Totaled Health Risks in Vascular Events Score Predicts Clinical Outcomes in Patients With Cardioembolic and Other Subtypes of Ischemic Stroke

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Background and Purpose—Whether totaled health risks in vascular events (THRIVE) score can be used to predict clinical outcomes and risk of hemorrhagic transformation in patients with special subtypes of ischemic stroke remains an open question.

Methods—We analyzed the possible relationships between THRIVE score and clinical outcomes in patients with cardioembolic stroke or noncardioembolic stroke who did not receive thrombolytic therapy. Clinical outcomes and hemorrhagic transformation within 3 months of admission were compared among 3 patient subgroups with initial THRIVE scores of 0 to 2, 3 to 5, or 6 to 9.

Results—A total of 505 patients with cardioembolic stroke and 3374 patients with noncardioembolic stroke were included in our analysis. As THRIVE score increased, the rate of patients showing good clinical outcome decreased, whereas the rate of mortality and hemorrhagic transformation increased after ischemic stroke. Increasing THRIVE score was independently associated with decreasing likelihood of good outcome, defined as a modified Rankin Scale score of 0 to 2 (cardioembolic stroke: odds ratio, 0.59; 95% confidence interval, 0.51–0.67; noncardioembolic stroke: odds ratio, 0.53; 95% confidence interval, 0.49–0.57), and with increasing likelihood of death (cardioembolic: odds ratio, 1.48; 95% confidence interval, 1.28–1.70; noncardioembolic: odds ratio, 1.95; 95% confidence interval, 1.76–2.16). THRIVE score showed good receiver operating characteristics for predicting good outcome and mortality in patients with cardioembolic stroke and noncardioembolic stroke.

Conclusions—The THRIVE score is a simple tool that helps clinicians estimate good outcome and death after ischemic stroke. (Stroke. 2014;45:1689-1694.)

Key Words: brain infarctions ■ cerebral embolism ■ intracranial hemorrhage ■ outcome measure

See related article, p 1603.

Hemorrhagic transformation is considered a complication of acute ischemic stroke that can occur with or without thrombolytic treatment, and it may be an adaptive response to the ischemic event, particularly in acute cardioembolism.1,2 Hemorrhagic transformation is associated with poor clinical outcomes after acute ischemic stroke, and it strongly limits the net benefit of antithrombotic therapy.3,4 In fact, hemorrhagic transformation occurs most often in the cardioembolic subtype of ischemic stroke.4 This elevated risk highlights the need to develop reliable tools for predicting prognosis of patients with cardioembolic stroke, particularly the risk of hemorrhagic transformation. Such prediction may help individualize therapy as much as possible to improve outcomes.

The totaled health risks in vascular events (THRIVE) score was first used to predict clinical outcomes among patients undergoing endovascular stroke treatment in the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, the Multi MERCI trial, and the Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischemic stroke (TREVO-2) trial.5,6 The THRIVE score has also been validated for predicting clinical outcome and hemorrhagic transformation in patients receiving intravenous tissue-type plasminogen activator (tPA) in the Virtual International Stroke Trials Archive (VISTA).7 Because the THRIVE score takes into account age, stroke severity, and comorbidities, all of which are strong risk factors for clinical outcome and hemorrhagic transformation after ischemic stroke,7 we hypothesized that this score might be useful for...
predicting prognosis after ischemic stroke, particularly in patients with cardioembolic stroke.

To explore this possibility, we analyzed data from a large-scale prospective database of patients with acute ischemic stroke in China.

Subjects and Methods

Patients and Evaluation

This study was conducted using prospective data from the Chengdu Stroke Registry.1 The overall registry project was approved by the Scientific Research Department of West China Hospital, Sichuan University, and procedures used to build the registry conformed to local and international standards of research ethics. West China Hospital is considered by some the largest single-site hospital in the world, with 4300 beds and >180 000 admissions in 2012. It serves as the principal hospital in western China; its patients come from greater Chengdu, with a population of >10 million people, as well as from elsewhere in Sichuan province and surrounding provinces. The incidence of stroke in Sichuan province was reported in 2013 to be 100.9 per 100 000 individuals, compared with 135.6 per 100 000 across all mainland China.2 The Chengdu Stroke Registry has continuously recruited consecutive stroke patients from 2000 to the present.

For the present analysis, patients were included if they were admitted to our hospital between January 1, 2005, and May 31, 2013, within 7 days of ischemic stroke onset, and if sufficient data were available to (1) compute the THRIVE score, (2) determine whether hemorrhagic transformation occurred, and (3) assess functional outcome and mortality at 3 months after admission.

THRIVE Score

The following data were recorded for each patient to calculate THRIVE score: 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, or atrial fibrillation. The THRIVE score was calculated by assigning 1 point for an age of 60 to 79 years, 2 points for an age ≥80 years, 2 points for an NIHSS score of 11 to 20, 4 points for an NIHSS score ≥21, and 1 point each for hypertension, diabetes mellitus, and atrial fibrillation. Thus, the THRIVE score could range from 0 to 9.

Data Collection

On admission, baseline information was collected on age, sex, NIHSS, and risk factors (hypertension, diabetes mellitus, atrial fibrillation, current smokers, and current drinkers). Hypertension was defined as current use of antihypertensive medications or systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as the use of antidiabetic medication or a fasting serum glucose level ≥7.0 mmol/L. Atrial fibrillation was defined as a history of persistent or paroxysmal atrial fibrillation, supported by past ECG or diagnosed by physicians based on ECG and 24-hour ECG monitoring during admission. Patients who had smoked ≥1 cigarette/d for ≥1 year were classified as current smokers. Patients who had consumed ≥50 mL of alcohol/d for >1 year were defined as current drinkers.

Brain computed tomography was performed on all participants within 24 hours of admission before the initiation of antithrombotic therapy. Follow-up brain MRI was performed on all participants, usually within 1 week of admission. Hemorrhagic transformation was defined as the appearance of a low-signal area (≥5-mm diameter) on follow-up T2 images3 that was consistent with the presence of blood within the acute ischemic lesion. Whether hemorrhagic transformation was present or not on brain images were determined independently by 2 neurologists blinded to clinical data (inter-rater reliability κ = 0.83). When there was disagreement, a third neurologist also blinded to clinical data was consulted, and a consensus decision was reached.

Stroke subtype was determined according to the Trial of ORG10172 in the Acute Stroke Treatment (TOAST) classification.4 Ischemic stroke was classified into the cardioembolic subtype or into one of the noncardioembolic subtypes based on the TOAST classification criteria: large-artery atherosclerosis, small-artery occlusion, stroke of undetermined cause, or stroke of other causes. The basic assessment included intracranial and extracranial angiography using computed tomography, MRI, or digital subtraction methods, as well as 12-lead electrocardiography, echocardiography, chest x-ray, lipid profile, and standard blood tests. The results were used to classify patients as having large-artery atherosclerotic disease or other stroke subtype, as well as to confirm the source of embolism. If these assessments failed to identify the source of embolism, 2-hour Holter monitoring and transesophageal echocardiography were performed. Cardioembolic stroke was diagnosed in patients who presented arterial occlusions presumably attributable to an embolus arising in the heart and showed no evidence of large-artery atherosclerotic disease or other determined cause. If patients had concomitant risk factors, such as risk factors of cardioembolic with carotid stenosis (≥50%) or other determined cause, their stroke was defined as being of undetermined cause.

Good outcome was defined as a modified Rankin Scale score of 0 to 2 at 3 months after admission. Experienced stroke neurologists blinded to patients’ clinical data calculated modified Rankin Scale scores. Stroke deaths at 3 months were confirmed by contacting family members. Functional outcome and mortality were compared among 3 subgroups of patients stratified by THRIVE score on admission (0–2, 3–5, or 6–9). These subgroups have been validated for predicting prognosis of patients after ischemic stroke.3–5

Statistical Analysis

All statistical analyses were performed using SPSS (version 16; IBM). Results were reported as percentages, as means±SD, or as odds ratios (ORs) with 95% confidence intervals (CIs), as appropriate. The χ² or Fisher exact test was used to compare group data for categorical variables. Student t test and the Mann–Whitney U test were used to compare group data for continuous variables. The Mantel–Haenszel test was used to identify trends across THRIVE score subgroups (0–2 versus 3–5 versus 6–9). Receiver operating characteristic curves were constructed by plotting test sensitivity against 1–specificity. A 2-sided P<0.05 was considered statistically significant.

Results

Patient Baseline Characteristics and Risk Factors

A total of 4238 patients with ischemic stroke were admitted to our hospital during the enrollment period, and we excluded 38 (0.88%) patients who had received tPA therapy. This low rate of tPA therapy is consistent with previous reports that tPA thrombolysis is used in <2% of patients with stroke in China.6 None of the patients enrolled in the registry during the study period had received endovascular treatment within 7 days of ischemic stroke onset. Of the 4200 patients enrolled in our study, 321 (7.6%) were lost to follow-up, so in the end 505 patients with cardioembolic stroke and 3374 patients with noncardioembolic stroke were included in our analysis. The baseline characteristics of the patients lost to follow-up did not differ significantly from those of the patients included in the final analysis.

Patients with cardioembolic stroke were more likely than those with noncardioembolic stroke to be women and older with higher NIHSS. The group with cardioembolic stroke showed significantly lower rates of hypertension, hyperlipidemia, current smokers, and current drinkers than did the group with noncardioembolic stroke group, as well as lower systolic and diastolic blood pressure (Table 1). Among patients with cardioembolic stroke, cumulative mortality at 3 months after...
admission was 19.4% and the proportion of patients with hemorrhagic transformation was 22.6%. All these outcomes were significantly more frequent than among patients with noncardioembolic stroke: 6.2% and 5.3%.

**THRIVE Score and Clinical Outcomes**

THRIVE score independently predicted good clinical outcome, defined as a modified Rankin Scale score of 0 to 2 at 3 months after admission, not only in patients with cardioembolic stroke but also in patients with noncardioembolic stroke (P<0.001). In both groups of patients, the proportion of individuals with good outcome was significantly higher when the initial THRIVE score was 0 to 2 than when it was 3 to 5 or 6 to 9 (P<0.001; Table 2 and Figure 1). Logistic regression showed that every 1-point increase in THRIVE score was associated with a decrease in the likelihood of good clinical outcome at 3 months: among patients with cardioembolic stroke, the OR was 0.59 (95% CI, 0.51–0.67; P<0.001); and among patients with noncardioembolic stroke, the OR was 0.53 (95% CI, 0.49–0.57; P<0.001).

Increasing THRIVE score also independently predicted an increase in 3-month mortality among patients with cardioembolic or noncardioembolic stroke (P<0.001). In both groups of patients, mortality was significantly lower when the initial THRIVE score was 0 to 2 than when it was 3 to 5 or 6 to 9 (P<0.001; Table 2 and Figure 1). Logistic regression showed that every 1-point increase in THRIVE score was associated with an increase in 3-month mortality: among patients with cardioembolic stroke, the OR was 1.48 (95% CI, 1.28–1.70; P<0.001); and among patients with noncardioembolic stroke, the OR was 1.95 (95% CI, 1.76–2.16; P<0.001).

To verify the association between THRIVE score and outcomes based on our analysis of 3 THRIVE score categories, we examined whether continuous THRIVE score was associated with good outcome and mortality (Figure 2). As THRIVE score increased, the rate of patients showing good clinical outcome decreased and the rate of mortality increased. Because only 93 patients (2.7%) had THRIVE scores of 7 to 9, the 3 scores were combined to simplify the graphical analysis.

**THRIVE Score and Risk of Hemorrhagic Transformation**

Higher THRIVE score was associated with higher rate of hemorrhagic transformation among patients with cardioembolic or noncardioembolic stroke (Table 2 and Figure 1). The risk of hemorrhagic transformation in both groups of patients was significantly lower when the initial score was 0 to 2 than when it was 3 to 5 (cardioembolic stroke, P=0.004; noncardioembolic stroke, P<0.001) or 6 to 9 (cardioembolic stroke, P=0.025; noncardioembolic stroke, P=0.002). Logistic regression showed that every 1-point increase in THRIVE score was associated with increased risk of hemorrhagic transformation: among patients with cardioembolic stroke, the OR was 1.15 (95% CI, 1.03–1.30; P=0.003); and among patients with noncardioembolic stroke, the OR was 1.29 (95% CI, 1.17–1.40; P<0.001).

### Table 1. Baseline Characteristics of Patients With Acute Ischemic Stroke Enrolled in This Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cardioembolic Stroke (n=505)</th>
<th>Noncardioembolic Stroke (n=3374)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>64.90±14.09</td>
<td>63.39±13.85</td>
<td>0.023</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>223 (44.2)</td>
<td>2147 (61.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>175 (34.7)</td>
<td>1793 (51.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>54 (10.7)</td>
<td>612 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>15 (3.0)</td>
<td>223 (6.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>98 (19.4)</td>
<td>1128 (32.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current drinkers, n (%)</td>
<td>61 (12.1)</td>
<td>741 (21.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS score, mean±SD</td>
<td>10.62±9.25</td>
<td>6.39±7.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mmHg, mean±SD</td>
<td>132.41±23.17</td>
<td>144.98±39.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg, mean±SD</td>
<td>80.66±14.85</td>
<td>84.16±18.22</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; and NIHSS, National Institutes of Health Stroke Scale.

### Table 2. Frequencies of Good Clinical Outcome (mRS, 0–2) and Hemorrhage Within 3 Months of Admission, Stratified by Initial THRIVE Score

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Frequency by Stroke Subtype, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardioembolic Stroke</td>
</tr>
<tr>
<td></td>
<td>THRIVE, 0–2 (n=196)</td>
</tr>
<tr>
<td>Good outcome (mRS, 0–2)</td>
<td>132 (67.3)</td>
</tr>
<tr>
<td>Mortality</td>
<td>180 (8.1)</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>30 (15.3)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale score; and THRIVE, totaled health risks in vascular events.
To verify the association between THRIVE score and hemorrhagic transformation based on our analysis of 3 THRIVE score categories, we examined whether continuous THRIVE score was associated with hemorrhagic transformation (Figure 2). Increasing THRIVE score seemed to be associated with higher proportions of hemorrhagic transformation ($P<0.001$).

### Receiver Operating Characteristic Curve Analysis of THRIVE Score

Receiver operating characteristic curves were generated to examine the ability of THRIVE score to predict good clinical outcome and death at 3 months, as well as hemorrhagic transformation in patients with cardioembolic or noncardioembolic stroke. The areas under the curves were similar between both groups of patients for good clinical outcome (0.729 versus 0.708; $P=0.39$), mortality (0.712 versus 0.755; $P=0.22$), and hemorrhagic transformation (0.602 versus 0.608; $P=0.45$; Figure 3).

We compared the sensitivity and specificity of initial THRIVE score for predicting good outcome, death, and hemorrhagic transformation in patients with cardioembolic or noncardioembolic stroke. Different cutoff values of the THRIVE scores were tested to generate the highest $J$ of diagnostic test. The best prediction was obtained with a score of 2 for good outcome, death, and hemorrhagic transformation. The sensitivity associated with good outcome, death, and hemorrhagic transformation among patients with cardioembolic stroke were 68.3%, 63.2%, and 62.5%, respectively; the corresponding specificity was 62.1%, 74.1%, and 73.5%, respectively. The sensitivity associated with good outcome, death, and hemorrhagic transformation among patients with noncardioembolic stroke were 78.7%, 76.1%, and 71.2%, respectively; the corresponding specificity was 65.1%, 69.1%, and 65.6%, respectively.

### THRIVE Score as Prognostic Indicator for Noncardioembolic Stroke Subtypes

Finally, we examined the ability of THRIVE score to predict good outcome, mortality, or hemorrhagic transformation for 3 subtypes of noncardioembolic stroke: large-artery atherosclerosis, small-artery occlusion, and stroke of undetermined cause. We could not perform such an analysis for the TOAST...
category of other-cause stroke because our study population contained only 67 such patients. The results were similar to those observed above when patients with noncardioembolic strokes of any subtype were considered together (Table 3).

Discussion

Our study, based on a large-scale, hospital-based registry project in China, suggests that THRIVE score is a good predictor of good outcome and mortality after cardioembolic or noncardioembolic stroke in patients who have not received tPA therapy. These findings complement and extend previous studies performed in North America and Europe. In fact, the THRIVE score performed similarly well as a prognostic indicator across the various stroke subtypes in our study. Using the THRIVE score may therefore allow physicians to predict prognosis after ischemic stroke and adjust treatment to minimize the risk of disability and mortality. The THRIVE score is a valuable tool because it is calculated from clinical data assessed immediately on admission, without the need for complex neuroimaging or laboratory testing.

The THRIVE score takes into account nonmodifiable predictors (age and NIHSS score) and modifiable ones (hypertension, diabetes mellitus, and atrial fibrillation) that have been shown to influence prognosis and are strong risk factors for hemorrhagic transformation after acute ischemic stroke. The THRIVE score has been validated as a tool to predict functional outcomes and mortality across the entire range of acute stroke treatments, including intravenous tPA therapy and treatment for endovascular stroke. The receiver operating characteristic areas under the curves for THRIVE score to predict good outcome and death in our study, which involved only patients who did not receive tPA therapy, were similar to areas under the curves reported for THRIVE to predict outcomes in other acute stroke treatment contexts. Based on our results and on those of previous studies, the THRIVE score seems to work well in patients from Europe, North America, and East Asia.

The THRIVE score can easily be calculated with readily available clinical data, yet its power to predict clinical outcomes seems to be comparable with that of scoring systems that are more difficult to calculate or that require complex neuroimaging techniques or laboratory tests, including the Houston Intra-Arterial Therapy score, ischemic stroke risk score, and hemorrhage after thrombolysis score. All these scores also take stroke subtype into account. The present results, together with past studies, highlight the advantages of using the THRIVE score, either alone or in conjunction with other more complex scores.

Our finding that THRIVE score may predict hemorrhagic transformation after ischemic stroke is consistent with previous studies identifying older age, atrial fibrillation, and

Table 3. Frequencies of Good Clinical Outcome, Mortality, and Hemorrhagic Outcomes for Patients With Noncardioembolic Stroke, Stratified by Initial THRIVE Score

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Frequency by Stroke Subtype, n (%)</th>
<th>Large-Artery Atherosclerosis</th>
<th>Small-Artery Occlusion</th>
<th>Stroke of Undetermined Cause</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>THRIVE, 0–2 (n=693)</td>
<td>THRIVE, 3–5 (n=313)</td>
<td>THRIVE, 6–9 (n=45)</td>
</tr>
<tr>
<td>Good outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
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<tr>
<td>Hemorrhagic transformation</td>
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</tbody>
</table>

THRIVE indicates totaled health risks in vascular events.
hypertension,\textsuperscript{17} and hyperglycemia\textsuperscript{18} as risk factors for hemorrhagic transformation after ischemic stroke. All these parameters are taken into account when calculating the THRIVE score. A strong relationship between THRIVE score and hemorrhagic transformation has also been reported in the VISTA\textsuperscript{7} and in the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial.\textsuperscript{19}

Our study has some limitations. First, our limited data prevented us from comparing THRIVE score with Houston Intra-Arterial Therapy score, ischemic stroke risk score, or hemorrhage after thrombolysis score for their ability to predict good clinical outcome and risk of hemorrhagic transformation across different stroke subtypes. Second, our study involved only inpatients, so although our findings have immediate relevance for routine hospital practice, additional study is needed to assess their validity in the general population. Third, our study involved a relatively small number of patients with hemorrhagic transformation, probably because none of the patients in our recruitment pool received tPA therapy. As a result, we cannot definitively confirm that THRIVE score can predict hemorrhagic transformation in patients with cardio-embolic or noncardioembolic stroke. Fourth, THRIVE score is a continuous variable, so each individual THRIVE score did not simultaneously show both good sensitivity and specificity in our study. This suggests the need to combine THRIVE score with other indicators.

In conclusion, our findings from this large-scale registry suggest that the THRIVE score provides a rapid, reliable tool for predicting functional outcomes and mortality in East Asian patients with any of various subtypes of ischemic stroke.

Sources of Funding
This research was supported by the National Natural Science Foundation of China (81371283, 81371282) and the National Key Technology R&D Program for the 12th Five-Year Plan of People’s Republic of China (2011BAI08B05).

Disclosures
None.

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*Stroke*. 2014;45:1689-1694; originally published online April 17, 2014; doi: 10.1161/STROKEAHA.113.004352

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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