ASTRAL-R score predicts non-recanalisation after intravenous thrombolysis in acute ischaemic stroke

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Summary
Intravenous thrombolysis (IVT) as treatment in acute ischaemic strokes may be insufficient to achieve recanalisation in certain patients. Predicting probability of non-recanalisation after IVT may have the potential to influence patient selection to more aggressive management strategies. We aimed at deriving and internally validating a predictive score for post-thrombolytic non-recanalisation, using clinical and radiological variables. In thrombolysis registries from four Swiss academic stroke centres (Lausanne, Bern, Basel and Geneva), patients were selected with large arterial occlusion on acute imaging and with repeated arterial assessment at 24 hours. Based on a logistic regression analysis, an integer-based score for each covariate of the fitted multivariate model was generated. Performance of integer-based predictive model was assessed by bootstrapping available data and cross validation (delete-d method). In 599 thrombolysed strokes, five variables were identified as independent predictors of absence of recanalisation: Acute glucose > 7 mmol/l (A), significant extracranial vessel STenosis (ST), decreased Range of visual fields (R), large Arterial occlusion (A) and decreased Level of consciousness (L). All variables were weighted 1, except for (L) which obtained 2 points based on β-coefficients on the logistic scale. ASTRAL-R scores 0, 3 and 6 corresponded to non-recanalisation probabilities of 18, 44 and 74 % respectively. Predictive ability showed AUC of 0.66 (95 %CI, 0.61–0.70) when using bootstrap and 0.66 (0.63–0.68) when using delete-d cross validation. In conclusion, the 5-item ASTRAL-R score moderately predicts non-recanalisation at 24 hours in thrombolysed ischaemic strokes. If its performance can be confirmed by external validation and its clinical usefulness can be proven, the score may influence patient selection for more aggressive revascularisation strategies in routine clinical practice.

Keywords
Cerebral infarction, thrombolytic therapy, decision support techniques, cerebral revascularisation, cerebrovascular occlusion

Introduction
Recanalisation of the occluded large vessels in acute ischaemic strokes (AIS) may occur spontaneously in a subset of acute ischaemic stroke patients, but is more effectively achieved by intravenous thrombolysis (IVT) (1–6). However, patients with strokes due to large vessel occlusions have low recanalisation rates with IVT alone, associated with poor functional outcome despite treatment (1, 5). More aggressive, endovascular treatment strategies are increasingly used to treat large vessel occlusive strokes, as they recanalise these occlusions more effectively and rapidly. However, recent endovascular trials as IMS III, SYNTHESIS and MR-RES-CUE (7) did not show superiority of endovascular therapy, although a trend of effectiveness was present in severe strokes (NIHSS ≥ 20). Further, recanalisation by an acute endovascular intervention is not always associated with reperfusion and better clinical outcome (8), given that multiple other factors (time, collaterals, core and penumbra volumes, peripheral occlusions, site of ischaemia, metabolic states etc.) interfere. A better selection of patients who are most likely to benefit from aggressive (endovascular) therapy is therefore necessary (9).

We intended to develop and internally validate a simple score for prediction of non-recanalisation after IV thrombolysis in AIS patients by using items easily assessable before IV thrombolysis. So far, clinical variables as admission glucose levels (10, 11) and cardiovascular risk factors as atrial fibrillation (12, 13), smoking (14) and metabolic syndrome (15) were identified as predictors. Further, the following radiological items were known to be independently associated with recanalisation after intravenous thrombolysis: location of the vessel occlusion (11, 13, 17),
ASPECTS scores (17), thrombus length (18) and thrombus density (19).

Patients and methods

Study design and patient selection

The study includes data from a prospective cohort of consecutive, ischaemic stroke patients in four Swiss academic stroke centres (University Hospitals of Lausanne: 2003–2012, Basel: 2007–2013, Berne: 2007–2012 and Geneva: 2007–2012). The coordinating centre (Lausanne) compiled the data of the different prospective registers and performed the analysis of the pooled data. The inclusion criteria for the analysis were A) acute noninvasive vascular imaging (CTA, MRA or duplex) before IVT showing B) arterial occlusion in cerebral and/or cerebral arteries in relation to the ischaemic territory, C) availability of a second arterial imaging (CTA, MRA, angiography or duplex) at 24 hours (h) (allowed range 12–48 h) permitting assessment of recanalisation and D) treatment with IVT alone within proven time windows (3 h after last proof of well-being up to 10/2008, 4.5 h thereafter). Arterial occlusions were defined according to standardised methodologies that were published elsewhere (19). Vascular imaging (CTA, MRA or duplex) was performed in all centres before or within minutes after administration of the IV thrombolysis bolus which should not influence arterial pathology. In the vast majority of patients (n=563, 94%) CTA angiography was the initial imaging technique. Indications for IVT with recombinant tissue plasminogen activator (rtPA) followed European Stroke Organisation guidelines (21). Patients with additional acute endovascular procedures after IVT were excluded.

Medical variables collected and analysed included demographics, cardiovascular risk factors, co-morbidities, pre-stroke medication, type of clinical deficit, NIHSS at admission (with all items individually collected), onset-to-admission time, vital signs and radiological imaging at admission. Pretreatment NIHSS scores were assessed by certified stroke physicians. The clinical signs “decreased range of visual fields” and “loss of consciousness” were defined as in the NIHSS scale. On the acute vascular imaging, large vessels pathology was analysed in each centre by both a neuroradiologist and stroke neurologist aware of clinical findings. As both raters collaborated as a team, inter-rater variability has not been assessed. The information on the presence and site of large vessel occlusions and significant intra- and extracranial stenoses were collected, based on pre-specified definitions. Intracranial occlusions in the ischaemic territory were categorised according to their site in large vs intermediate occlusions. Large intracranial occlusions were defined as an occlusion of the basilar artery (with our without intracranial vertebral artery occlusion), the intracranial carotid siphon (large and/or including carotid T) and large middle cerebral artery (M1) both with and without ipsilateral extracranial carotid occlusion. Intermediate intracranial occlusions were defined as occlusions in anterior cerebral artery (A1 or A2 segments), peripherial middle cerebral artery (M2), posterior cerebral artery (P1 or P2 segments), intracranial part of the vertebral artery (V4) and siphon of the internal carotid artery without distal T-occlusion; the latter two were considered “intermediate” because thrombus load and clinical symptoms are usually minor in the absence of extension into the basilar artery and the carotid T, respectively. Recanalisation of initially occluded arteries was defined for intra- and extracranial vessel occlusions and for the different imaging techniques separately, and was classified as “absent” vs “partial or complete”. These criteria were published elsewhere (20) If several good quality studies are available at 12–48 h, priority was given to DSA > CTA > MRA > Doppler.

The collection, analysis and publication of data in the four stroke registries were performed according to the guidelines of the respective ethical boards of each centre.

Statistical analyses

Continuous variables are summarised using median and inter-quartile range, while categorical ones with count and percentage. Univariate comparisons for all the variables considered, between the patients who recanalise after intravenous thrombolysis and those who did not, were performed using logistic regression analysis, where the significance of each variable was assessed separately. Before starting the multiple analysis, imputation of the missing values of the covariates considered was performed using the method of chained equations (i.e. filling in the missing values on a variable-by-variable basis, by first specifying the imputation model for each incomplete variable and then using this model to fill in the gaps). Five imputed datasets were generated using this method. Multiple logistic regression analysis was performed on each imputed dataset separately. Stepwise methods were implemented on each one of the five analysis, to identify significant main effects and interactions. Final results were derived as combinations of the outcome of the five imputed analysis. The log-odds of the final model were used to define the coefficients in the proposed score. Predictive ability of the score is measured via the area under the receiver-operating characteristic curve (AUC-ROC), calculated for the imputed datasets using bootstrapping and cross validation. Bootstrapping assesses the predictive ability of our model by creating copies of the imputed datasets and recalculating AUC on these copies. Cross-validation splits the imputed dataset in two parts (not necessarily in half), fits a model to one part, and assesses its predictive ability using the other part. As the two methods might be considered as complementary to the other, both techniques were used to evaluate the predictive ability of models. The ROC analysis was carried out on the imputed datasets separately, and final results were derived as combination of the outcome of these analyses. All tests were carried out at 5% significance level. All analyses performed using the statistical package R (version 3.0.2).

Results

Prevalence of partial or complete recanalisation within 24 h (12–48 h) after IV thrombolysis was 66% or 396 patients in our multi-centre cohort (n=599). The demographics and baseline characteristics of patients with and without recanalisation are

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shown partially in Table 1. Numbers of included patients per centre were as follows: Lausanne (n=210), Basel (n=217), Bern (n=136) and Geneva (n=35). Recanalisation was assessed by CTA in 82% (n=491), by MRA in 12% (n=72) and by duplex only in 6% (n=36). Five clinical and radiological variables were identified as independent predictors of non-recanalisation: Acute glucose > 7 mmol/l (A), STenosis or occlusion of extracranial vessels (ST), Range of visual fields decreased (R), Arterial occlusion in a large site (A) and an decreased level of consciousness (L) (Table 2). The cut-off value for acute glucose levels was chosen on a tree-based method, suggesting that a cut-off of 7 mmol/l would be the most adequate. As the initial multivariate analysis failed to acknowledge the role of time in relation to recanalisation, additional statistical analyses were performed to check the effect of different cut-off values for the onset-to-needle times (< 1.5 h, < 3 h, < 4.5 h) on the prediction of recanalisation. No significant correlation was detected between dichotomisation at 3 h (OR 1.2, 95% CI 0.8–1.8) and at 4.5 h (OR 1.5, 95% CI 0.5–4.9) with recanalisation after IV thrombolysis. Only, dichotomisation at 1.5 h was significantly associated with recanalisation (OR 1.97, 95% CI 1.1–3.5). This parameter, however, did not improve the predictive performance of the ASTRAL-R score in terms of AUC-ROC.

The ordering of the predictors used in our score, according to their significance in the final model, judged from the p-value of the imputation analysis and starting from the most significant to the least significant, is as follows: decreased consciousness, extracranial pathology, visual field defect, acute glucose level and proximal intracranial occlusion. A predictive model with the item decreased consciousness only has AUC 57.7%, adding extracranial pathology the AUC raises to 62.1%, adding further visual field defect AUC is estimated at 64.6% and adding acute glucose level AUC goes to 65.0% and finally adding proximal occlusion gives an AUC of 66.2% (Suppl. Figure 1, available online at www.thrombosis-online.com).

Table 1: Selection of baseline characteristics and radiological findings, dichotomised according to presence or absence of post-thrombolytic recanalisation. Values are expressed as medians and interquartile range (IQR) for continuous variables unless stated otherwise, and as absolute counts and percentage for categorical variables.

<table>
<thead>
<tr>
<th>Medical history</th>
<th>Non-recanalisation (n=203)</th>
<th>Recanalisation (n=396)</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>75 (39%)</td>
<td>156 (42%)</td>
<td>1.13</td>
<td>0.79–1.61</td>
<td>0.49</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>138 (68%)</td>
<td>258 (65%)</td>
<td>0.89</td>
<td>0.62–1.27</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>108 (53%)</td>
<td>185 (47%)</td>
<td>0.77</td>
<td>0.55–1.09</td>
<td>0.14</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>28 (14%)</td>
<td>53 (14%)</td>
<td>0.99</td>
<td>0.60–1.62</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Table 2: The ASTRAL-R Score: Independent predictors of absence of post-thrombolytic recanalisation at 24 h with the respective score points.
Figure 1 displays the predicted probability of non-recanalisation after IV thrombolysis based on the ASTRAL-R score. The absolute risk of non-recanalisation for the corresponding ASTRAL-R scores 0, 1, 2, 3, 4, 5 and 6 were 17.7%, 24.8%, 33.5%, 43.6%, 54.2%, 64.4% and 73.5%, respectively. Patients with an ASTRAL-R score more than 3 have a likelihood of absence of post thrombolytic recanalisation of more than 50%. Suppl. Figure 2 (available online at www.thrombosis-online.com) shows the distribution of the overall ASTRAL-R score and its components among the population.

The predictive ability of the model was assessed in two ways: a) by calculating the AUC of the ROC curve using the original sample (599 patients after imputing for missing values) and attaching uncertainty using bootstrap methodology (1,000 repetitions), and b) by cross-validation (deleted-d method repeated 1,000 times). The estimated AUC in both cases was 0.66 with a 95% CI of 0.61–0.70 (Suppl. Figure 3, available online at www.thrombosis-online.com) using the first method, while the corresponding 95% CI for the cross validation was 0.63–0.68 (Suppl. Figure 4, available online at www.thrombosis-online.com).

Discussion

This study describes the derivation and internal validation of the ASTRAL-R score in a multi-centre cohort which estimates the likelihood of non-recanalisation 24 h after IVT. A linear relationship between the total score and non-recanalisation could be shown, and the performance of the model was assessed in a multi-centre cohort.

The score consists of five easily available variables already before IVT: acute glucose (cut-off >7 mmol/l), extracranial stenosis >50% or occlusion, visual field defects, decreased level of consciousness and a large artery intracranial occlusion. Hyperglycaemia in acute stroke patients is common and may decrease plasma t-PA activity. Further, acute hyperglycaemia may be related to atherosclerotic disease, which has been shown to be more resistant to recanalisation after tPA treatment (10, 22). The concomitant presence of extracranial arterial stenosis or occlusion may lead to less recanalisation because of decreased inflow of blood into the blocked arteries, leading to less arrival of IV rt-PA and less wash-out of clots (23). Occlusion of larger intracranial arteries is likely to be related to less recanalisation because of higher thrombus burden than in smaller arteries, as shown previously (13, 14). It is unclear why decreased level of vigilance and visual field defects were independent predictors of recanalisation, although these factors have been associated with worse clinical outcome (24). One hypothesis may be that these signs of clinical severity may indicate poorer collaterals which could also contribute to recanalisation (25).

Some previously described predictors of recanalisation, such as onset-to-needle time (10), atrial fibrillation (12, 13), smoking (14) and metabolic syndrome (15) and ASPECTS scores (17) were not confirmed in our logistic regression analysis. This may be related to differences in the cohorts or the sample size.

Use of the ASTRAL-R score in clinical practice has the potential to improve acute stroke management. Given several negative interventional revascularisation trials, a more careful selection of patients is mandatory (9). A more individualised patient selection based not only on the severity of the stroke but also on the non-recanalisation risk after IV thrombolysis could be promising. In individual cases with a high likelihood of non-recanalisation after IVT (e.g. large vessel occlusions, extracranial stenosis, hyperglycaemia), endovascular intervention for non-recanalising patients may be of added benefit, in particular if salvageable tissue can be demonstrated by multimodal imaging (26, 27). In addition, successful recanalisation is associated with better outcome also in severe stroke patients (28).

Some items in the ASTRAL-R score (level of consciousness, visual field defects and acute glucose level) are the same as in the prognostic ASTRAL score for clinical outcome (24). Both scores may be used as selection tools for future clinical trials on endovascular treatment after IVT.

One of the strengths of the ASTRAL-R score is the large number of patients and variables included and the multi-centre design including four sites with a longstanding experience in acute stroke research. Data were available on the specific site of arterial occlusions sites in all cohorts. Validation of the score was performed by a bootstrap and cross validation (delete-d method).

Several limitations apply: First, implementation in routine clinical practice may be hampered by the moderate predictive ability of the model with areas under the ROC curve of 0.66. This corresponds to other predictive scores in acute stroke care (e.g. SEDAN score) which have similar c-statistic values (29). This can partially be explained by combing four different cohorts of thrombolysed stroke patients. Adding factors such as collateral vessel status (25), perfusion imaging (30) and thrombus length (13) could further improve the score. However, such radiological data and imaging techniques are not routinely used in clinical practice and are hampered by standardisation issues. Secondly, external validation in independent cohorts will be necessary to confirm the performance of the score. The validity of the score in patients who...
underwent endovascular treatment needs to be assessed, as these patients were excluded in the current analysis. Thirdly, large vessel occlusions were classified into large and intermediate arterial occlusions, mainly based on anatomical location. The likelihood of recanalisation between the location sites may be more variable than expected. This arbitrary classification is debatable, but clinically relevant in the absence of a standardised classification of the intracranial arteries. Fourthly, our definition of recanalisation was not based on a single imaging modality but on heterogeneous methods, the degree of recanalisation was dichotomised at an arbitrary point (between none and partial or complete) and the best timing for recanalisation assessment is still unknown. Fifthly, a pre-selection bias may have been introduced in the study by excluding stroke patients with additional acute endovascular procedures after insufficient IV t-PA recanalisation. Potentially, lower recanalisation rates and different predictive parameters would have been found in this subgroup of patients. And finally, reading of the vascular imaging data was not centralised in order to prevent high inter-rater variabilities.

Conclusions

In conclusion, the ASTRAL-R score is an easy-to-assess 5-item score moderately predicting non-recanalisation after IVT in acute ischaemic strokes.

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Author contributions

Vanacker P: Study concept and design, analysis, interpretation, preparation of the manuscript. Heldner MR: Data acquisition and analysis, critical revision of the manuscript for important intellectual content. Seiffge D: Data acquisition and analysis, critical revision of the manuscript for important intellectual content. Mueller H: Data acquisition and analysis. Traenka C: Data acquisition and analysis. Ntaios G: Study concept and design, data acquisition and analysis, critical revision of the manuscript for important intellectual content. Stajzel R: Data acquisition and analysis. Lyrer P: Data analysis, critical revision of the manuscript for important intellectual content. Fischer U: Data acquisition, data analysis, critical revision of the manuscript for important intellectual content. Lambrou D: Data analysis, statistical analysis. Arnold M: Data analysis, critical revision of the manuscript for intellectual content. Michel P: Study concept and design, data acquisition, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

What is known about this topic?

- A few clinical and radiological factors influencing the recanalisation rate in IV thrombolysis-treated acute ischaemic strokes, are known from small single-centre studies.

What does this paper add?

- By performing a logistic regression analysis in a multi-centre cohort, we could detect independent predictors of arterial recanalisation after IV thrombolysis.
- For the first time, a diagnostic tool (ASTRAL-R score) has been shown to have a good predictive accuracy for recanalisation after IV thrombolysis.
- The ASTRAL-R score is an easy-to-use 5 items score (0->6).
- In the future, some additional radiological can be detected to improve the accuracy of ASTRAL-R score.

Conflicts of interest

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