Clinical Scores for Predicting Recurrence After Transient Ischemic Attack or Stroke
How Good are They?
Robin Lemmens, MD, PhD; Stephanie Smet, MD; Vincent N. Thijs, MD, PhD

Risk scores are commonly used in the prediction of disease outcome. In the context of cerebrovascular diseases, risk scores have been created to identify stroke risk after transient ischemic attack (TIA) and (minor) stroke, to identify subgroups of patients with high risk of stroke (for instance, correlated with grade of carotid stenosis), or to predict functional outcome after stroke.

Identifying high-risk patients after TIA is important because early assessment and management of these patients is pivotal. Confident detection of the low-risk patient, however, is of similar importance. Performing multiple acute diagnostic investigations for all suspected TIA and stroke patients might overwhelm the medical system and might not be feasible because of resource limitations. Simple and reliable risk estimation of recurrence might be beneficial to high-risk patients to be admitted and investigated early. Additionally, the medical health system might benefit as well, because low-risk patients can be seen in less expensive outpatient clinics. We performed a systematic review of published risk scores that predict recurrence risk after stroke or TIA. We checked the quality of the risk scores based on the characteristics of the various derivation and replication studies.

Methods
One investigator (S.S.) performed a PubMed search with the search terms prognostic models stroke and prognostic scores stroke for the period 1992 to 2011, and additionally explored the reference lists of the identified articles. We excluded specific risk scores for stroke risk in atrial fibrillation, for instance, CHADS2, CHADS2VASc2, or global vascular estimates, such as the QRISK and SCORE. The other exclusion criteria, internal and external validity, statistical methodology, validation of the models, and clinical applicability were evaluated (for details, see Methods and Table I in the online-only Data Supplement) by 3 independent researchers (R.L., S.S., and V.T.). All results were compared between researchers and inconsistencies were resolved by reevaluation of the original article.

Results
We identified 17 risk scores that were derived from TIA or stroke cohorts (Table I) to predict short-term or long-term recurrence and one that was derived from a prospective population-based study in the general population but was validated in a TIA/stroke cohort. The characteristics and quality criteria for the risk scores are shown in Tables II and III in the online-only Data Supplement. The studies were performed in heterogeneous study populations with various designs and inclusion/exclusion criteria. Qualification of these reports was, therefore, not always possible according to the criteria presented in Table I in the online-only Data Supplement. Ten of the predictive models were derived in cohorts that used TIA as an index event, 5 models included both TIA and (minor) stroke, whereas 2 scales were developed in a population that only included stroke patients. In general, cardiovascular risk profiles were adequately collected in the majority of the study populations. The diagnostic work-up after the incident event varied largely between studies, which might have indirectly influenced recurrence rates; for instance, performing ECG or holter monitoring to identify atrial fibrillation likely has an effect on the treatment of patients and the frequency of recurrence. Primary end points were rarely adjudicated by 2 independent persons and were often not determined by a patient visit, but by patient file review. Different studies used various clinical end points: recurrence of stroke, vascular disease, (vascular) death, or combined end points. The nature of the recurrent stroke (ischemic vs hemorrhagic) was frequently not specified. Race characteristics were rarely provided, which is of relevance because recurrence rates could differ between races. The various risk scores and their clinical applicability will be discussed.

Californian Risk Score
A simple 5-point score using age, diabetes mellitus, symptom duration, the presence of weakness, and speech impairment was found predictive of stroke within 90 days in a retrospective study of 1000 patients admitted with TIA to an emergency department. This risk score was externally validated in large cohorts and population-based studies, although c-statistics did not reach 0.8. Whether addition of brain imaging to the score might be of additive value has not been determined.

Received November 13, 2012; final revision received December 4, 2012; accepted December 16, 2012.
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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.000141/-/DC1.
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(Stroke. 2013;44:1198-1203.)
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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.111.000141

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ABCD, ABCD2, and Additional Variables

The 7-day risk for stroke after TIA was estimated based on clinical characteristics within the OXVASC study. The following significant predictors were included in calculation of the score (with different weights, as indicated in parentheses): age ≥60 years (1); blood pressure ≥140/90 mm Hg (1); unilateral weakness (2); speech impairment without weakness (1); duration ≥60 minutes (2) or 10 to 59 minutes (1). Since publication, this ABCD score has been replicated in most studies, which included >200 patients, with some of these also extending the prediction horizon to 90 days after the incident TIA (or minor stroke). In none of the replication cohorts, c-statistics reached 0.8, with the exception of one validation cohort (Table III in the online-only Data Supplement). The score can be used to identify those patients at increased risk who need admission, but caution is warranted because several studies identified recurrence in patients with low scores and high-risk disease has been underscored by additional data from the discovery cohort of the ABCD/ABCD2 score, which showed the ABCD2 score to be predictive for severity of recurrence rather than risk.

In summary, the ABCD2 has rather low specificity and positive predictive value but good sensitivity and negative predictive value. C-statistics in none of the publication reached 0.8, with the exception of one validation cohort (Table III in the online-only Data Supplement). The score can be used to identify those patients at increased risk who need admission, but caution is warranted because several studies identified recurrence in patients with low scores and high-risk disease has been shown to be present in patients in the low-risk group. This was underscored by additional data from the discovery cohort of the ABCD/ABCD2 score, which showed the ABCD2 score to be predictive for severity of recurrence rather than risk.

Potentially adding other characteristics, such as hyperglycemia, history of hypertension (AB2CD/AB2CD2/AB2CD3), or dual TIA (ABCD3), might increase the negative predictive value, but validation is lacking. Additionally, several groups have explored whether adding imaging findings to the ABCD/ABCD2 scores might improve their performance. Computed tomography, diffusion-weighted imaging (DWI), and vessel occlusion status data were analyzed. Initially, imaging data on any evidence...
of infarction and leukoaraiosis were joined to the ABCD score to create the ABCD1, which resulted in similar accuracy compared with ABCD.\textsuperscript{18,35} The ABCD2I score, which included the presence of brain infarction on computed tomography or DWI, has been extensively studied in a multicentric approach.\textsuperscript{20} Three studies included acute DWI lesions on MRI in the prediction of stroke model, which clearly improved the accuracy to c-statistics >0.8 in all cohorts.\textsuperscript{22–24} Moreover, in the prediction of stroke model, which clearly improved the reliability.

Support a role for imaging data, in particular DWI lesions, to approach.\textsuperscript{28} Three studies included acute DWI lesions on MRI or DWI, has been extensively studied in a multicentric population was included in this study.\textsuperscript{21} These findings clearly increase the reliability.

### Oxford TIA (Hankey Score)

In a population-based cohort from Oxford, several vascular risk rates were calculated, and prognostic factors were determined for stroke, myocardial infarction, and combined end points, and they were translated into a 5-year risk percentage. The model for stroke was established by using the following 8 clinical factors: age, sex, affected region (amaurosis fugax as well as carotid and vertebrobasilar), frequency of TIA, residual neurological deficits, peripheral vascular disease, and left ventricular hypertrophy.\textsuperscript{30} Although the risk score was able to discriminate high-risk patients from low-risk patients (depending on the cut-off), a clear cut-off that was able to divide patients in high-risk vs low-risk groups could not be confidently recommended.\textsuperscript{41} In 2 other studies, the Hankey score was found to overestimate the risk; although the model could be used for prediction of recurrence, the accuracy seemed relatively weak\textsuperscript{36,42} (Table III in the online-only Data Supplement). Additionally, the risk prediction did not simply involve the collection of several clinical data set, but also a calculation of these variables in a formula probably reducing its clinical applicability.

### Stroke Prognosis Instrument

The Stroke Prognosis Instrument (SPI-I) was developed in patients with suspected carotid TIA or minor stroke. In a small patient sample of 142 patients, 5 predictors (age, diabetes mellitus, hypertension, coronary heart disease, and distinction between TIA and stroke) were included to define 3 risk groups for recurrence in a 2-year follow-up.\textsuperscript{43} Ten years later, this score was externally validated in 4 cohorts, and although the risk score was validated, even in the low-risk group, the recurrence rate was 10%.\textsuperscript{44} A modified SPI-II was created that included the additional variables previous stroke and congestive heart failure. The patients were more evenly distributed, and the c-statistics improved moderately, although they remained <0.8. Still, the recurrence rate remained 10% in the lowest-risk group. Furthermore, application of this score was restricted to patients with carotid territory TIA or minor stroke based on clinical characteristics, impeding the clinical utility for primary care physicians.

In 3 additional large cohort studies, the SPI-II was evaluated.\textsuperscript{36,38,42} The results were disparate, with both confirming the risk score as well as showing poor predictive power.

### Dutch TIA Trial and Life Long After Cerebral Ischemia Trial

Data from >3000 patients enrolled in the Dutch TIA trial were analyzed for their prognostic value for a 2-year risk analysis.\textsuperscript{46,47} Based on the hazard ratios in the initial publication, the predictive value of 13 parameters (Table IV in the online-only Data Supplement) was calculated in the same population but showed no strong discriminative value.\textsuperscript{37} This was confirmed in another cohort comparing 7 models in which this score was found to overestimate risk.\textsuperscript{36} The original Dutch TIA cohort was followed-up during a mean period of 10 years, and the data were reanalyzed (Life long after cerebral ischemia trial [LiLAC]). Three different models were designed based on subcategories of variables: demographics (sex and age) and medical history (myocardial infarction, intermittent claudication, diabetes mellitus, peripheral vascular surgery, and hypertension) in model 1; addition of event characteristics (TIA vs stroke, Rankin grade, and vertigo) in model 2; and addition of brain imaging (white matter lesions and any infarct) and ECG data (Q wave on ECG and negative T wave) in model 3. Areas under the curve were clearly improved and reached values >0.8 for all 3 models\textsuperscript{48}; however, this could not be confirmed in a validation cohort.\textsuperscript{52}

### Framingham: Stroke-Specific

A stroke risk score was derived based on 472 stroke events occurring within the initially stroke-free subjects from the Framingham study. A sex-specific risk model was developed that included age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, smoking, previous cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy (on ECG). There is only 1 publication that evaluated the Framingham stroke risk score in a cohort of patients with previous TIA and stroke. The score was not validated and had poor c-statistics.\textsuperscript{36}

### Essen Stroke Risk Score

The Essen Stroke Risk Score (ESRS) was derived from the stroke subgroup of the CAPRIE (clopidogrel vs aspirin in patients at risk of ischemic events) trial, which compared the effect of clopidogrel over aspirin in patients with vascular disease during a mean follow-up of 1.9 years. This model used 8 clinical parameters: age, hypertension, diabetes mellitus, myocardial infarction, other cardiovascular disease, peripheral artery disease, smoking status, and history of TIA or stroke.\textsuperscript{49} Patients with indications for oral anticoagulants were not enrolled in CAPRIE. In a validation cohort, this score was unable to significantly distinguish between high-risk and low-risk patients.\textsuperscript{50} Thereafter, the ESRS was calculated in various study populations in which the dichotomization cut-off between high risk and low risk was either confirmed\textsuperscript{62,51} or refuted.\textsuperscript{38} However, even in the replication cohorts, which confirmed the predictability, the positive predictive values were low, questioning the usefulness of these risk scores in daily clinical practice.
Recurrence Risk Estimator at 90 Days
A Web-based prognostic 6-point score (the recurrence risk estimator at 90 days) was derived from a sample of 1500 stroke patients to estimate the 90-day risk of recurrence. Recurrent stroke was confirmed by MRI. Two models, either with or without baseline imaging data, were validated in derivation and validation cohorts. The area under the curve for the 90-day risk of recurrence was 0.80 for the derivation cohort, which was reasonably well-replicated in the validation cohort (0.76).

The models include the following factors: presence of multiple infarcts of different ages, simultaneous infarcts in different circulations, multiple acute infarcts, isolated cortical infarcts, history of stroke or TIA, and stroke subtype based on the Causative Classification of Stroke System. Stroke attributable to other causes, as typed by Classification of Stroke System, was identified as the highest-risk subtype. Interestingly, conventional risk factors identified by scores estimating the risk after TIA (such as hypertension and diabetes mellitus) were not identified as short-term (90 days) risk factors for recurrence after ischemic stroke.

Discussion
Several prediction models have been developed to evaluate the stroke recurrence risk after TIA and (minor) stroke (Table IV in the online-only Data Supplement). Ideally, one would like to know which is the best score. However, comparison of risk scores is hampered by the different study paradigms, particularly inclusion criteria of the index event (TIA vs stroke) and duration of follow-up to determine recurrence (Table 1). Therefore, studies that directly compare various scores need to be interpreted with some caution. In an independent Dutch cohort, the 2-year risk was obtained in patients after TIA or minor stroke, and the SPI-II, Hankey, Dutch TIA, and ABCD2 scores were validated. However, the ABCD2 was not developed to estimate the long-term risk of recurrence, and both the ABCD2 and Hankey derivation cohorts only included TIA patients. Another prospective study assessed the prognostic value of the ABCD2, ESRS, and SPI-II in patients presenting with minor stroke. The accuracy of all 3 models was poor in predicting recurrence rate at 7 and 90 days. However, the ESRS and SPI-II were developed in stroke, not TIA, patients to predict long-term recurrence. It can be assumed that risk factors of a second cerebrovascular event differ between early and late recurrence, as well as between TIA and stroke as the index event. This is underscored by the recurrence risk estimator at 90 days, a model predicting recurrence after stroke in a period of 90 days, which includes other prognostic factors compared with the ABCD2 score (which evaluates recurrence at 90 days after TIA). Only a large prospective study in German stroke centers evaluated the risk in patients after TIA or minor stroke (with a median follow-up of 1 year) with scores that were derived to estimate the recurrence rate after follow-up of at least 1 year in patients with TIA or minor stroke: the ESRS, SPI-II, Oxford TIA, and LiLAC scores. None of these models could convincingly reproduce the prediction models. The finding that risk factors might differ in patients, based on either TIA or stroke as index event, might explain the difficulty in replicating the accuracy of a scale, especially in the 5 models that were derived from cohorts that included both TIA and stroke patients. Potentially, variations in proportions of TIA and stroke patients could have resulted in different findings in the replication cohorts compared with the derivation sample.

Studies replicating only 1 risk score occasionally evaluated risk in patients with a dissimilar preceding event compared with the derivation population or used longer or shorter duration of follow-up to determine recurrence. Additionally, patient characteristics varied between studies because patients with atrial fibrillation were sometimes excluded or imaging was used as an inclusion criteria. Many studies lacked a clear clinical confirmation of a recurrent event by a physician because patient files were used to obtain end points. This was illustrated by the fact that a difference between hemorrhagic and ischemic stroke was rarely reported. Furthermore, it is only recently that imaging has been added in the study design to validate recurrent stroke.

When designing a predictive model, high event rates are desirable, with occurrence of at least 10 events per studied prediction variable; in several derivations and in half of the validation cohorts, this criterion was not met. Almost all models suffer from low c-statistics (<0.8) and, therefore, cannot be confidently used in the clinic, because this implies that cutoffs cannot be reliably introduced to make decisions regarding individual patients. This is reflected by the relatively high event rates in low-risk patients in some studies. Individual treatment decisions based on the current prognostic models cannot be justified.

In efforts to improve the precision of the predictive models, researchers have increased the number of variables into risk models. Although adding more factors to a model can increase accuracy and reliability, this often compromises its utility in daily clinical practice. Including imaging findings, such as diffusion lesions and the presence of vessel stenoses, increases accuracy. However, the initial purpose of risk stratification scores was to support emergency doctors and primary care doctors to identify patients at high risk for recurrence with limited resources. Therefore, the addition of costly imaging will face resistance by emergency doctors and primary care physicians. One can wonder whether the addition of MRI data interferes with the purpose of these models. Therefore, adjusted models with increased accuracy might be more useful in epidemiological studies or clinical trials rather than in aiding clinicians in therapeutic decision-making. Additionally, requirement of neuroimaging may result in selection bias. For instance, one of the first studies to report on imaging data and ABCD score in TIA patients identified a substantial age difference between patient with and without MRI. Furthermore, in the assessment of recurrence risks of TIA, the yield of diffusion in addition to the ABCD2 versus the yield of commonly recommended diagnostic tests, such as ECG and carotid ultrasound, has not been specifically assessed.

Direct comparison studies evaluating various predictive models can be criticized for the reasons mentioned above; however, the existence of multiple models, including different index events for the evaluation of short-term as well as long-term recurrence, does reflect the real-life clinical experience. It is not likely that 1 model will be developed to evaluate...
short-term and long-term risk after stroke or TIA. Moreover, given the various causes of stroke, a one-size-fits-all prediction risk model is unlikely to be perfect under all circumstances. The heterogeneity of predictive models can be helpful to evaluate diverse patients in various scenarios. Therefore, it may be less relevant to directly compare the models, but more important to validate each model in the population cohort for which it was designed and for the end point that was chosen in the derivation study.

At present, the early risk of stroke after TIA, the issue that has been most extensively studied, seems to be predicted best by the ABCD2 combined with DWI data. For early recurrence risk after stroke in the 2 models developed, the recurrence risk estimator at 90 days is optimally suited, but it requires both very accurate subtyping and neuroradiological assessment (Table 2). Long-term risk after TIA and stroke cannot be reliably assessed based on the current knowledge. Whether these models can be used for decision-making on an individual-patient level remains speculative. Further large prospective studies involving TIA and stroke patients using various models are still necessary to strongly validate the predictive models and, even more importantly, to evaluate the added value regarding improving care.

Sources of funding
Drs Lemmens and Thijs are Senior Clinical Investigators for FWO Flanders.

Disclosures
Dr Thijs has declared to have received modest support from Boehringer Ingelheim (Speakers’ Bureau) and from Boehringer Ingelheim, Sygnis, Bayer, and Pfizer (Consultant/Advisory Board). The other authors have no conflicts to report.

References

Table 2. Key Points

| Predictive models for recurrent stroke ultimately should be able to guide physicians in early decision-making after TIA and stroke |
| Risk factors for recurrence differ between TIA and stroke as initial event |
| The majority of predictive scales have been derived from cohorts that include patients with TIA as the index event |
| Adding neuroimaging to predictive models increases accuracy but reduces simplicity |
| High event rates have been reported in predicted low-risk categories |
| The ABCD2 with diffusion imaging data seems most reliable to estimate the early risk of recurrence after TIA; RRE-90 might be an interesting tool to establish the early risk of recurrence after stroke by stroke specialists |
| Validation in large sample sizes with adequate and similar inclusion criteria of the index event and end points as in the derivation study is of importance to confidently use these tools in daily clinical practice |
| Stratification of the best therapeutic and diagnostic pathway for an individual patient based on simple predictive scales might be difficult to achieve |
| When evaluating risk models, changes in diagnostic and therapeutic avenues need to be investigated to identify a correlation with improved patient care; thus far, this has not been clearly determined |

RRE-90 indicates recurrence risk estimator at 90 days; and TIA, transient ischemic attack.
Use of Clinical Scores in Predicting Stroke Risk

Lemmens et al


Key Words: clinical score ■ predictive model ■ recurrence risk ■ review
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Stroke. 2013;44:1198-1203; originally published online March 12, 2013; doi: 10.1161/STROKEAHA.111.000141
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/4/1198

Data Supplement (unedited) at:
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Clinical scores for predicting recurrence after TIA or stroke: How good are they?
Robin Lemmens, MD, PhD 1,2,3, Stephanie Smet, MD 3, Vincent N. Thijs, MD, PhD 1,2,3

Supplementary methods (see Supplementary Table 1)

All prognostic score models designed to determine recurrence of stroke after TIA or stroke as index event were included in this review. Replication studies needed to have follow-up of the reported cohort in order to determine validation: publications only mentioning scores at admission of patients without follow-up were excluded. Additionally, studies had to show actual replication by showing risk stratification of patients or mentioning of c-statistics. Meta-analyses of predictive models were excluded since only original publications were subject of this review.

External validity (I) was examined using the following criteria: 1) Population- versus hospital-based cohorts: Patients admitted in for instance specialized centers may have different baseline features compared to smaller centers. This might affect whether the findings can be generalized. (2) Diagnosis of index event: Who made the diagnosis of TIA or stroke and was this differentiated? Were patient evaluated by a (stroke) physician or was the diagnosis based on reviewing patients files? (3) Were strict exclusion criteria used which might influence the utility of the model in the general population? (4) Was a cardiovascular workup organized after the index event and subsequently adequate treatment initiated? Recurrence rates will very likely be affected by various diagnostic strategies 1,2. The internal validity (II) of the cohorts was analyzed by: (1) Was the time since the index event provided and were patients studied at a similar stage of disease? Recurrence rates are affected by the time since index events as has also been shown in clinical trials after TIA or stroke 3. (2) Was the loss to follow-up provided and less than 10%? (3) Were potential predictive variables
prospectively studied in adequate numbers in order to prevent exclusion of predictors in the model? (4) Was the outcome reliably measured and documented? If recurrence was only based on reviewing of patient files without examination by a physician, outcome percentages could be affected.

Statistical methodology (III) and power of the studies were checked by (1) sample size; (2) the events per variable (EPV) ratio, which should be more than 10; (3) execution of stepwise analysis.

The validation of the models developed (IV) was evaluated. (1) Was internal validation performed? (2) Was external validation performed in an independent cohort? (3) Did the model distinguish between low versus high risk patients?

Finally the clinical applicability (V) was investigated by (1) determining the simplicity of the clinical variables and whether clinicians could easily use the model. Two researchers independently defined the various models as well as the different studies on the same prediction scores. (2) Presence of confident intervals for prediction and (3) performance of c-statistics and/or area under the curve (AUC) for accuracy were identified. Since clinical decision making will depend on accuracy when physicians make use of a prediction model, the accuracy should be over or equal to 0.84. 


### Supplementary Table 1. Assessment of various studies on predictive models

| **External validity** | Community versus hospital-based  
TIA versus stroke as index event: Difference in inclusion  
Diagnosis by patient visit of file inspection  
Diagnosis by physician: Stroke-specialist or other/general  
Major exclusion criteria used  
Race details provided  
Gender details provided  
Age details provided  
Stroke work up for initial event: Difference between total and partial was made  
Initiated treatment details provided  
| **Internal validity** | Similar stage in disease; time from event provided  
Similar stage in disease: Most patients < 7 days after index event  
Loss to follow up provided for prospective studies  
Percentage of loss to follow up <5%  
Prospectively collection of baseline characteristics  
Measurement of recurrent event rate by patient visit or file  
Measurement of recurrent event rate by stroke-specialist or other/general  
Measurement of recurrent event rate by two independent physicians  
Long term follow-up: fixed end points  
Long term follow-up: various fixed end points  
Long term follow-up: > 90 days follow-up  
Outcome measured: (well specified) stroke  
Outcome measured: composite endpoint  
Which variables collected (known risk factors of recurrence)  
- Age  
- Hypertension  
- Diabetes  
- Duration of symptoms  
- Speech impairment  
- Weakness  
- Smoking status  
- Peripheral artery disease  
- Carotid artery disease  
- Coronary Artery disease |
| **Statistical validity** | Sample size: < 50, 50-200, >500  
Events per variable (EPV) ratio > 10  
Stepwise regression |
| **Evaluation** | Validated on data used to create model  
|               | External validation in an independent cohort  
|               | Correct evaluation of as high or low risk patients |
| **Practicality of use** | Applicability of the model: simple or complicated variables  
|               | Utility in the clinic based on model and validity  
|               | CI's for provided  
|               | AUC or c-statistics  
|               | AUC or c-statistics>0.8 |
Supplementary Table 2. General quality characteristics of external and internal validity of a total of 43 studies: n (%)  

### External validity

<table>
<thead>
<tr>
<th>Community versus hospital-based</th>
<th>TIA versus stroke as index event</th>
<th>Diagnosis by a physician or by patient file</th>
<th>No major exclusion criteria identified</th>
<th>Race details provided</th>
<th>Gender details provided</th>
<th>Age details provided</th>
<th>Stroke work up for initial event</th>
<th>Details of initiated treatment provided</th>
<th>Period of study</th>
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</thead>
<tbody>
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<td>Difference is made</td>
<td>Physician</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Total</td>
<td>1. Total</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>2. Partial</td>
<td>2. Partial</td>
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<tr>
<td>6 (14)</td>
<td>38 (88)</td>
<td>32 (74)</td>
<td>26 (60)</td>
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<td>3. 32 (74)</td>
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<td>3. 32 (74)</td>
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</table>

### Internal validity

<table>
<thead>
<tr>
<th>Similar stage in disease</th>
<th>Loss to follow up</th>
<th>Outcome</th>
<th>Measurement of recurrent event</th>
<th>Long term follow-up</th>
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</thead>
<tbody>
<tr>
<td>Time from event provided</td>
<td>Most patients &lt;7 days</td>
<td>Prospectively studies: provided</td>
<td>Percentage&lt; 5% (pro- or retrospective studies)</td>
<td>Stroke only investigated</td>
</tr>
<tr>
<td>32 (74)</td>
<td>25 (85)</td>
<td>29 (67)</td>
<td>30 (70)</td>
<td>38 (88)</td>
</tr>
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</table>

### Variables collected (potential risk factors for recurrence)

<table>
<thead>
<tr>
<th>Prospective measurement</th>
<th>Age</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Duration of symptoms</th>
<th>Speech impairment</th>
<th>Weakness</th>
<th>Smoking status</th>
<th>Peripheral artery disease</th>
<th>Carotid artery disease</th>
<th>Coronary artery disease</th>
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<td>36 (74)</td>
<td>43 (100)</td>
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<td>42 (98)</td>
<td>34 (79)</td>
<td>35 (81)</td>
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<td>34 (97)</td>
<td>21 (49)</td>
<td>15 (35)</td>
<td>31 (72)</td>
</tr>
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Supplementary Table 3. Statistical methodology, evaluation and validation of a total of 43 studies on predictive models (n / total studies)

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Sample size &gt;500</th>
<th>Events per variable (EPV) ratio &gt;10</th>
<th>Stepwise regression to develop the model</th>
<th>Internal validation of derivation sample</th>
<th>Correct evaluation of high versus low risk</th>
<th>Easily applicable (^a)</th>
<th>Study provides evidence to use the model (easy and reliable) (^b)</th>
<th>CIs for prediction provided</th>
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A Not all replication studies evaluated and reported risk stratification by categories; some only included c-statistics. Here total \( n \) includes also these studies.

B As evaluated by two reviewers, based on parameters studied and included in the model, since complex variables and models will not be easily introduced in rapid clinical assessment.

C When more populations and time points were reported in one publication, half or more of the cohorts and/or time points studied needed to be \( \geq 0.8 \).

D And at one time point in one cohort \(^{13}\).

E In derivation, but not in validation cohort \(^{35,49}\).
Supplementary Table 4. Predictors of stroke or TIA used in various models

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^A AHT: Antihypertensive therapy

^B PAD: Peripheral vascular disease (claudicatio or peripheral vascular surgery)

^C MI: Myocardial Infarction or CAD: Coronary artery disease
CVD: Cardiovascular disease
LVH: Left ventricular hypertrophy
CHF: Congestive heart failure
NI: Neuroimaging