The THRIVE score predicts symptomatic intracerebral hemorrhage after intravenous tPA administration in SITS-MOST

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Background The Totaled Health Risks in Vascular Events (THRIVE) score is a clinical prediction score that predicts ischemic stroke outcomes in patients receiving intravenous tissue plasminogen activator, endovascular stroke treatment, or no acute therapy. We have previously found an association between THRIVE and risk of post-tissue plasminogen activator symptomatic intracranial hemorrhage in the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator trial and risk of radiographic hemorrhage in Virtual International Stroke Trials Archive.

Aims The study aims to validate the relationship between THRIVE and symptomatic intracranial hemorrhage among tissue plasminogen activator-treated patients in the large Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST).

Methods This is a retrospective analysis of the prospective SITS-MOST to examine the relationship between THRIVE and symptomatic intracranial hemorrhage after tissue plasminogen activator treatment. Symptomatic intracranial hemorrhage was defined according to each of three standard definitions: the NINDS, European Cooperative Acute Stroke Study (ECASS), and Safe Implementation of Thrombolysis in Stroke (SITS) criteria. Multivariable logistic regression was used to confirm the relationship of THRIVE and individual THRIVE components with the risk of symptomatic intracranial hemorrhage and to examine the relationship of THRIVE, symptomatic intracranial hemorrhage, and functional outcome.

Results The odds ratio for symptomatic intracranial hemorrhage at each increased level of THRIVE score is 1.34 (95% CI 1.27 to 1.41, P < 0.001) for symptomatic intracranial hemorrhage by NINDS criteria, 1.36 (95% CI 1.27 to 1.46, P < 0.001) for symptomatic intracranial hemorrhage by ECASS criteria, and 1.21 (95% CI 1.09 to 1.36, P < 0.001) for symptomatic intracranial hemorrhage by SITS criteria. In receiver-operator characteristics analysis, the C-statistic for THRIVE prediction of symptomatic intracranial hemorrhage was 0.65 (95% CI 0.62 to 0.67) for symptomatic intracranial hemorrhage by NINDS criteria, 0.66 (95% CI 0.63 to 0.69) for symptomatic intracranial hemorrhage by ECASS criteria, and 0.61 (95% CI 0.56 to 0.66) for symptomatic intracranial hemorrhage by SITS criteria. Each component of the THRIVE score predicts the risk of symptomatic intracranial hemorrhage, with independent impact of each component in multivariable analysis.

Conclusions The THRIVE score predicts the risk of symptomatic intracranial hemorrhage after intravenous tissue plasminogen activator administration. This external validation of the relationship between THRIVE and symptomatic intracranial hemorrhage in a prospective study further strengthens the role of the THRIVE score in the prediction of poststroke outcomes.

Key words: acute stroke therapy, cerebral infarction, intracerebral hemorrhage, ischemic stroke, rtPA, treatment

Introduction

The Totaled Health Risks in Vascular Events (THRIVE) score is a simple-to-use outcome prediction score for ischemic stroke that is based on clinical variables available at the time of stroke presentation [National Institutes of Health Stroke Scale (NIHSS), age, and presence of hypertension (HTN), diabetes mellitus (DM), or atrial fibrillation (AF)]. The THRIVE score was developed with data from the MERCI and Multi-MERCI trials (1) and has subsequently been validated with data from the Merci Registry (2), the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trial (3), Virtual International Stroke Trials Archive (VISTA) (4), and the TREVO-2 trial (5). Across all validation cohorts, increased THRIVE score strongly predicts decreased chance of good outcome [modified Rankin Scale (mRS) 0–2] and increased chance of death by 90 days (2–5).

Among patients receiving intravenous (i.v.) tPA in the NINDS trial (3) and VISTA (4), we also found that THRIVE predicts the risk of hemorrhage in the first 48 h after tPA administration. Among patients randomized to i.v. tPA in NINDS (n = 312), THRIVE predicted an increased risk of symptomatic intracranial hemorrhage (sICH) (3). Among tPA-treated patients in VISTA (n = 2398), THRIVE predicted an increased risk of parenchymal hemorrhage type 2 (PH2)-type ICH or a finding of significant adverse event related to intracranial bleeding (4), but data on
sICH after tPA were not available in the VISTA cohort used for this analysis.

Here, we use data from the Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST) (6), a large, prospective, multicenter European study of tPA-treated patients, to validate the relationship between THRIVE score and sICH, and to explore the relationship between THRIVE and the three established definitions of sICH [using NINDS, European Cooperative Acute Stroke Study (ECASS), and Safe Implementation of Thrombolysis in Stroke (SITS) criteria].

Aims

We sought to validate the relationship between THRIVE and sICH among tPA-treated patients in the large SITS-MOST study.

Methods

Data source and subjects

We obtained demographic data, clinical data, rates of sICH on follow-up computed tomography (CT), three-month functional outcome on the mRS, and three-month mortality from the SITS-MOST study (n = 6483) (6). SITS-MOST was an open-label, post-market study of tPA administration within three-hours of ischemic stroke onset, performed in 285 centers across 14 European countries (6). Institutional review board and regulatory approvals for the SITS-MOST study were obtained from the Karolinska Institute in Stockholm, Sweden, and from participating centers, where required (6). For the present analysis, deidentified SITS-MOST data were transmitted to the investigators via the VISTA-plus (7).

Measurements

The THRIVE score was calculated from age, initial stroke severity on the NIHSS score, and the presence or absence of HTN, DM, or AF. The THRIVE score assigns 1 point for age 60–79 years, 2 points for age ≥80 years, 2 points for NIHSS score 11–20, 4 points for NIHSS score ≥21, and 1 point each for HTN, DM, and AF.

Our primary outcome measure was sICH on follow-up CT performed at 22–36 h after stroke onset, a co-primary outcome in the original SITS-MOST study (6). We applied standard definitions of sICH, according to the NINDS, ECASS, and SITS criteria. The NINDS criteria for sICH is any hemorrhage together with an increase by 1 point or more in the NIHSS or hemorrhage leading to death within seven-days (8,9). The ECASS criteria for sICH is any hemorrhage together with an increase by 4 points or more in the NIHSS or hemorrhage leading to death (8,9). The SITS criteria for sICH is PH-2 together with an increase by 4 points or more in the NIHSS or hemorrhage leading to death (6). sICH adjudication according to each of the three criteria was performed in the SITS-MOST study as previously described (6).

Secondary outcome measures were functional outcome on the mRS at three-months (with good outcome defined as mRS = 0–2) and mortality by three-months.

Statistical analysis

Categorical data in contingency tables were analyzed with the Fisher’s exact test and the Mantel–Haenszel chi-square test for trend. Multivariable logistic regression was performed using standard techniques to model sICH. To clarify the relationship between THRIVE score, sICH, and outcome, we performed mediation analysis using seemingly unrelated bivariate probit regression. Receiver-operator characteristics (ROC) curves were constructed and analyzed as previously described (4). Patients with missing data on THRIVE components or outcomes were excluded from analysis. All statistical analyses were performed using Stata MP version 12.1 (Stata Corp., College Station, TX, USA).

Results

Patient characteristics

Table 1 shows baseline characteristics of the subjects enrolled in the SITS-MOST study as well as overall outcomes (sICH, good outcome at 90 days, and death by 90 days).

THRIVE score and risk of sICH

Higher trichotomized THRIVE scores are associated with a higher rate of sICH by all three definitions of sICH (NINDS, ECASS, and SITS). The relationship between trichotomized THRIVE score and sICH by each definition is shown in Fig. 1. The odds ratio for sICH for each increased level of trichotomized THRIVE score is 2.09 (95% CI 1.79 to 2.43, Mantel–Haenszel chi-square test for trend). Multivariable logistic regression was performed using standard techniques to model sICH. To clarify the relationship between THRIVE score, sICH, and outcome, we performed mediation analysis using seemingly unrelated bivariate probit regression. Receiver-operator characteristics (ROC) curves were constructed and analyzed as previously described (4). Patients with missing data on THRIVE components or outcomes were excluded from analysis. All statistical analyses were performed using Stata MP version 12.1 (Stata Corp., College Station, TX, USA).

Table 1 Patient characteristics and outcomes in SITS-MOST

<table>
<thead>
<tr>
<th></th>
<th>SITS-MOST Study (n = 6483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.6 ± 11.5</td>
</tr>
<tr>
<td>Female</td>
<td>39.8% (1507/6483)</td>
</tr>
<tr>
<td>HTN</td>
<td>58.7% (2608/6318)</td>
</tr>
<tr>
<td>DM</td>
<td>16% (1020/6374)</td>
</tr>
<tr>
<td>AF</td>
<td>23.9% (1507/6306)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>12 (8–17)</td>
</tr>
<tr>
<td>THRIVE score</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>CDS</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>SPAN-100</td>
<td>2.1% (136/6338)</td>
</tr>
<tr>
<td>sICH (NINDS)</td>
<td>7.3% (468/65970)</td>
</tr>
<tr>
<td>sICH (ECASS)</td>
<td>4.6% (296/6146)</td>
</tr>
<tr>
<td>sICH (SITS)</td>
<td>1.7% (107/6337)</td>
</tr>
<tr>
<td>mRS 0–2 at 90 days</td>
<td>54.8% (3362/6136)</td>
</tr>
<tr>
<td>Death by 90 days</td>
<td>11.3% (701/5517)</td>
</tr>
</tbody>
</table>

Age is presented as mean ± SD. NIHSS and other ordinal scores are presented as median (interquartile range). Dichotomous values (comorbidities and female gender) are presented as % (number out of total). Denominators for comorbidities vary because of missing information for some subjects; THRIVE score analyses required complete information for all THRIVE components (n = 6085). AF, atrial fibrillation; CDS, chronic disease scale; DM, diabetes mellitus; ECASS, European Cooperative Acute Stroke Study; HTN, hypertension; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; sICH, symptomatic intracranial hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke – Monitoring Study; THRIVE, Totaled Health Risks in Vascular Events.
Similarly, continuous THRIVE score predicts sICH risk, as shown in Fig. 2. The odds ratio for sICH for each increased level of THRIVE score is 1.34 (95% CI 1.27 to 1.41, P < 0.001) for NINDS sICH, 1.36 (95% CI 1.27 to 1.46, P < 0.001) for ECASS sICH, and 1.21 (95% CI 1.09 to 1.36, P < 0.001) for SITS-MOST sICH.

In ROC analysis, the C-statistic (the area under the ROC curve) for THRIVE prediction of sICH was 0.65 (95% CI 0.62 to 0.67) for sICH by NINDS criteria, 0.66 (95% CI 0.63 to 0.69) for sICH by ECASS criteria, and 0.61 (95% CI 0.56 to 0.66) for sICH by SITS criteria.

**THRIVE components and risk of sICH**

Each component of the THRIVE score [trichotomized NIHSS, trichotomized age, and chronic disease scale (CDS; 1 point each for HTN, DM, and AF)] predicts sICH risk in SITS-MOST. Figure 3 shows an increased risk of sICH (as defined by NINDS criteria) as NIHSS, age, or CDS increase. When CDS is added to NIHSS and age in a multivariable logistic regression model of sICH (as defined by NINDS criteria), each factor is an independent predictor of sICH and model fit is improved (Table 2). Similar results are obtained with the other two definitions of sICH (ECASS and SITS, data not shown).

**THRIVE score and clinical outcomes in SITS-MOST**

As we have found in other cohorts of patients treated with i.v. tPA (3,4), the THRIVE score in SITS-MOST also strongly predicts a reduced chance of good outcome (mRS 0–2) and increased chance of death by 90 days (Fig. S1).

THRIVE and sICH each predict outcome at 90 days independently. When sICH (by each of the three criteria) is added to THRIVE score in a model predicting good outcome, THRIVE and sICH independently predict worsened chance of good outcome (Table 3). Because sICH negatively influences outcomes only for the small minority of tPA-treated patients in whom this complication occurs, the strength of the relationship between THRIVE and outcome is only modestly reduced by the addition of sICH to these models (Table 3). Consistent with this observation, mediation analysis using seemingly unrelated bivariate probit regression (modeling the direct relationship of THRIVE and outcome and the potential indirect relationship of THRIVE with outcome by way of sICH-NINDS) showed that the coefficient of the direct effect between THRIVE and outcome (−0.315) is not substantially altered when compared with the coefficient for the relationship between THRIVE and outcome in single-equation...
probit regression ($-0.320$). Similar results were obtained using the alternate definitions of sICH (data not shown). The minimal impact of sICH as a potential mediator appears to be in part due to the infrequent occurrence of this complication and in part due to the strong direct relationship between THRIVE and outcome.

**Discussion**

Here, we show that the THRIVE score predicts sICH after i.v. tPA administration in the large, prospective SITS-MOST study, across three accepted definitions of sICH (NINDS, ECASS, and SITS criteria).

The THRIVE score has been found to predict functional outcome and mortality in all three acute ischemic stroke treatment contexts: i.v. tPA treatment (3,4), endovascular stroke treatment (1,2,5), and no acute stroke treatment (3,4). Previous analyses also found that THRIVE predicts risk of thrombolytic hemorrhage in the NINDS tPA trial (3) and in the VISTA (4). In the NINDS data set, THRIVE score predicted sICH after tPA, but the number of tPA-treated patients was small ($n=312$) (3). In VISTA, THRIVE predicted PH2 on CT or significant adverse hemorrhage events after tPA administration in a much larger cohort of tPA-treated patients ($n=2398$), but data regarding sICH (the combination of clinical worsening and radiographic hemorrhage) were not available (4). Therefore, the present analysis serves as external validation of the specific relationship between THRIVE score and sICH determined from clinical and radiographic end-points.

Several predictive scores have been previously developed to predict the risk of thrombolytic hemorrhage, including the

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**Fig. 2** Continuous THRIVE score and risk of sICH. Increased risk of sICH according to three different definitions of sICH (NINDS sICH (a), ECASS sICH (b), and SITS sICH (c)) across the range of the THRIVE score. % sICH is pooled for THRIVE scores of 7, 8, and 9 because of the small number of subjects at THRIVE = 8 ($n=41$) and THRIVE = 9 ($n=5$). Open circles represent % with sICH at each level, and error bars represent ± 95% CIs for the point estimate. ECASS, European Cooperative Acute Stroke Study; NINDS, National Institute of Neurological Disorders and Stroke; sICH, symptomatic intracranial hemorrhage; SITS, Safe Implementation of Thrombolysis in Stroke; THRIVE, Totaled Health Risks in Vascular Events.
Hemorrhage After Thrombolysis (HAT) score (11), the Safe Implementation of Thrombolysis in Stroke-SICH (SITS-SICH) score (12), the Glucose Race Age Sex Pressure Stroke severity (GRASPS) score (13), and the Multicentre Stroke Survey score (14). Other predictive scores have been developed that predict both poststroke clinical outcomes and risk of hemorrhage after thrombolysis, including the iScore (15), the Early infarct signs and hyperDense cerebral artery sign Age and NIHSS (SEDAN) score (16), and the Stroke Prognostication using Age and NIHSS (SPAN-100) score (17). Other post-tPA hemorrhage prediction scores have been compared in external cohorts and have similar performance (with the exception of poorer discrimination by the dichotomous SPAN-100 score) (18,19). Although a direct comparison of scores was not a goal of the present study, the C-statistics for THRIVE predicting sICH reported here are comparable with the C-statistics for the SITS-SICH score in the broader SITS-ISTR cohort (12).

For a stroke prediction score to be useful in providing information to patients and families, the score should ideally be based on readily available data at the time of clinical presentation and not require special expertise beyond the scope of the typical primary stroke center (18). The HAT score (11) and the SEDAN score (16) both incorporate early change on noncontrast CT, and the SEDAN score additionally incorporates the presence or absence of a hyperdense artery sign (16). These radiographic elements may require expertise beyond the typical capabilities of primary stroke centers (18). Several predictive scores, including the HAT score (11), Multicentre Stroke Survey score (14), GRASPS score (13), and iScore (15), require knowledge of laboratory results that may not be available at the time of thrombolytic decision-making, particularly in light of recent protocols to reduce door-to-needle times in tPA administration (20,21). Other scores, including SITS-SICH (12), factor in time from onset to thrombolysis, which is by definition not known at the time that tPA decision-making is taking place (although one might reasonably estimate time to treatment in calculating such a score). Score complexity is another important factor in determining clinical utility: more complex scores with more than 10 input variables such as iScore (15) and SITS-SICH (12) may be more challenging to determine at the bedside during acute stroke decision-making. On the other end of the spectrum, the SPAN-100 (17) is an easily computed dichotomous score, but it only serves to identify a very small group of patients [only 10% of patients in our VISTA analysis were SPAN-100 positive (4), and only 2% of patients in SITS-MOST were SPAN-100 positive].

The THRIVE score may be useful to provide information to patients and families about overall prognosis and the risks of treatment, but it is critical to recognize the limitations of this or any other clinical prediction score. First, there is no evidence that patients with higher THRIVE scores would not benefit from tPA. Even in the face of an increased short-term risk of sICH, the net impact of tPA to improve long-term outcomes is likely to remain: we have previously found that tPA and the THRIVE score are independent and without interaction in their prediction of outcomes in the NINDS tPA trial (3). Second, the increased risk of sICH predicted by the THRIVE score represents a low probability
event that only mediates a very small proportion of the overall relationship between THRIVE and outcome. The THRIVE score should therefore not be used to exclude patients from candidacy for i.v. tPA treatment.

The THRIVE score is an easy-to-use clinical tool in ischemic stroke that predicts functional outcome, mortality, and the risk of sICH after tPA treatment. The THRIVE score can be determined from variables available at the time of clinical presentation (age, NIHSS, HTN, DM, and AF), and is in the public domain (Creative Commons license). Free THRIVE score web calculators are provided at www.thrivescore.org and www.mdcalc.com/thrive-score-for-stroke-outcome/.

**Acknowledgements**

Dr. Flint 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.

**References**


**Supporting information**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Figure S1.** Trichotomized THRIVE score and clinical outcomes. (a) Reduced chance of good outcome (modified Rankin Scale 0–2 at 90 days) across the three levels of the trichotomized THRIVE score (0–2, 3–5, and 6–9). Mantel–Haenszel chi-square test for trend P<0.001. (b) Increased chance of death by 90 days across the three levels of the trichotomized THRIVE score (0–2, 3–5, and 6–9). Mantel–Haenszel chi-square test for trend P<0.001.