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Background and Purpose—Acute stroke patients with unknown time of symptom onset are ineligible for thrombolysis. The diffusion-weighted imaging and fluid-attenuated inversion recovery (FLAIR) mismatch is a reasonable predictor of stroke within 4.5 hours of symptom onset, and its clinical usefulness in selecting patients for thrombolysis is currently being investigated. The accuracy of the visual mismatch rating is moderate, and we hypothesized that the predictive value of stroke onset within 4.5 hours could be improved by including various clinical and imaging parameters.

Methods—In this study, 141 patients in whom magnetic resonance imaging was obtained within 9 hours after symptom onset were included. Relative FLAIR signal intensity was calculated in the region of nonreperfused core. Mean $T_{\text{max}}$ was calculated in the total region with $T_{\text{max}} > 6$ s. Mean relative FLAIR, mean $T_{\text{max}}$ lesion volume with $T_{\text{max}} > 6$ s, age, site of arterial stenosis, core volume, and location of infarct were analyzed by logistic regression to predict stroke onset time before or after 4.5 hours.

Results—Receiver-operating characteristic curve analysis revealed an area under the curve of 0.68 (95% confidence interval 0.59–0.78) for the visual diffusion-weighted imaging/FLAIR mismatch, thereby correctly classifying 69% of patients with an onset time before or after 4.5 hours. Age, relative FLAIR, and $T_{\text{max}}$ increased the accuracy significantly ($P<0.01$) to an area under the curve of 0.82 (95% confidence interval 0.74–0.89). This new predictive model correctly categorized 77% of patients according to stroke onset before versus after 4.5 hours.

Conclusions—In patients with unknown stroke onset, the accuracy of predicting time from symptom onset within 4.5 hours is improved by obtaining relative FLAIR and perfusion imaging. (Stroke. 2016;47:2559-2564. DOI: 10.1161/STROKEAHA.116.013903.)

Key Words: fluid-attenuated inversion recovery imaging • perfusion imaging • prediction • thrombolysis • time-window

Intravenous thrombolysis can be administered ≤4.5 hours after symptom onset. Unfortunately, the exact time of stroke onset cannot be determined in a large subset (20%) of patients. In this subgroup, the time when patients were last seen normal is used to safely estimate the stroke onset time. As a result, many of these patients are ineligible for any acute stroke treatment. Neuroimaging characteristics have been explored as surrogate markers to predict time after symptom onset as an alternative for witnessed stroke onset times. In the PRE-FLAIR study, a mismatch between diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) hyperintensities was shown to be associated with time from symptom onset. The presence of a DWI/FLAIR mismatch predicted patients to be within a time interval of 4.5 hours after stroke onset, with 62% sensitivity and 78% specificity. Clinical implementation of the DWI/FLAIR mismatch is currently being explored in the WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke). This study enrolls patients with unknown stroke onset time and randomizes the subgroup of patients with a visual DWI/FLAIR mismatch to placebo versus thrombolysis.
The predictive power of the DWI/FLAIR mismatch pattern to accurately classify patients in the appropriate time epoch is variable. Performing a quantitative analysis of FLAIR imaging by determining intensities in defined region of interests (ROI) did not improve the accuracy compared with the visual DWI/FLAIR mismatch. In addition, clinical and other neuroimaging parameters, for example, age and DWI volume, have been identified as modifiers of the DWI/FLAIR mismatch. Recently, we identified an interaction between collateral status and the association between FLAIR lesion intensity and stroke onset time. Based on these findings, we aimed to construct an improved model to determine stroke onset time within 4.5 hours by adding other predictive, clinical, and neuroimaging variables.

In addition, we studied the power of the predictive models for a time window within 3 and 6 hours after onset. The 3-hour time interval is of interest because it is used for thrombolysis selection of some patients, and the 6-hour time window is relevant in the decision to initiate endovascular treatment of acute stroke patients with large vessel occlusions. To our knowledge, the predictive value of the DWI/FLAIR mismatch has only been studied limited to correctly classify patients within 3 and 6 hours after stroke onset.

### Methods

Clinical and neuroimaging data from a large Phase IIb, multicenter, placebo-controlled, randomized and double-blind trial the AXIS 2 (AX200 for ischemic stroke trial) were used. In AXIS 2, the clinical efficacy of recombinant granulocyte colony-stimulating factor (AX200) in acute ischemic stroke patients was evaluated. The primary and secondary end points of the trial were not met. The full details of the methodology of AXIS 2 have been described previously. In short, patients were included in a time window of ≤9 hours after symptom onset or after last seen normal. The main exclusion criteria used were signs of severe stroke on neuroimaging, hemorrhagic strokes, and lacunar infarcts.

The presence of a DWI/FLAIR mismatch was rated visually by 2 independent readers (Dr Wouters and Thijs) according to the criteria implemented in the ongoing WAKE-UP trial. The relative FLAIR (rFLAIR) signal intensity was calculated in voxel-based manner as described previously. For every voxel, the rFLAIR was calculated as the ratio of the FLAIR signal intensity in that voxel and the median FLAIR signal intensity of the sphere, with radius 15 mm around the homologue voxel in the contralateral hemisphere. Currently, we have developed prototype software, and rFLAIR is calculated by a Matlab script. At the moment, the analyses are done retrospectively, and the mean time per scan is around 30 minutes and depends on the spatial resolution. A summary of both methods can be found in Methods I in the online-only Data Supplement. To exclude the possibility that our results would critically depend on the method used to obtain rFLAIR values, another technique was used to calculate rFLAIR signal intensity. In this method, the ROI was mirrored to the contralateral hemisphere. Mean rFLAIR signal intensity for this method was defined as the ratio of the mean FLAIR signal intensities in the ROI by the mean FLAIR signal intensities in the mirrored ROI. RAPID software (iSchemaView, Menlo Park) for magnetic resonance imaging analysis was used for diffusion and perfusion imaging analysis. The infarcted tissue (core) was determined based on the apparent diffusion coefficient images as the region of Apparent Diffusion Coefficient (ADC) <620 mm²/s. T_max, defined as the maximum of the residue function after deconvolution, was adopted as a measure of hypoperfusion when the delay was longer than 6 s. Mean rFLAIR signal intensity for both previously mentioned methods was obtained in the nonreperfused core, defined as the overlap between the core and the region of hypoperfusion (T_max >6 s). The nonreperfused core was chosen because we intended to study the association between rFLAIR and time after excluding the potential effect of reperfusion on FLAIR hyperintensity. When an overlap occurred of more than one third of the contralateral lesion and an area of leukoaraiosis or an old ischemic lesion, as visually assessed by Dr Wouters, patients were excluded (see Figure I in the online-only Data Supplement for an example). This exclusion criterion was chosen because in these cases, the rFLAIR values would be less reliable as a result of the critical influence by the contralateral FLAIR intensity not related to the acute stroke. Figure 1 gives an overview of the different imaging modalities used in the prediction models.

We constructed a logistic regression model with stroke symptom onset before or after 4.5 hours as dependent variable. Age, National Institutes of Health Stroke Scale, DWI volume, hypoperfused lesion volume, mean T_max in hypoperfused lesion, site of arterial stenosis, location of infarct (with cortical involvement versus without), rFLAIR signal intensities with the interaction of the mean T_max on the relation between time from symptom onset and rFLAIR were added as explanatory variables. This model was simplified by removing variables that are not sufficiently contributing according to the Akaike information criterion method. The smaller the Akaike information criterion, the better the model. Predictive tables with a threshold of 0.5 and receiver-operating characteristic curves were calculated for the different models. Areas under the curve (AUCs) were compared with the DeLong’s test. The same multivariate analysis was performed with symptom onset before or after 3 and 6 hours as dependent variable.

To validate our predictive model, we used the leave-one-out cross validation technique. We repeatedly calculated the coefficients of

![Figure 1](https://example.com/fig1.png)

**Figure 1.** Imaging parameters used in the multivariate predictive model. DWI (A) and FLAIR (B) imaging reveal a DWI/FLAIR mismatch. The perfusion imaging map (C) shows the T_max in the region of hypoperfusion with a T_max >6 s, whereas in (D), the rFLAIR in the nonreperfused core is represented. DWI indicates diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery imaging; and rFLAIR, voxelwise relative FLAIR.
Results

In 206 patient from the original 324 patients of the AXIS 2 trial (63.8%), the necessary imaging sequences were available and of sufficient quality to be evaluated. As prespecified, 12 patients (5.2%) were excluded because confluent or large FLAIR lesions were present in the contralateral hemisphere or leukoaraiosis overlapped the acute lesion. No DWI lesion detected or complete reperfusion of the DWI lesion led to the exclusion of an additional 53 (25.7%) patients because a nonreperfused core was absent. Reasoning for including only patients with a nonreperfused core is mentioned in the methods, and in addition, in patients with complete reperfusion, the estimation of stroke onset seems less relevant because reperfusion therapy is no longer required.

Here we report the results of a total of 141 included patients. Baseline characteristics are shown in Table 1. Median time of symptom onset was 320 minutes. The time distribution of the whole study population can be found in Figure II in the online-only Data Supplement. When comparing the patients included in this analysis versus the excluded cohort, baseline National Institutes of Health Stroke Scale was more severe, and the percentage of good functional outcome at 90 days was slightly lower in the excluded cohort (Table I in the online-only Data Supplement).

Table 2 presents the models predicting delay since time of onset. In the final model, rFLAIR signal intensity, mean $T_{\text{max}}$ in the hypoperfused lesion, age, and the interaction terms were retained. These variables provided the highest predictive power for stroke onset within the time window of 4.5 hours (Table 2). When evaluating patients with the visual DWI/FLAIR mismatch rating, with good interobserver reliability (kappa=0.70), 69% patients were correctly classified with stroke onset before versus after 4.5 hours. This could be improved to 77% of the patients by the newly constructed predictive model (Table 3). The positive predictive value for this model was 0.75 (95% confidence interval [CI] 0.57–0.87), and the negative predictive value was 0.78 (95% CI 0.69–0.85) compared with 0.55 (95% CI 0.42–0.68) and 0.79 (95% CI 0.68–0.87) for the visual DWI/FLAIR mismatch. Interestingly, by only including perfusion imaging in the model with rFLAIR, the accuracy was already significantly improved compared with the visual mismatch rating (Figure III in the online-only Data Supplement). The visual DWI/FLAIR mismatch had an AUC of 0.68, which was improved to 0.82 ($P<0.01$) in the multivariate predictive model (Figure 2 and Table 3). The model was internally validated, resulting in a similar improvement of the accuracy (AUC of 0.79; $P=0.01$, Table II in the online-only Data Supplement). Figure IV in the online-only Data Supplement shows an example of a patient without a visual DWI/FLAIR mismatch being correctly classified by the multivariate predictive model.

In a sensitivity analysis to determine if the method used to obtain the rFLAIR would be critically important for our results, the rFLAIR was evaluated by the ROI technique. The same explanatory variables were retained in the final model with hypoperfused lesion volume as additional variable. This model resulted in correctly categorizing 77% of patients, and the accuracy showed a similar trend toward improvement (AUC 0.78; $P=0.06$).

In addition, we studied the power of a predictive multivariate model for stroke symptom onset before or after 3 and 6 hours. In our study, 15 patients (11%) presented within 3 hours after stroke onset and 92 (65%) within 6 hours. In the model to predict stroke onset before versus after 3 hours, the following explanatory variables were retained: rFLAIR, mean $T_{\text{max}}$, rFLAIR×mean $T_{\text{max}}$, and DWI lesion volume (Table 2). This multivariate model correctly classified 93% of the patients in the time epoch of 3 hours with a positive predictive value of 0.78 (95% CI 0.40–0.96) and a negative predictive value of 0.94 (95% CI 0.88–0.97). In this model, the AUC improved to 0.90 compared with 0.67 for the visual DWI/FLAIR mismatch ($P<0.01$; Figure 2).

To predict stroke onset before versus after 6 hours, the following explanatory variables were retained in the final model: rFLAIR, mean $T_{\text{max}}$, rFLAIR×mean $T_{\text{max}}$, and location of infarct (Table 2). This multivariate regression model correctly classified 67% of patients with a positive predictive value of 0.71 (95% CI 0.61–0.79) and a negative predictive value of 0.55 (95% CI 0.36–0.72). The AUC improved to 0.72 compared with 0.59 when using the visual DWI/FLAIR mismatch ($P=0.01$; Figure 2).

Discussion

In this analysis of acute neuroimaging in stroke patients, the accuracy of visual judgment of DWI/FLAIR mismatch to predict stroke onset within 4.5 hours was improved by combining quantitative FLAIR analysis (rFLAIR), hypoperfusion status, and age. This multivariate model correctly classified 77% of stroke patients in the time window before versus after 4.5 hours. Similarly, multivariate models that included clinical and neuroimaging parameters were more accurate in predicting stroke onset before or after 3 and 6 hours. Our results show...
exists for qualitative assessments of the DWI/FLAIR mismatch. In addition, we hypothesized that by including other variables, we would be able to improve the estimation of the time window. Recently, we have identified collateral status as a novel modifier of the DWI/FLAIR mismatch. These data suggested that the severity of hypoperfusion interacted with the association between time and FLAIR intensity. By including the severity of hypoperfusion, the accuracy to detect time of onset was further improved in our study.

Currently, the WAKE-UP trial is studying the effect of thrombolysis in patients with a DWI/FLAIR mismatch on clinical outcomes and 90 days. The results of this study could have potential implications for the treatment of patients with unknown time of stroke onset. Clinical implementation of the DWI/FLAIR mismatch is dependent on both the accuracy of the currently used visual rating versus the complexity of alternative methods used to improve the predictive value. Potentially, the automated quantitative measurements of FLAIR and perfusion imaging presented here could be of benefit to estimate duration of stroke symptoms. In the PRE-FLAIR study, the DWI-FLAIR mismatch pattern has been introduced and validated as a useful tool with moderate accuracy to predict stroke onset within the thrombolysis time window of 4.5 hours. Several factors may influence the predictive value of the DWI/FLAIR mismatch. One of these factors is whether a qualitative visual rating or a potentially more objective quantitative analysis is performed. Automated quantitative measurements could eliminate the interrater variability that exists for qualitative assessments of the DWI/FLAIR mismatch.

However, solely using quantitative measurements of rFLAIR did not result in increased accuracy in 2 prior studies. In addition, relative DWI intensities could approximate but not improve the predictive value of the DWI/FLAIR mismatch. In our study, the voxel-based relative FLAIR technique did result in a small improvement of the prediction of time for symptom onset. In a sensitivity analysis, a nonvoxel-based approach to calculate rFLAIR was performed, which showed a less robust improvement in time prediction compared with the voxel-based analysis. This underscores that a voxel-based rFLAIR calculation is more accurate to determine FLAIR hyperintensities.

We hypothesized that by including other variables, we would be able to improve the estimation of the time window. Recently, we have identified collateral status as a novel modifier of the DWI/FLAIR mismatch. These data suggested that the severity of hypoperfusion interacted with the association between time and FLAIR intensity. By including the severity of hypoperfusion, the accuracy to detect time of onset was further improved in our study.

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<table>
<thead>
<tr>
<th>Time After Stroke Onset</th>
<th>Visual (n)</th>
<th>Model 1 (n)</th>
<th>Model 2 (n)</th>
<th>Model 3 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4.5 h</td>
<td>64</td>
<td>82</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>≤4.5 h (n=50)</td>
<td>17</td>
<td>29</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Correctly classified (n=141)</td>
<td>97 (69%)</td>
<td>103 (73%)</td>
<td>105 (74%)</td>
<td>109 (77%)</td>
</tr>
<tr>
<td>AUC</td>
<td>0.68</td>
<td>0.76</td>
<td>0.80</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Actual and predicted patients within or after the 4.5 time window after stroke onset. The explanatory variables for every model are as follows: Visual, visual DWI/FLAIR mismatch; Model 1, rFLAIR; Model 2, rFLAIR+mean Tmax+rFLAIR×mean Tmax; Model 3, rFLAIR+mean Tmax+rFLAIR×mean Tmax+age. AUC indicates area under the curve of the complimentary ROC curve; DWI, diffusion-weighted imaging; mean Tmax, time to the maximum of the residue function obtained by deconvolution; rFLAIR, relative fluid-attenuated inversion recovery imaging; and ROC, receiver-operating characteristic.
versus excluded cohort and did not identify major differences except for stroke severity. Second, in the AXIS 2 study, exact stroke onset times were recorded when known, and when this was unclear, the time when patients were last seen normal was assumed as the onset time. Potentially, our results would have been even more striking if we could have limited our analysis to patients with exact stroke onset times, but unfortunately the method (exact versus last seen normal) of determining stroke onset was not documented. Third, the created predictive models could not be externally validated because we did not have access to an additional sample set of patients in whom all required imaging parameters have been obtained and stroke onset times are known. To partially overcome this limitation, we performed an internal validation that confirmed our results. Last, we would like to emphasize that, currently, we have developed prototype software to determine rFLAIR values. If clinical implementation of this model is considered, optimization of the postprocessing will be required to quickly predict the time window in patients with unknown stroke onset time.

Conclusions
We conclude that a multivariate predictive model integrating quantitative rFLAIR measurement, information on the severity of hypoperfusion, and age has greater accuracy than the visual judgment of DWI/FLAIR mismatch for determining stroke onset time within 4.5 hours. After further validation, this model may be useful for selecting patients for stroke therapies in whom the time of symptom onset is unknown.

Acknowledgments
Dr Lemmens is a Senior Clinical Investigator of FWO Flanders.

Sources of Funding
Dr Albers received grant funding from the National Institutes of Health.

Figure 2. Performance of the various models for different time windows. Receiver operating characteristic curves. x axis represents 1-specificity and y axis, the sensitivity. Curves in solid lines correspond to the final logistic regression models; curves in dotted lines correspond to the simple regression with DWI/FLAIR mismatch as explanatory variable. Left, Time window of 3 h as dependent variable; middle, 4.5 h; right, 6 h. DWI indicates diffusion-weighted imaging; and FLAIR, fluid-attenuated inversion recovery imaging.

Disclosures
Dr Wouters received grants from European Union. Soren Christensen reports consultant of iSchemaView. Dr Norrving reports fees paid to the institution from SYGNIS for steering committee work in the AXIS2 trial. Dr Thomalla reports receiving grants from European Union. Dr Albers reports consultant of iSchemaView, Covidien, and Lundbeck. He has an equity interest in iSchemaView. Dr Thijs reports receiving fees for serving on the steering committee of the AXIS 2 trial. The other authors report no conflicts.

References


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SUPPLEMENTAL MATERIAL

Supplementary methods I

Overview FLAIR analyzing techniques

<table>
<thead>
<tr>
<th>Visual DWI/FLAIR mismatch</th>
<th>Voxel-based rFLAIR calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The assessment of the visual DWI/FLAIR mismatch is in accordance with the protocol of the ongoing Wake-Up trial. A visual mismatch is defined as an acute DWI lesion without a marked parenchymal hyperintensity on FLAIR. Patients with leukoariosis overlapping with the DWI lesion are excluded (i.e. DWI/FLAIR mismatch negative).</td>
<td>For every voxel the relative FLAIR signal intensity was determined by the ratio of the signal intensity in that voxel and the median of the signal intensity in a sphere with a radius of 15 mm around the homologue voxel in the contralateral hemisphere. This process was repeated for every voxel in the way that for all voxels the rFLAIR signal intensity was calculated.</td>
</tr>
</tbody>
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### Supplementary table I

<table>
<thead>
<tr>
<th></th>
<th>Excluded (n=183)</th>
<th>Included (n=141)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>71 (65-78)</td>
<td>70 (62-76)</td>
<td>0.2</td>
</tr>
<tr>
<td>Gender (f)</td>
<td>89 (49%)</td>
<td>66 (47%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Time from symptom onset (min)</td>
<td>310 (229-401)</td>
<td>320 (233-396)</td>
<td>0.8</td>
</tr>
<tr>
<td>IV tPA</td>
<td>121 (66%)</td>
<td>90 (64%)</td>
<td>0.7</td>
</tr>
<tr>
<td>NIHSS</td>
<td>11 (8-15)</td>
<td>13 (9-17)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>mRS D90 (0-2)</td>
<td>85 (46%)</td>
<td>49 (35%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are median (IQR) or n (%). Group comparison was done by Chi Square test for categorical variables and Mann-Whitney-U for continuous variables. IV tPA = intravenous tissue plasminogen activator, NIHSS= National Institute Stroke Scale, mRS = Modified Rankin Scale at day 90.
Supplementary table II

Prediction of stroke onset within 4.5 h after cross validation

<table>
<thead>
<tr>
<th>Time after stroke onset</th>
<th>&gt;4.5h</th>
<th>&lt;4.5h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4.5h (n=91)</td>
<td>79</td>
<td>12</td>
</tr>
<tr>
<td>&lt;4.5h (n=50)</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Correctly classified (total n=141)</td>
<td>106 (75%)</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.79</td>
<td></td>
</tr>
</tbody>
</table>

The predictive values in this table were obtained after internal validation with the Leave-One-Out approach. The AUC improved (0.79) compared to the visual DWI/FLAIR mismatch (0.68) as predictive model (p=0.01).

AUC = area under the curve.
Supplementary figure I

Example of an excluded patient due to an old ischemic contralateral lesion.
A. FLAIR imaging
B. Diffusion weighted imaging
Supplementary figure II

Time distribution of stroke onset time as documented in the total study population.
Supplementary figure III

Receiver operating characteristic curves with stroke onset before 4.5h as dependent variable. X-axis represent 1-specificity, Y-axis the sensitivity.

**Model 1**: rFLAIR (AUC = 0.76); p=0.08

**Model 2**: rFLAIR + meanTmax + rFLAIR*meanTmax (AUC = 0.80); p < 0.01

**Model 3**: rFLAIR + meanTmax + rFLAIR*meanTmax + age (AUC = 0.82); p < 0.01

**Model Mismatch**: DWI/FLAIR mismatch (AUC = 0.68)

p-values represent differences in AUC compared to the model with visual DWI/FLAIR mismatch as dependent variable. (DeLong’s test).

rFLAIR = relative Fluid Attenuated Inversion Recovery Imaging, DWI= diffusion weighted imaging, Mean Tmax = mean Tmax (= time to the maximum of the residue function obtained by deconvolution), AUC= area under the curve
Imaging example of a patient who presented 252 minutes after stroke onset. The patient had no visual mismatch since a FLAIR hyperintensity was present in the DWI lesion; therefore this patient was classified beyond the 4.5h time window. The multivariate model classified the patient correctly within 4.5h.

**Panel A:** Diffusion weighted imaging  
**Panel B:** FLAIR imaging  
**Panel C:** Tmax perfusion imaging  
**Panel D:** rFLAIR map