Ischaemic stroke occurs unwitnessed or in sleep in as many as a quarter of cases.1,2 However, the decision to give thrombolytic stroke treatment is made on the basis of time since symptom onset, and the effectiveness of treatment is time dependent—late treatment is associated with a slight increase in harm and, more importantly, is ineffective.3 Because stroke onset is defined by the time at which a patient is last seen well and because guidelines recommend thrombolytic therapy within 4·5 h of symptom onset,4 an unknown time of stroke onset can preclude the decision to begin treatment. Identification of a surrogate marker of time from stroke onset is therefore important because patients with an unknown time of symptom onset might still benefit from thrombolysis.

One promise of MRI was that the penumbra, the region of tissue that is salvageable with reperfusion, could be defined in real time with the mismatch between diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). This promise has not yet been realised, but the focus on imaging has spawned the idea of a tissue window for stroke thrombolysis. The existence of a tissue window is attractive: this hypothesis states that an imaging-defined region exists in which thrombolysis (or reperfusion) is beneficial. The corollary is that some patients within the 4·5 h time window are not in the tissue window and thus would not benefit from thrombolysis, whereas some patients beyond the 4·5 h time window are still in the tissue window and would benefit from thrombolysis.

Patients with stroke on awakening are an ideal population in which to test the tissue-window hypothesis. They have a stroke onset time defined by the last time they were seen well—the time at which they went to bed—which most often means that the time from stroke onset to emergency department arrival is 8–10 h. However, their brain imaging often looks the same as that of patients with known stroke onset times of 90 min or less before imaging. Many of the patients who are treated and recover later say that they got up to go to the toilet and then had their stroke only an hour before arrival, implying that brain imaging is a good surrogate for the age of an acute ischaemic stroke.

In this issue of The Lancet Neurology, Götz Thomalla and colleagues present results from the PRE-FLAIR study, an analysis of observational data from patients included in the VISTA and STIR initiatives.5 In this study, patients with well defined times of symptom onset were reviewed to identify presence of lesions on DWI and fluid-attenuated inversion recovery (FLAIR) sequences. Imaging was done within 12 h of onset. Mismatch was judged qualitatively as “a visible acute ischaemic lesion...on DWI with no traceable parenchymal hyperintensity in the corresponding region on FLAIR imaging”. Mismatch defined this way was moderately sensitive (62%) and showed good specificity (78%) in the identification of patients in the 4·5 h window for stroke thrombolysis.

The key features of interest in this study are the use and validation of imaging as a biomarker, the simplicity of use of FLAIR-DWI mismatch, and the obvious implication for planned large trials of thrombolysis in patients with stroke on awakening.

Biomarkers for stroke are in short supply. Although imaging is the most likely biomarker to be of clinical use, the technical challenges of PWI and the clinical care issues of nursing patients with stroke have resulted in a failure to prove the diffusion-perfusion mismatch hypothesis. FLAIR-DWI mismatch is technically much simpler. DWI is sensitive to cytotoxic oedema early after a stroke, whereas FLAIR is sensitive to the later vasogenic oedema, but far less sensitive to cytotoxic oedema. Stroke physicians and radiologists can recognise the cortical T2 hyperintense signal on FLAIR imaging of an ischaemic stroke several hours old. However, the changes

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are subtle, and Thomalla and colleagues recorded only moderate interobserver agreement (κ=0.569).

FLAIR images can be acquired with differing techniques. In this study, standard spin-echo techniques were used and it is important not to assume that these results will be reproduced with echo-planar FLAIR image acquisition. Similarly, DWI can be acquired at different b values; in this case b=1000, the standard at 1·5 T, was used. Higher b values can provide greater contrast at 3 T. An inversion recovery sequence before the DWI (eg, FLIP-DWI) might be useful in the suppression of CSF signal around the insula, further improving the FLAIR-DWI mismatch approach. Alternatively, different approaches to the post-processing of diffusion-tensor imaging data (eg, to generate exponential apparent diffusion coefficient or fractional anisotropy maps) could be investigated. All of these possibilities suggest that the refinement of the approach might be possible by tweaking the image acquisition parameters or types.

Recognition of the limitations of the DWI-FLAIR mismatch approach is important. Chronic lesions (leukoaraiosis) can substantially impair the ability to identify acute stroke lesions on FLAIR images. In the multivariable models reported by Thomalla and colleagues, age and white matter lesions on FLAIR scans were negative predictors of the ability to see a FLAIR-DWI mismatch. This is expected and its effect could be substantial in view of the prevalence of white matter lesions in elderly people with stroke.

This study sets the stage for optimisation and validation of the FLAIR-DWI mismatch biomarker. Validation would allow this biomarker to be used as a participant selection method for randomised trials of thrombolytic stroke therapy in patients with stroke on awakening or with unwitnessed stroke onset. Such trials are on the drawing board and it will be these kinds of imaging biomarkers—which are simple, practical, and easily implementable at many sites—that will allow relevant candidates to be selected for enrolment in these trials.

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We declare that we have no conflicts of interest.