score ≥21, and 3 points for Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ≤7.8 The HAT score assigns 1 point for the presence of either DM or glucose ≥200 mg/dL, 1 point for NIHSS score 15 to 20, 2 points for NIHSS ≥21, 1 point for ASPECTS 7 to 9, and 2 points for ASPECTS ≤7.6 The SPAN-100 is a single-point score; the score is positive if the sum of the patient’s age plus NIHSS is ≥100.3

Our outcome measures were functional outcome on the mRS at 3 months (cut between a score of 2 and 3, such that good outcome is 0–2 and poor outcome is 3–6), mortality by 3 months, and hemorrhage within 72 hours of stroke onset among patients treated with tPA. Hemorrhage after tPA administration was defined in the present analysis as parenchymal hematoma type 2 within 72 hours of stroke onset or the presence of a symptomatic intracerebral hemorrhage with 72 hours recorded in the significant adverse event table of the trial.

**Statistical Analysis**

We analyzed categorical data in contingency tables with the Fisher exact test and continuous data with the nonparametric Kruskal–Wallis equality-of-populations rank test. Logistic regression was performed using standard techniques to model good outcome (mRS 0–2). Model fit was determined by calculating Pseudo $R^2$ and receiver operator characteristic (ROC) area under the curve (AUC). ROC curves were constructed by plotting test sensitivity against (1-specificity). We compared pairwise score discrimination for 3-month outcomes by comparing the AUC for ROC curves using the $χ^2$ statistic. In cases in which a particular score could only be calculated for a subset of patients in the total data set, only that subset of patients was used to perform the pairwise ROC curve comparison. Statistical analysis was performed with Stata/MP (Version 12.1, StataCorp; College Station, TX).

**Results**

**Patient Characteristics**

Patient characteristics are summarized in Table 1, which displays patient age, NIHSS, comorbidities (hypertension, DM, and AF), and clinical prediction scores (THRIVE, HIAT, HIAT-2, HAT, and SPAN-100) according to administration or nonadministration of tPA.

**THRIVE Score and Clinical Outcomes in VISTA**

Increasing THRIVE score strongly predicts a decreasing chance of good outcome (mRS of 0–2 at 3 months; Figure 1A) in VISTA. In logistic regression, each 1-point increase in THRIVE score is associated with an odds ratio of 0.55 for good outcome at 3 months (95% confidence interval [CI], 0.53–0.57; $P<0.001$). Increasing THRIVE score also predicts an increased chance of death by 3 months (Figure 1B) in VISTA. Each 1-point increase in THRIVE score is associated with a 1.57 odds ratio for death by 3 months (95% CI, 1.50–1.64; $P<0.001$). The relationship of the continuous THRIVE score to good outcome (mRS, 0–2), death, and mean mRS is shown in Figure 1 in the online-only Data Supplement.

As we have found previously in several data sets,8–11 when the chronic disease scale (reflecting the medical comorbidities of hypertension, DM, and AF) is added to age and NIHSS, all 3 components are independent predictors of good outcome in multivariable logistic regression, and model fit is improved (Table 2).

**THRIVE Score and tPA Treatment in VISTA**

In the NINDS trial, THRIVE score and tPA administration were found to each be independent predictors of outcome without statistical interaction.11 In other words, administration of tPA did not alter the relationship between THRIVE score and outcome, and THRIVE score did not alter the relationship between tPA administration and outcome. We found a similar independence and lack of interaction between THRIVE score and tPA administration in the prediction of good outcome using multivariable logistic regression in VISTA (Table 3).

**THRIVE Score and Risk of Thrombolytic Hemorrhage in VISTA**

The relationship between THRIVE score and risk of hemorrhage after thrombolysis with intravenous tPA was confirmed in VISTA: increasing THRIVE score predicted increased risk of parenchymal hemorrhage type 2 or significant adverse events-hemorrhage in the VISTA trials (Figure 1C). In logistic regression, each 1-point increase in THRIVE score was associated with an odds ratio of 1.29 for hemorrhage after...
intravenous tPA (95% CI, 1.16–1.43; P<0.001). The THRIVE prediction of intracerebral hemorrhage (ICH) risk after intravenous tPA did not explain the prediction of good outcome; addition of ICH after intravenous tPA to multivariable logistic regression did not alter the THRIVE odds ratio for good outcome among patients treated with tPA (odds ratio, 0.56 [95% CI, 0.53–0.60] without ICH; 0.56 [95% CI, 0.52–0.60] with ICH added to the model).

**ROC Curve Analysis Comparing THRIVE With Other Outcome Prediction Scores**

To better understand the relative use of available ischemic stroke outcome prediction scores, we used ROC curve analysis to compare the THRIVE score with other scores for which sufficient data were available in the VISTA-Acute data set (HIAT, HIAT-2, HAT, and SPAN-100).

The ROC curve for the THRIVE score had a significantly greater AUC than other clinical outcome prediction tools (HIAT, HIAT-2, and SPAN-100) in the prediction of both poor outcome and death (Figure 2A and 2B). For prediction of poor outcome at 3 months (mRS, 3–6), the THRIVE ROC AUC was 0.756 compared with 0.686 for HIAT (P<0.001; n=5118), the THRIVE ROC AUC was 0.744 compared with 0.709 for HIAT-2 (P<0.001; n=2603), and the THRIVE ROC AUC was 0.755 compared with 0.566 for SPAN-100 (P<0.001; n=5419). For the dichotomous SPAN-100 measure, the ROC plot is represented by a single point (Figure 2; n=574 of 5724 [10%] were SPAN-100 positive).

For prediction of death by 3 months, the THRIVE ROC AUC was 0.721 compared with 0.694 for HIAT (P=0.003; n=5390), the THRIVE ROC AUC was 0.699 compared with 0.665 for HIAT-2 (P<0.001; n=2822), and the THRIVE ROC AUC was 0.718 compared with 0.596 for SPAN-100 (P=0.003; n=5724).

The ROC curve for the THRIVE score was comparable with the ROC curve for a score designed to specifically predict intracerebral hemorrhage after tPA administration (Figure 2C; n=1784). Post-tPA hemorrhage was defined here as parenchymal hematoma type 2 (PH-2) or significant adverse event-hemorrhage (SAE-H) within 72 hours of stroke onset among patients treated with intravenous tPA.

**Table 2. THRIVE Score Components and Outcome**

<table>
<thead>
<tr>
<th>Model 1: good outcome</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.47</td>
<td>0.43–0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.23</td>
<td>0.21–0.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 3. Independence of THRIVE Score and tPA Effect**

<table>
<thead>
<tr>
<th>Model 1: good outcome (among patients not treated with tPA)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>THRIVE</td>
<td>0.53</td>
<td>0.51–0.56</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

In models 1 and 2, THRIVE score predicts good outcome, stratified on tPA administration. Model 1 includes only patients not treated with tPA and model 2 includes only patients treated with tPA. In models 3 and 4, all patients are included. THRIVE and tPA are each independent predictors of good outcome (model 4), and addition of tPA to the model does not alter the relationship of THRIVE score and outcome (model 3 compared with model 4). CI indicates confidence interval; THRIVE, Totaled Health Risks in Vascular Events; and tPA, tissue-type plasminogen activator.
hemorrhagic risk, the HAT score, and superior to the SPAN-100 (Figure 2C). For the prediction of ICH (parenchymal hemorrhage type 2 or significant adverse events-hemorrhage) after tPA, the THRIVE ROC AUC was 0.633 compared with 0.602 for the HAT score ($P=0.08; n=1708$), and the THRIVE ROC AUC was 0.653 compared with 0.534 for the SPAN-100 score ($P<0.001; n=1784$).

**Discussion**

We find that the THRIVE score strongly predicts clinical outcome, mortality, and risk of hemorrhage after thrombolysis in an analysis of 5724 subjects from VISTA. **THRIVE** was found to be superior to other clinical prediction scores (HIAT, HIAT-2, HAT, and SPAN-100) in several direct comparisons using ROC curve analysis.

The THRIVE score has been validated with similar performance in the 3 main acute ischemic stroke treatment contexts: intravenous tPA treatment, EST, and no acute stroke treatment. In addition, the THRIVE score has been found to predict outcomes independent of recanalization therapy (intravenous tPA or EST); there is no statistical interaction between THRIVE and recanalization therapy in the prediction of outcomes. In other words, THRIVE strongly predicts outcomes, and recanalization strongly influences outcomes, but the relationship between THRIVE and outcome does not influence the relationship between recanalization and outcome.

The relative impact of recanalization therapy is the same at a high THRIVE score and a low THRIVE score, but the overall chances of a good outcome will be separately influenced by both THRIVE and recanalization therapy. This consistent lack of interaction between THRIVE and recanalization therapy may result from THRIVE representing a set of nonmodifiable predictors of outcome (age, clinical stroke severity, and medical comorbidities [hypertension, DM, and AF]).

We find 1 major difference in the performance of THRIVE in the context of non-EST (intravenous tPA or no acute treatment) patients versus EST patients: THRIVE strongly predicts risk of ICH after intravenous tPA, but we have not found a clear relationship between THRIVE and risk of ICH after EST with the Merci or Trevo devices. This difference may be because of smaller sample sizes in the EST data sets we have analyzed, but it is also possible that the biological determinants of ICH with EST are dissimilar from those that predict ICH after intravenous tPA.

The THRIVE score has certain advantages over more recently developed ischemic stroke prediction scores. The THRIVE score is simple to calculate because it is based on clinical factors known to the clinician immediately on the patient’s presentation and it does not require high-level neuroimaging techniques or laboratory testing. Scores such as the iScore and Acute Stroke Registry and Analysis of Lausanne (ASTRAL) are more complex; they yield a much broader range of possible scores but require more effort on the part of the clinician, such as entering laboratory values and examination findings beyond the standard NIHSS. Some scores, such as HIAT-2 and hyperDense MCA, Rankin, Age, Glucose, OTT, NIHSS (DRAGON) score, require interpretation of neuroimaging findings such as the ASPECTS score.

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**Figure 2.** Comparison of Totaled Health Risks in Vascular Events (THRIVE) to other outcome prediction scores by receiver operator characteristic (ROC) curve analysis. **A**, ROC curves for score prediction of good outcome at 3 months (modified Rankin Scale [mRS], 0–2), comparing THRIVE, HIAT, HIAT-2, and SPAN-100. Higher area under the curve (AUC) values in ROC analysis indicate better discrimination of the score for the measured outcome. SPAN-100 is represented by a single point because it is a dichotomous predictor. **B**, ROC curves for score prediction of death by 3 months (mRS, 0–2), comparing THRIVE, HAT, HIAT-2, and SPAN-100. **C**, ROC curves for score prediction of death by 3 months (mRS, 0–2), comparing THRIVE, HAT, and SPAN-100 (HIAT and HIAT-2 are not presented here because they have not been associated previously with risk of hemorrhage after tissue-type plasminogen activator [tPA]).
in HIAT-2 and the hyperdense artery sign and early infarct signs in DRAGON. The complexity of scores such as iScore, ASTRAL, and DRAGON prevented us from directly comparing THRIVE to these scores in the present study because all components of these scores were not available in the present VISTA data set.

Other predictive scores are extremely simple, such as the SPAN-100, which requires the least effort on the part of the clinician (SPAN-100 is obtained by adding age and NIHSS and is positive if the sum is ≥100), but as a result, it displays very low sensitivity: it only allows a clinician to identify a very small percentage of older patients with larger strokes that have a poor chance of outcomes (only 10% of patients in the present VISTA data set were SPAN-100 positive), thus missing a significant proportion of patients with poor outcomes. Another prediction tool also based on age and NIHSS was previously tested in VISTA, but, unlike SPAN-100, requires the use of a nomographic tool to predict outcome.

The THRIVE score is an easy-to-use prediction score to assess poststroke functional outcome, mortality, and risk of hemorrhage after intravenous tPA. THRIVE has been validated across the full range of acute stroke treatment contexts, including treatment with intravenous tPA, no acute treatment, and EST. The THRIVE score performs favorably when compared with other outcome prediction scores, and the THRIVE score is in the public domain (Creative Commons license: free Web calculators are provided at http://www.thrive-score.org and http://www.mdcalc.com/thrive-score-for-stroke-outcome/).

Appendix


Disclosures

Data were transmitted in anonymized form from VISTA to Dr Flint, who designed the present study and performed all statistical analyses. He was a member of the TREVO-2 Clinical Events Committee. Dr Kamel has served on speakers’ bureaus and scientific advisory boards for Genentech. Dr Bath is a member of the VISTA Executive Committee. Dr Donnan has served on scientific advisory boards for Boehringer Ingelheim, Sanofi, Bayer, Pfizer, and Amgen. The other authors report no conflicts.

References

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Supplementary Figure I: Continuous THRIVE score and outcomes
A. Percentage of patients with a good outcome (mRS 0-2) at 3 months at each level of the THRIVE score. Because only a very small number of patients in VISTA have a THRIVE score of 9 (n=21, 0.37% of the total), THRIVE levels of 8 and 9 were combined for graphical display.
B. Percentage of patients dead by 3 months at each level of the THRIVE score.
C. Mean (+ standard deviation [S.D.]) mRS at each level of the THRIVE score.
Supplemental Figure II:
A. Relationship between trichotomized THRIVE score (0-2 vs. 3-5 vs. 6-9) and good outcome as defined as a modified Rankin Scale (mRS) of 0 to 1 at 90 days.
B. Relationship between continuous THRIVE score and good outcome as defined as mRS of 0 to 1 at 90 days.