Prediction of Major Vascular Events in Patients With Transient Ischemic Attack or Ischemic Stroke

A Comparison of 7 Models

Annemarie D. Wijnhoud, MD; Lisette Maasland, MD; Hester F. Lingsma, MSc; Ewout W. Steyerberg, PhD; Peter J. Koudstaal, MD, PhD; Diederik W.J. Dippel, MD, PhD

Background and Purpose—In patients with a recent TIA or minor stroke, prediction of long-term risk of major vascular events is important, but difficult. We aimed to study the external validity of currently available prediction models.

Methods—We validated predictions from 3 population-based models (Framingham, SCORE, and INDIANA project) and 4 stroke cohort-based models (Stroke Prognosis Instrument II, Oxford TIA, Dutch TIA study, and the ABCD² study) in an independent cohort of patients with a recent TIA or minor stroke. The validation cohort consisted of 592 patients with TIA or minor stroke, with a mean follow-up of 2 years. The primary outcome was the 2-year risk of the composite outcome event of nonfatal stroke, myocardial infarction, or vascular death. We used calibration graphs and c-statistics to evaluate the 7 models.

Results—The 2-year risk of the primary outcome event was 12%. Calibration was adequate for stroke population-based studies. After adjustment for baseline risk and for prevalence of risk factors, calibration was adequate for the Dutch TIA, the ABCD², and Stroke Prognosis Instrument II models. Discrimination ranged from 0.61 to 0.68.

Conclusions—Discrimination was poor for all currently available risk prediction models for patients with a recent TIA or minor stroke, indicating the need for stronger predictors. Clinical usefulness may be best for the ABCD² model, which had a limited number of easily obtainable variables, a reasonable c-statistic (0.64), and good calibration. (Stroke. 2010; 41:00-00.)

Key Words: outcome ■ risk ■ stroke

Patients with a recent stroke have an increased long-term risk of new cerebrovascular and cardiovascular events. Estimates of long-term risk of cardiovascular and cerebrovascular events are important for patients who want to know their individual risks, and for treating physicians because in patients with increased long-term risk, more expensive or more hazardous interventions could be worthwhile. Long-term risk seems to be dependent on the underlying risk factors.1

In an American Heart Association statement, it was pointed out that validated prediction models for long-term cardiovascular risk in patients with ischemic stroke or TIA were not available.2 The use of a population-based prediction model, ie, the Framingham risk score,3 was recommended; however, this model has not been evaluated and compared with other prediction models to predict long-term cerebrovascular and cardiovascular risk in clinical practice. Treatment recommendations based on predictive models have been published and are currently used for patients with a significant carotid artery stenosis and for patients with atrial fibrillation.4,5 For patients without atrial fibrillation or a carotid artery stenosis, more precise risk estimations are needed.6 For this purpose, we need a reliable prognostic model with good discrimination between patients who will have new events and those who will not.

The aim of the present study is to determine which prediction models are adequate for long-term risk estimation for cardiovascular or cerebrovascular events in TIA and minor stroke patients. We primarily focused on major vascular events, ie, nonfatal stroke, myocardial infarction, and vascular death, because these affect health status most and are the focus of intervention studies. Secondarily, we considered fatal and nonfatal stroke.

Materials and Methods

Selection of Prediction Models
We compared the external validity (ie, calibration and discrimination) of 3 population-based models (the Framingham risk score

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for cardiovascular events, the Framingham risk score for stroke, SCORE, and the INDIANA project cardiovascular risk score and 4 stroke cohort-based models (Stroke Prognosis Instrument [SPI] II, the Oxford TIA study, the Dutch TIA study, and the ABCD² score) in an independent cohort of patients with a recent TIA or minor stroke (Table 1). All models were designed to predict long-term outcomes, except for the ABCD² score, which predicts 90-day risk of stroke. The stroke population-based models were designed to predict events after TIA or stroke; the population-based models were designed to predict first-ever stroke or cardiovascular events. These models were based on well-described large cohorts of patients with TIA or minor stroke and had the relative risks of the predictors estimated in a multiple (logistic or proportional hazards) regression model. The models predicted stroke and other cardiovascular events.

The SPI-II was developed in a small cohort of patients with a recent stroke. Kernan et al. created SPI-II by incorporating new predictive variables identified in a cohort of patients from the WEST study and validated it in 3 cohorts of patients from several secondary prevention trials.

Hankey et al. developed a prediction equation for recurrent vascular events based on 8 clinical prognostic factors from a cohort of 469 hospital-referred TIA patients. The prediction model was validated in cohorts of TIA patients from the Oxfordshire Community Stroke Project and the UK-TIA study.

The Dutch TIA trial investigators developed a set of predictors of major vascular events and of stroke. Their prediction model was based on data of patients with a TIA or minor stroke who entered a multicenter, randomized, controlled clinical trial with a factorial design of high-dose vs low-dose aspirin and pentoxyfylline vs placebo.

The ABCD² score calculates the 2-, 7-, and 90-day stroke risk in TIA patients. This prediction model was based on TIA patients presenting within 1 day of onset of symptoms. We used the 90-day risk score because this was closest to the 2-year risk calculated in the validation cohort.

The 3 other models were population-based models that have been widely used to assess cardiovascular risk. For risk of major vascular events, we used the Framingham risk score for cardiovascular events published in 1998. This model is based on categorical variables. For risk of stroke, we used the Framingham risk score for stroke published in 1994.

The SCORE prediction model, methodology differs slightly from the other models. Annual age- and gender-dependent rates of coronary and vascular event were estimated from the data in an accelerated failure time model (Weibull). This model made use of age as a measure of exposure time to risk rather than a risk factor. Estimates of mortality rates were based on observations in age categories.

Pocock et al. published a prediction instrument based on data from 8 randomized controlled trials of antihypertensive treatment in asymptomatic individuals: the INDIANA project. They developed 3 separate models for overall cardiovascular mortality, fatal coronary heart disease, and fatal stroke.

### Table 1: Overview of the 7 Prediction Models

<table>
<thead>
<tr>
<th>Study</th>
<th>SPI-II</th>
<th>Oxford TIA</th>
<th>Dutch TIA</th>
<th>ABCD²</th>
<th>Framingham</th>
<th>SCORE</th>
<th>INDIANA Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source population</td>
<td>Stroke trials</td>
<td>Hospital cohort</td>
<td>Stroke RCT</td>
<td>Hospital cohort</td>
<td>Population cohort</td>
<td>Prevention trials</td>
<td>Prevention trials</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Stroke or death</td>
<td>Stroke, MI, or vascular death</td>
<td>Stroke, MI, or vascular death</td>
<td>Stroke</td>
<td>Vascular events</td>
<td>Fatal coronary heart disease</td>
<td>Fatal coronary heart disease</td>
</tr>
<tr>
<td>Time window</td>
<td>2 years</td>
<td>5 years</td>
<td>4 years</td>
<td>2, 7, 90 days</td>
<td>10 years</td>
<td>10 years</td>
<td>2.0 to 6.9 years</td>
</tr>
<tr>
<td>Predictors (n)</td>
<td>7</td>
<td>8</td>
<td>17</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Demographics</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Stroke vs TIA</td>
<td>Amaurosis fugax only</td>
<td>Amaurosis fugax only</td>
<td>Duration of symptoms, clinical symptoms of TIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td>Previous stroke</td>
<td>Severe hypertension</td>
<td>Peripheral arterial disease</td>
<td>Diabetes mellitus</td>
<td>Systolic BP</td>
<td>Total cholesterol/HDL cholesterol*</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>Borderzone infarct</td>
<td>Any other infarct</td>
<td>WML</td>
<td>Left ventricular hypertrophy</td>
<td>Increased term P wave</td>
<td>Anterosetal infection</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Left ventricular hypertrophy</td>
<td>Left ventricular hypertrophy</td>
<td>Left ventricular hypertrophy†</td>
<td>Left ventricular hypertrophy†</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; MI, myocardial infarction; RCT, randomized controlled trial; SPI, Stroke Prognosis Instrument; TIA, transient ischemic attack; WML, white matter lesion.

*Cardiovascular risk only. †Cerebrovascular risk only.
The validation cohort consisted of 592 consecutive patients included in the Rotterdam Transcranial Doppler study. Patients were recruited in our hospital. This study was designed to evaluate the diagnostic and prognostic value of transcranial Doppler ultrasonography in patients with a recent TIA or minor ischemic stroke. Patients were 18 years and older and had the index event within the preceding 6 months. They were independent (a score of 0/3 on the modified Rankin scale), and the TIA or stroke was of presumed atherosclerotic origin; this implied that patients with a mechanical heart valve and a proven dissection were excluded. Patients with atrial fibrillation or a significant symptomatic carotid artery stenosis were also excluded. Follow-up started at time of recruitment. The mean time between index event and recruitment was 51 ± 45 days. The mean follow-up in this study was 755 days or 2.1 years (interquartile range, 0.9–3.1). The study population consisted of patients for whom no other treatment than risk factor modification and antiplatelet medication were available.

### Validation Cohort

The validation cohort consisted of 592 consecutive patients included in the Rotterdam Transcranial Doppler study. Patients were recruited in our hospital. This study was designed to evaluate the diagnostic and prognostic value of transcranial Doppler ultrasonography in patients with a recent TIA or minor ischemic stroke. Patients were 18 years and older and had the index event within the preceding 6 months. They were independent (a score of ≤3 on the modified Rankin scale), and the TIA or stroke was of presumed atherosclerotic origin; this implied that patients with a mechanical heart valve and a proven dissection were excluded. Patients with atrial fibrillation or a significant symptomatic carotid artery stenosis were also excluded. Follow-up started at time of recruitment. The mean time between index event and recruitment was 51 ± 45 days. The mean follow-up in this study was 755 days or 2.1 years (interquartile range, 0.9–3.1). The study population consisted of patients for whom no other treatment than risk factor modification and antiplatelet medication were available.

#### Procedure and Definitions

The primary outcome was the composite end point of stroke, myocardial infarction, and vascular death. The secondary outcome was the occurrence of TIA or stroke.

### Table 2. Baseline Characteristics of the 7 Prediction Model Cohorts and the Validation Cohort

<table>
<thead>
<tr>
<th>Validation Cohort</th>
<th>SPI-II (%)</th>
<th>Oxford TIA (%)</th>
<th>Dutch TIA (%)</th>
<th>ABCD² (%)</th>
<th>Framingham (%)</th>
<th>SCORE (%)</th>
<th>INDIANA Project (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N in study</td>
<td>592</td>
<td>525</td>
<td>469</td>
<td>3127</td>
<td>4809</td>
<td>5345</td>
<td>205 178</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62</td>
<td>...</td>
<td>62</td>
<td>65</td>
<td>70</td>
<td>49</td>
<td>...</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>44%</td>
<td>73%</td>
<td>...</td>
<td>53%</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>29%</td>
<td>57%</td>
<td>25%</td>
<td>34%</td>
<td>...</td>
<td>5%</td>
<td>...</td>
</tr>
<tr>
<td>Male</td>
<td>60%</td>
<td>0%</td>
<td>68%</td>
<td>65%</td>
<td>47%</td>
<td>47%</td>
<td>57%</td>
</tr>
</tbody>
</table>

**Stroke characteristics**

- TIA (not stroke): 54% (23%); 100% (32%); 100% (100%); NA; NA; NA
- Multiple attacks: 20% (32%); NA; NA; NA
- Amaurosis fugax only: 6% (34%); NA; NA; NA

**Risk factors**

- Previous stroke: 21% (20%); 0% (0%); 0% (0%); ...; 0% (0%); NA; 1%
- Previous MI*: 24% (24%); 21% (10%); ...; 0% (0%); NA; 5%
- Diabetes mellitus: 11% (31%); 5% (8%); 17% (17%); 4.6% ...; 3%
- Angina pectoris: 9% (6%); NA; NA; ...; 0%
- Current smoker: 26% (47%); 44% (39%); 40%
- Total cholesterol (mmol/L): 5.7 (6.7); 5.4 (6.1)
- LDL cholesterol (mmol/L): 3.8 (3.6); 3.5 ...
- HDL cholesterol (mmol/L): 1.3 (1.3); 1.3 ...
- SBP (mm Hg): 148 (158); 146; 133; 162
- DBP (mm Hg): 86 (91); 82 ...
- BMI (kg/m²): 26.2 ...

**Table 3. Estimated 2-Year Risk in the Validation and Derivation Cohorts**

<table>
<thead>
<tr>
<th>Validation Cohort (%)</th>
<th>SPI-II (%)</th>
<th>Oxford TIA (%)</th>
<th>Dutch TIA (%)</th>
<th>ABCD² (%)</th>
<th>Framingham (%)</th>
<th>SCORE (%)</th>
<th>INDIANA Project (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>0.5</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Stroke or death</td>
<td>13</td>
<td>20</td>
<td>...</td>
<td>9</td>
<td>3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>MI</td>
<td>4</td>
<td>6</td>
<td>...</td>
<td>3</td>
<td>3.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Stroke, MI, or vascular death</td>
<td>12</td>
<td>14</td>
<td>12</td>
<td>...</td>
<td>3</td>
<td>5.7</td>
<td></td>
</tr>
</tbody>
</table>
Calibration and Discrimination

Two aspects of validity were examined: calibration and discrimination. Calibration, or reliability, measures how closely predicted outcomes agree with actual outcomes. Discrimination refers to the ability to distinguish patients with different outcomes. The predicted probabilities of vascular events should be trustworthy (calibration) and extreme (discrimination).

Calibration-in-the-large reflects whether the overall outcome of the study cohort was close to the average predicted 2-year risk from a model. We constructed calibration plots in which observed 2-year outcome was plotted against predicted 2-year risk (using a Kaplan-Meier survival curve). A c-statistic of 1 implies a test with perfect sensitivity and specificity, whereas a value of 0.5 implies that the model predictions are no better than chance.

Table 4. Calibration and Discrimination of the 7 Prediction Models: Major Vascular Events

<table>
<thead>
<tr>
<th></th>
<th>Calibration</th>
<th>Discrimination*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted 2-Year Risk (%)</td>
<td>Observed 2-Year Risk (%)</td>
</tr>
<tr>
<td>SPI-II</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Oxford TIA</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Dutch TIA</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>ABCD²</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Framingham</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>SCORE</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>INDIANA project</td>
<td>21</td>
<td>12</td>
</tr>
</tbody>
</table>

SPI indicates Stroke Prognosis Instrument; TIA, transient ischemic attack.

*The null hypothesis that all values were equal was rejected (P<0.02; χ² =15, 27; 6 degrees of freedom).

Table 5. Calibration and Discrimination of the 7 Prediction Models for Stroke

<table>
<thead>
<tr>
<th></th>
<th>Calibration</th>
<th>Discrimination*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted 2-Year Risk (%)</td>
<td>Observed 2-Year Risk (%)</td>
</tr>
<tr>
<td>SPI-II</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Oxford TIA</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Dutch TIA</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>ABCD²</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Framingham</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>SCORE</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>INDIANA project</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

SPI indicates Stroke Prognosis Instrument; TIA, transient ischemic attack.

*The 0 hypothesis that all areas were equal was not rejected (P=0.55; χ² =4.93; 6 degrees of freedom).
stated. In this study, relatively young subjects had participated, and subjects aged 40 to 60 were particularly well-represented. In the Oxford TIA cohort, all patients had a TIA, and approximately one-third had amaurosis fugax (Table 2). In the validation cohort, 57 major vascular events occurred during follow-up, for a 2-year risk of 12%, and 41 fatal or nonfatal stroke, for a 2-year-risk of 9% (Table 3).

Table 4 shows the observed predicted 2-year risk of stroke, myocardial infarction, or vascular death. Table 5 shows the observed predicted 2-year risk of fatal or nonfatal stroke. The SPI-II overestimated the risk for both outcome events in patients at low risk and underestimated in patients at high risk, whereas Oxford TIA, the Dutch TIA trial, and ABCD² score overestimated the risk for both outcome events (Figure).
Discrimination varied between 0.61 and 0.68 for the risk of stroke, myocardial infarction, or vascular death, and between 0.58 and 0.65 for the risk of fatal or nonfatal stroke (Table 4). Discrimination was higher in the stroke cohort-based studies than in the population-based studies but remained <0.70.

Discussion
This is the first study to our knowledge comparing the external validity of long-term prediction models. In a scientific statement for health care professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association,
the Framingham study was recommended for long-term cardiovascular risk in patients with TIA or ischemic stroke. The purpose of our study was to find out whether stroke cohort-based studies perform better and should be used in the future to estimate long-term risk of major vascular events in patients with TIA or ischemic stroke.

Calibration was fairly good in most models; however, in the SPI-II study, the Dutch TIA study, and the ABCD² study, calibration was best. All models were adjusted for baseline risk and prevalence of risk factors, as suggested by several authors. Without these adjustments, calibration was poor. Overall, stroke-based prediction models from the Dutch TIA trial, the SPI-II study, and the ABCD² study showed best calibration and discrimination. A clinically useful prediction model shows good calibration, discrimination, and uses a limited number of clear-cut, easily available variables.

The ABCD² score and the SCORE prediction model used the smallest number of variables in their prediction rule for long-term cardiovascular risk, 5 and 6, respectively, and risk estimation derived from these studies therefore is easy to obtain. The Framingham prediction model for cerebrovascular risk included 8 factors, which are all easy to obtain, except for left ventricular hypertrophy for which an ECG is needed. The Dutch TIA study used 17 variables in the prediction rule. The Oxford TIA prediction rule and the INDIANA project prediction rule included ECG variables, which are more difficult to ascertain. The Dutch TIA prediction rule used ECG variables that require some expertise, such as left ventricular hypertrophy by the Casale criteria and anteroseptal infarction (Table 1), and also included CT scan variables. This makes these models less attractive to use.

Limitations of the Study
Some limitations of this study should be discussed. First, although the validation cohort was of reasonable size (598 patients), the effective sample size was not large, with 57 major events and 41 fatal or nonfatal strokes. Second, predictions from all models, except for the ABCD² study, exceeded the 2-year risk observed in our validation cohort. We have overcome this miscalibration by adjusting for this difference in follow-up in our analysis.

We excluded patients with atrial fibrillation or a severe carotid artery stenosis and focused on patients with TIA or minor ischemic stroke. This reduces the heterogeneity of the validation cohort and may reduce the discriminatory ability of the models. Risk estimates are more readily available for carotid artery stenosis, as well as for patients with atrial fibrillation. For the remaining group of patients with TIA or minor stroke, there is a particular need for a prediction model.

In the validation cohort as well as in 2 of the 4 stroke cohorts, the mean age was rather low (Table 2). These cohorts consisted of a hospital population. Hospital populations tend to be of lower age. Therefore, they may not be representative of patients with TIA and minor strokes in the community.

The time between index event and recruitment in the validation cohort was 51 days, which differs substantially from the ABCD² study but not the remaining stroke-based population studies. We have overcome this problem by adjusting for the baseline risk in all validation studies. In this way, we adjusted for the low number of outcome events compared to the ABCD² study.

Validity
Although this was a study on long-term risk, we also included the ABCD² model, which was developed for estimation of short-term risk. Calibration and discrimination in the ABCD² study, however, did not differ substantially from the long-term prediction models. Comparisons with other studies cannot be made, because similar studies of long-term risk assessment in patients with TIA or ischemic are not available.

Possible Improvements
The 7 models used dichotomized variables instead of continuous variables. Perhaps with continuous variables, estimations of risk would have been more precise and discrimination may improve. Furthermore, the stroke-based prediction models were derived from trial populations with certain inclusion and exclusion criteria. The best-fitting model for everyday practice will probably be derived from a representative cohort; this means a consecutive stroke population without exclusion criteria.

Conclusion
Current prediction models for long-term prognosis in TIA and stroke patients have limited validity. Calibration seems to be adequate for most models, but discrimination between patients at high risk and patients at low risk is especially relatively poor. Improvements such as implementation of continuous variables are needed, as well as extension with stronger predictors of outcome. For now, the SPI-II and the ABCD² prediction models seem to be most adequate. Of these 2, the ABCD² may be preferred because of its easy applicability in clinical practice.

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This study was supported by a grant from the Netherlands Heart Foundation (97.155).

Disclosures
None.

References


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(Stroke. 2010;41:2178-2185.)

Key Words: outcome ■ risk ■ stroke

배경과 목적
최근 일과성허혈발작(transient ischemic attack, TIA)이나 경한 뇌졸중이 있었던 환자에서의 주요 혈관 사전의 장기 위험 예측은 중요하다. 저자들은 현재 유용한 예측 모델의 외적 타당도(external validity)를 조사하고자 하였다.

방법
저자들은 최근 TIA나 경한 뇌졸중이 있었던 환자들의 독립적 인 코호트인 3개의 인구 기반 모델(Framingham, SCORE, INDIANA project)과 4개 뇌졸중 코호트 기반 모델(Stroke Prognosis Instrument II, Oxford TIA, Dutch TIA study, ABCD² study)로부터 예측 타당도를 조사하였다. 타당도 코호트는 592명의 TIA나 경한 뇌졸중 환자로 구성되어 있었고, 평균 추적 관찰 기간은 2년이었다. 1차 결과(primary outcome)는 치명적이지 않은 뇌졸중, 심근경색, 또는 혈관성 사망의 복합 결과(composite outcome) 사건의 2년 위험도였다. 7개 모델 평가를 위해 검정 도표(calibration graph)와 c-통계
(c-statistic)를 사용하였다.

결과
1차 결과 사전의 2년 위험은 12%였다. 검정은 뇌졸중 인구 기반 연구에서 적절하였다. 초기 위험 및 위험인자의 유병률을 보정한 후, 측정은 Dutch TIA, ABCD², Stroke Prognosis Instrument II 모델에서 적합하였다. 구별(discrimination) 정도는 0.61~0.68이었다.

결론
최근 TIA나 경한 뇌졸중이 있었던 환자를 대상으로 한 모든 현 재 유용한 위험 예측 모델에서 구별은 험들었으며, 더 강한 예측 인자의 필요성을 시사하였다. 임상적 유용성은 ABCD² 모델에서 가장 좋았고, 쉽게 얻을 수 있는 변수의 제한, 믿을 만한 c-통계(0.64), 좋은 검정을 보였다.
Prediction of Major Vascular Events in Patients With Transient Ischemic Attack or Ischemic Stroke
A Comparison of 7 Models
Annemarie D. Wijnhoud, MD; Lisette Maasland, MD; Hester F. Lingsma, MSc; Ewout W. Steyerberg, PhD; Peter J. Koudstaal, MD, PhD; Diederik W.J. Dippel, MD, PhD

背景和目的：预测近期有短暂性脑缺血发作 (TIA) 或小卒中的病人的远期主要血管事件风险非常重要，但非常困难。我们的目的在于研究当前几个预测模型的外在有效性。

方法：我们通过三个以社区为基础的模型 (Framingham 研究、SCORE 研究和 INDIANA 研究) 和四个卒中队列研究的模型 (Stroke Prognosis Instrument II、牛津 TIA 研究、荷兰 TIA 研究和 ABCD² 研究) 来进行验证。验证对象包括 592 例 TIA 或小卒中患者，平均随访 2 年。主要终点是 2 年非致命性卒中、心肌梗死或血管性死亡的复合终点事件。我们使用校准曲线 (calibration graphs) 和 c- 统计量来评价这 7 个模型。

结果：两年发生危险事件的概率为 12%。对于以卒中人群为基础的研究，校准 (可靠性) 是适当的。在对基线风险和危险因素患病率调整后，荷兰 TIA、ABCD² 和 Stroke Prognosis Instrument II 模型的校准是适当的。风险识别力在 0.61-0.68 之间。

结论：对于近期有 TIA 或小卒中的病人，当前所有风险预测模型识别力不足，提示需要更好的预测工具。从临床应用来看，ABCD² 模式最实用，因为其使用的变量较少而且容易获得，且具有一个可以接受的 c- 统计量 (识别力 0.64) 和良好的校准 (可靠性)。

关键词：结果，风险，卒中

(Stroke. 2010;41:2178-2185. 暨南大学附属第一医院神经内科 赵颖 译 徐安定 校)

ABCD2 评分预测 TIA 患者第 2、7、90 天的卒中风险[13]。这个预测模式是基于在发生症状后一天内的 TIA 病人。我们使用 90 天的风险评分，因为其最接近验证队列中的 2 年风险值。其他三个以社区人群为基础的模型已被广泛用来评估心血管疾病的风险。对于主要血管事件风险，
表 2 7个预测模型队列和验证队列的基本特征

<table>
<thead>
<tr>
<th>预测队列</th>
<th>SPI-II</th>
<th>牛津</th>
<th>荷兰</th>
<th>ABCD²</th>
<th>Framingham</th>
<th>SCORE</th>
<th>INDIANA研究</th>
</tr>
</thead>
<tbody>
<tr>
<td>患者数量</td>
<td>592</td>
<td>525</td>
<td>469</td>
<td>3127</td>
<td>4809</td>
<td>5345</td>
<td>205178</td>
</tr>
<tr>
<td>年龄 (岁)</td>
<td>62</td>
<td>...</td>
<td>62</td>
<td>65</td>
<td>70</td>
<td>49</td>
<td>...</td>
</tr>
<tr>
<td>年龄 &gt;60岁</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>77%</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>年龄 &gt;65岁</td>
<td>44%</td>
<td>73%</td>
<td>...</td>
<td>...</td>
<td>53%</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>年龄 &gt;70岁</td>
<td>29%</td>
<td>57%</td>
<td>25%</td>
<td>34%</td>
<td>...</td>
<td>5%</td>
<td>...</td>
</tr>
<tr>
<td>男性</td>
<td>60%</td>
<td>0%</td>
<td>68%</td>
<td>65%</td>
<td>47%</td>
<td>47%</td>
<td>57%</td>
</tr>
</tbody>
</table>

卒中特点：
- TIA (非卒中)：54% 23% 100% 32% 100% NA NA NA
- 多次发作：20% ... ... ... ... ... NA NA NA
- 一过性黑朦：6% ... ... ... ... ... NA NA NA

危险因素：
- 卒中史：21% 20% 0% 0% ... ... NA NA NA
- 心肌梗死病史*：24% 24% 21% 10% ... ... 0% NA 5%
- 糖尿病：11% 31% 5% 8% 17% 4.6% ... ... 3%
- 高血压：9% 6% ... ... ... ... NA 0%
- 吸烟：26% ... ... ... 47% 44% ... ... 39% 40%
- 总胆固醇 (mmol/L)：5.7 ... ... ... ... ... ... 5.4 6.1
- LDL (mmol/L)：3.8 ... ... ... ... ... ... 3.5 ... ... 
- HDL (mmol/L)：1.3 ... ... ... ... ... ... 1.3 1.4 ... 
- 收缩压 (mmHg)：148 ...† ... 158 ... ... 146‡ ... 133 162
- 舒张压 (mmHg)：86 ... ... ... 91 ... ... 82 ... ... 
- 收缩压 >140 mmHg：... ... ... ... 69% ... ... ... ... 
- 舒张压 >90 mmHg：... ... ... ... 30% ... ... ... ... 
- BMI (kg/m²)：26.2 ... ... ... ... ... ... 25.8 ... ... 

...表示无此项数据。
除非有特别说明，数据为平均值。
*任何心肌梗死，基于既往 ECG。
†严重高血压 (收缩压 >180 mmHg 或舒张压 >100 mmHg) 有 31 人 (6%)。
‡Framingham 研究发表的是收缩压和舒张压的中位数而不是平均数。

我们使用 1998 年出版的基于分类变量的 Framingham 心血管事件风险评分[3]。对于卒中风险评估，我们使用 1994 出版的卒中 Framingham 风险评分[8]。

SCORE 预测模型与其他模式相比，方法略有不同。它通过加速失败时间模式 (Weibull) 来评估不同年龄、性别的年冠心病或血管事件风险。这个模型以年龄作为参数以衡量其作用于危险因素下的暴露时间，而不是某一个危险因素。死亡率评估基于不同年龄段的观察[9]。

表 3 验证队列和预测队列 2年风险的估计

<table>
<thead>
<tr>
<th>预测队列</th>
<th>SPI-II</th>
<th>牛津</th>
<th>荷兰</th>
<th>ABCD²</th>
<th>Framingham</th>
<th>SCORE</th>
<th>INDIANA研究</th>
</tr>
</thead>
<tbody>
<tr>
<td>总中</td>
<td>9</td>
<td>...</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>0.5</td>
<td>...†</td>
</tr>
<tr>
<td>中卒或死亡</td>
<td>13</td>
<td>20</td>
<td>...</td>
<td>...</td>
<td>9</td>
<td>3</td>
<td>...†</td>
</tr>
<tr>
<td>心肌梗死</td>
<td>4</td>
<td>...</td>
<td>6</td>
<td>...</td>
<td>...</td>
<td>3</td>
<td>3.5‡</td>
</tr>
<tr>
<td>总中，心肌梗死或血管性死亡</td>
<td>12</td>
<td>...</td>
<td>14</td>
<td>12</td>
<td>...</td>
<td>3</td>
<td>5.7</td>
</tr>
</tbody>
</table>

*ABCD² 研究中估计的是 90 天风险。
†除了 SCORE，其他所有研究结果的界限估计。
‡年龄为 65 岁的累积风险。

Pocock 等[10]根据无症状人群抗高血压治疗的 8 个随机对照研究 (INDIANA 研究) 的数据提出了一个预测工具。他们分别对整体心血管死亡、致命性冠心病和致命性卒中制定了三个模型。

验证队列

验证对象由鹿特丹经颅多普勒超声 (TCD) 研究中连续入选的 592 例患者组成[16]。患者被招募到我们医院。这项研究旨在评估 TCD 对近期 TIA 或小缺
血性卒中病人的诊断及预后价值。病人年龄≥18岁，发病时间在6个月内，非严重残疾（改良Rankin量表评分≤3）。

TIA或卒中的病因被假定为动脉粥样硬化性，这意味着机械心脏瓣膜和动脉夹层的患者被排除在外。房颤患者或严重颈内动脉狭窄也被排除在外。病人入选后立即开始随访。症状发作到入选时间的间隔为51±45天。平均随访时间为755天或2.1年（四分位数间距，0.9-3.1年）。研究对象仅包括只需要危险因素控制和抗血小板治疗而不需要其他治疗的病人。

程序和定义
主要终点是非致命性卒中、心肌梗死或血管性死亡的复合终点事件。次要终点事件是致命性或非致命性卒中的复合终点。在验证队列中，Kaplan-Meier生存曲线用于估计2年主要或次要终点事件风险。

每一个预测模型的验证程序基本一致。首先，用Kaplan-Meier生存曲线得到验证队列中每个患者2年实际主要或次要终点事件风险。对于丢失值，用一个变量的平均值推算。然后分别用上述7个模型预测2年风险。为此，我们使用每一个模型的原始预测方程。按照几个作者的推荐，在有效性评估中每个方程根据平均整体风险和危险因素患病率进行调整[18,19]。

校准和识别力
本研究采用两个有效性的指标：校准和识别力（Calibration and Discrimination）。校准，或可靠性，是指评价预测结果与实际结果的一致性。识别力是指能够区分不同的预后[20]。血管性事件的预测应该具有可靠性（校准）和预测性（识别力）。

大型校准反映了研究对象的总体结果是否很接近一个模式预测的平均2年风险。我们建立2年终点事件与2年预测结果（使用Kaplan-Meier生存曲线）的校准曲线。用预测可能性的五分相位法表示终点事件。校准曲线由回归直线（或校准曲线）的截距（α）

### 表4 关于主要血管疾病的7个预测模型的校准和识别力

<table>
<thead>
<tr>
<th></th>
<th>预测的2年风险 (%)</th>
<th>观察到的2年风险 (%)</th>
<th>队率 (95% CI)</th>
<th>c-统计 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPI-II</td>
<td>13</td>
<td>12</td>
<td>1.62(0.57-2.66)</td>
<td>0.68(0.61-0.75)</td>
</tr>
<tr>
<td>牛津TIA</td>
<td>17</td>
<td>12</td>
<td>0.60(0.32-0.88)</td>
<td>0.66(0.58-0.74)</td>
</tr>
<tr>
<td>荷兰TIA</td>
<td>14</td>
<td>12</td>
<td>0.92(0.27-2.11)</td>
<td>0.64(0.56-0.72)</td>
</tr>
<tr>
<td>ABCD²</td>
<td>14</td>
<td>12</td>
<td>0.68(0.40-0.96)</td>
<td>0.64(0.57-0.70)</td>
</tr>
<tr>
<td>Framingham</td>
<td>14</td>
<td>12</td>
<td>0.37(0.46-1.21)</td>
<td>0.64(0.57-0.72)</td>
</tr>
<tr>
<td>SCORE</td>
<td>12</td>
<td>12</td>
<td>0.34(0.29-0.97)</td>
<td>0.61(0.53-0.69)</td>
</tr>
<tr>
<td>INDIANA 研究</td>
<td>21</td>
<td>12</td>
<td>0.21(0.22-0.63)</td>
<td>0.61(0.54-0.69)</td>
</tr>
</tbody>
</table>

* 拒绝无效假设（所有面积相等）(P=0.02; χ²=15.27; 自由度 6)。
和斜率 (β) 表示。良好的校准模式为 α=0 和 β=1。我们计算每个预测模式的斜率。识别力用一致性 (c) 统计值量化。C- 统计法代表了接受者操作特征曲线下的面积。C- 统计为 1 者意味着这个研究具有完美的特异性和敏感性，而 0.5 则意味着该模式结果为偶然 [20]。

结果

我们首先比较了 7 个原有预测模型预测因素的
分布（表2）。在INDIANA和Framingham这两个基于社区人群的研究中发现，人群年龄小于以卒中人群为基础的研究。更确切的说，这类人群没有卒中或心肌梗死病史。在SCORE中没有说明人群的平均年龄或年龄分布，相对年轻的受试者参加了这项研究，对于年龄在40岁至60岁的人群颇具代表性。在牛津TIA模型中，所有病人都有TIA，几乎三分之一的病人有一过性黑朦（表2）。
中，随访期内发生 57 起主要血管事件（2 年风险为 12%），41 起致命性或非致命性卒中（2 年风险 9%），见表 3。

表 4 显示了所观察到的预测 2 年卒中、心肌梗死或血管性死亡的风险。表 5 显示了所观察到的预测 2 年致命性或非致命性卒中中的风险。SPI-II 模式高估了低风险患者的上述终点事件风险，低估了高风险患者的事件风险，然而牛津 TIA、荷兰 TIA 和 ABCD² 模式高估了终点事件的风险（图）。

识别力

对主要血管事件（卒中、心肌梗死或血管性死亡）的风险识别力在 0.61 和 0.68 之间，对致命性或非致命性卒中中的风险识别力在 0.58 至 0.65 之间（表 4）。以卒中人群为基础研究的识别力高于以社区人群为基础的研究，但仍<0.7。

讨论

就我们所知，这是首次比较长期预测模式外在有效性的研究。美国心脏协会 / 美国卒中协会卒中委员会 / 临床心血管委员会的一份医学专业声明推荐 Framingham 风险评分 [1] 用于有 TIA 或缺血性卒中病人长期心血管疾病风险的预测 [2]。我们研究的目的是确定基于卒中人群为基础的预测模型是否更好，是否应在将来应用于有 TIA 或缺血性卒中病人远期主要血管事件的风险评估。

研究发现，校准（可靠性）在多数预测模型中效果还是相对较好的，而 SPI-II、荷兰 TIA 和 ABCD² 模型最优。所有模型按照几个作者的建议进行了基准风险和危险因素患病率的调整 [1,19]。如果不做调整，校准（可靠性）将很差。总体而言，以卒中人群为基础，荷兰 TIA、SPI-II 和 ABCD² 模型显示出识别远期风险的最佳校准和识别力。一个有效的临床预测工具应具有良好的校准和识别力，并使用一个明确的、数量有限的和容易获得的变量。

ABCD² 评分和 SCORE 预测模式在长期心血管疾病风险的预测中使用的变量数最少，分别是 5 个和 6 个。因此，以这些模型预测风险相当容易。Framingham 预测模式通过 8 个因素预测脑血管事件风险，除了左心室肥厚需要心电图，其他变量也很容易获得。荷兰 TIA 研究在预测中使用了 17 个变量。牛津 TIA 模型和 INDIANA 预测模型则包括相对较难获得的心电图变量。荷兰 TIA 模型中使用的心电图参数比如左室肥厚的 Casale 标准 [21] 和前间壁梗死需要专家意见（表 1），另外还需要通过 CT 扫描获得变量，因而该模型的使用缺乏吸引力。

研究的局限性

本研究有一些局限性。首先，尽管验证队列有一个合理的规模（598 例病人），但是有效样本并不大，仅包括 57 个主要血管事件和 41 个致命性或非致命性卒中。其次，除了 ABCD² 研究，其他所有的预测模型在验证队列中观察到了超过 2 年的风险。在随访中，我们已经通过调整这些差异克服了错误的校准。

我们排除了房颤或严重颈内动脉狭窄的患者，并且关注 TIA 或小缺血性卒中中的病人，这减少了验证队列的异质性，有可能降低预测模式的识别能力。对于颈内动脉狭窄和房颤的病人，风险的估计更容易得到。对于 TIA 和小卒中病人，特别需要一个预测模型。

在验证队列以及 4 个卒中队列中的 2 个队列，平均年龄较小（表 2）。这些人群由医院病人组成。医院病人年龄往往偏小，因此他们可能不能代表社区中有 TIA 和小卒中的病人。

在出现先兆症状到招募至医院的时间为 51 天，这大大不同于 ABCD² 研究，但与其他基于卒中人群的研究基本一致。在验证队列的研究中，我们已经通过调整基准风险（调整了低终点事件数）克服了这一问题。

有效性

虽然本研究是观察长期风险，但我们的研究也包括了对短期风险评估的 ABCD² 模型。然而 ABCD² 研究的校准和识别力与长期预测模式没有很大的差别。因为尚缺乏 TIA 或缺血性卒中病人长期风险评估的类似研究，所以无法与其他研究进行比较。

可能的改进

7 个预测模式采用二分变量代替连续变量。使用连续变量对风险的评估可能会更精确、识别力可能更佳 [22]。此外，以卒中人群为基础的预测模型来自于有特定入选标准和排除标准的临床研究。对于日常应用的最佳预测模型可能会来自于一个有代表性的群体，这意味着入选连续发生卒中的病人，而且没有排除标准。

结论

对于患有 TIA 和卒中的病人长期风险的预测，
目前的预测模式有局限性。多数模型的校准（可靠性）似乎是合适的，但是对高风险、低风险病人的识别力仍相对较低。一些改善措施比如使用连续型变量和拓展更强的预测指标都是必要的。目前 SPI-II 和 ABCD² 预测模式似乎是最合适的。二者之中，ABCD² 预测模式可能更好，因为它更容易在临床中使用。

参考文献