Patients waking up with stroke symptoms represent a distinct but underprivileged subgroup of patients with stroke. Because in wake-up stroke the time of symptom onset is unknown these patients are a challenge to acute stroke treatment. On the basis of licensing criteria and international guideline recommendations, the unknown time window since symptom onset excludes the majority of patients with wake-up stroke from reperfusion treatment with intravenous thrombolysis.1,2 The same applies for endovascular reperfusion treatment that recently was demonstrated to be effective in 5 randomized controlled trials (RCTs).3–7 In 3 of these trials, treatment was restricted to a time window of <6 hours onset, and in the others the vast majority of patients was also treated within 6 hours of symptom onset. Thus, the time point when a patient with wake-up stroke was last seen well usually also lies beyond the time window within which endovascular stroke treatment was demonstrated to be safe and effective. However, a relevant number of these patients might benefit from reperfusion treatment. In this review, we will give an overview on brain imaging concepts suggested to guide reperfusion treatment in patients with unknown time of symptom onset. We will summarize available information on reperfusion treatment and provide an update on ongoing clinical trials of intravenous thrombolysis and endovascular treatment in these patients.

Epidemiology and Characteristics of Wake-Up Stroke

Wake-up stroke is a frequent condition, affecting ≈20% of patients with stroke.8–11 Adding cases with unknown time of symptom onset for other reasons, for example, nonwitnessed stroke with aphasia or disturbance of consciousness, to these numbers, in ≤30% of patients with acute stroke time of symptom onset is unknown.8–11 Imaging studies suggest that stroke onset may have occurred only shortly before waking up in a large proportion of these patients, as frequency of early ischemic signs on computed tomography (CT) and penumbral tissue was comparable with patients with known symptom onset within the first 3 to 6 hours of stroke.8,12,13

Imaging Concepts to Guide Reperfusion Treatment in Wake-Up Stroke

Various approaches have been suggested to identify patients with unknown time of symptom onset who might be eligible for reperfusion treatment. They rely on different brain imaging concepts.

Exclusion of Intracranial Hemorrhage or Large Early Ischemic Signs by Noncontrast CT

There are reports of intravenous thrombolysis in stroke patients with unknown time window based on standard brain imaging to guide intravenous thrombolysis being noncontrast CT only. This involves the exclusion of intracranial hemorrhage, and in some reports also the exclusion of early ischemic signs involving more than one third of the territory of the middle cerebral artery.14,15

Identification of Tissue at Risk by Perfusion–Diffusion Magnetic Resonance Imaging or Perfusion CT

The use of penumbral imaging to identify patients likely to benefit from reperfusion treatment has been a matter of debate for more than a decade and is supported by proof-of-concept studies, whereas evidence for clinical benefit from a large RCT is still pending. Magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) and perfusion imaging, allows for the characterization of tissue at risk for infarction by the mismatch between irreversibly damaged tissue depicted by DWI and critically hypoperfused while still viable tissue captured by perfusion imaging. Penumbral MRI was shown to be feasible to guide thrombolysis in an extended time window in observational studies with encouraging results as to safety and patient outcome.16,17 Secondary analyses from observational studies and RCT have led to further refinement of the perfusion–diffusion mismatch mainly resulting in a more strict definition of the perfusion lesion.18 As a consequence, the relevant perfusion lesion is now mostly defined by a $T_{\text{max}}$ delay >6 s and a perfusion–diffusion mismatch ratio of >1.2 is recommended to define a penumbral pattern, while large infarct core (eg, DWI lesion >70 mL) is excluded.
While the routine use of MRI as first line diagnostic tool in stroke imaging in the acute setting is still restricted to large stroke centers, multiparametric CT is more widely available. Perfusion CT (CTP) is also increasingly used to identify tissue at risk in patients with stroke by the combination of different perfusion parameters to define the ischemic core representing irreversibly damaged tissue and the surrounding viable but hypoperfused tissue. As with penumbral MRI, the optimal parameter and threshold for the definition of the relevant perfusion lesion is still a matter of debate. In current studies, infarct core is usually defined by thresholded relative cerebral blood flow values, for example, <30% of that in normal tissue or a cerebral blood volume ≤2 mL/100 g, or, while the relevant area of hyperperfusion is defined by a mean transit time >145% or CT-T$_{max}$ >6 s comparable with the perfusion MRI findings.

**Estimation of Stroke Lesion Age by DWI–FLAIR Mismatch**

The use of MRI as surrogate marker of lesion age follows a different rationale. It is beyond doubt that intravenous thrombolysis with tissue-type plasminogen activator (tPA) is safe and effective within 4.5 hours of symptom onset. Thus, an imaging surrogate marker that identifies patients with stroke lesions <4.5 hours of age will identify patients likely to benefit from thrombolysis. On the basis of these considerations, the mismatch between a visible acute ischemic lesion on DWI and the absence of marked parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR) images (DWI–FLAIR mismatch) has been demonstrated to identify patients likely to be within 4.5 hours of stroke onset.

The MRI signature of ischemic stroke lesions shows dynamic changes within the first hours of stroke with a characteristic course. Initially, disruption of cellular energy metabolism leads to cytotoxic edema, which can be depicted by a reduced apparent diffusion coefficient on DWI within minutes of stroke. With a certain delay during the following 1 to 4 hours, tissue osmolality increases, leading to net increase of tissue which can be detected by T2-weighted MRI. FLAIR imaging incorporates a strong T2 weighting with suppression of cerebrospinal fluid and is widely used in clinical practice, as it was found to be superior to T2-weighted image in the detection of ischemic lesions as it is not affected by partial volume effects from cerebrospinal fluid. On the basis of these observations, the concept of DWI–FLAIR mismatch was introduced and found to have a high positive predictive value in the identification of patients with stroke presenting within 3 hours of symptom onset. The promising results of this first report were corroborated in the large multicenter Predictive Value of FLAIR and DWI for the Identification of Acute Ischemic Stroke Patients ≤3 and ≤4.5 h of Symptom Onset—a Multicenter Observational Study (PRE-FLAIR) study. In this retrospective study, the DWI–FLAIR mismatch pattern identified patients within 4.5 hours with a positive predictive value of nearly 90% from a target population for thrombolysis, that is, patients with stroke in the territory of middle cerebral artery and a relevant neurological deficit.

**Intravenous Thrombolysis in Wake-Up Stroke**

There is no data from RCTs allowing for conclusions on efficacy and safety of intravenous thrombolysis in stroke patients with unknown time of symptom onset. There are case series of intravenous tPA treatment in wake-up stroke and stroke with unknown time of symptom onset but numbers are small, data reporting is inconsistent, and reported outcomes vary within a wide range so that no conclusion can be drawn as to risk or benefit of intravenous tPA in this group of patients. There are 5 casuistic reports of intravenous tPA treatment in unknown time of symptom onset stroke in >5 patients with numbers ranging from 10 to 68 (Table 1). One observational study relied on noncontrast CT and clinical inclusion and exclusion criteria for thrombolysis to select patients amended by CTP based on the discretion of the treating physician. One case series relied on penumbral MRI with perfusion–diffusion mismatch complemented by the exclusion of patients with marked FLAIR hyperintensities. On the basis of this approach, 22% of patients presenting with wake-up stroke were treated with intravenous tPA. In another report of MRI-based thrombolysis criteria for patient selection for thrombolysis are not specified. Two further studies used the DWI–FLAIR mismatch together with exclusion of large DWI lesions to guide intravenous tPA treatment in patients with unknown time of symptom onset. Of interest, patients with marked FLAIR hyperintensities were also excluded in all previous case series of reperfusion therapy in wake-up stroke based on perfusion–diffusion mismatch. Across all reports, independent outcome defined by a modified Rankin Scale (mRS) score of 0 to 2 after 90 days of treated patients ranged from 28% to 50%, mortality was between 0% and 15%. Rates of symptomatic intracranial hemorrhage were consistently low with a maximum of ≈3%.

Extra diagnostic efforts and risk–benefit evaluation may result in delays in off-label thrombolysis in stroke with unknown time of symptom. In 1 study, door to needle time was significantly longer in patients with unknown time of symptom onset as compared with patients with known symptom onset (median, 86 minutes versus 60 minutes), whereas in both the groups MRI was used as primary diagnostic measure. In another MRI-based study, median door to needle time was in a comparable range (80 minutes), also being clearly beyond the range of door to needle times that are usually reached by intravenous thrombolysis and aimed at according to international guidelines. In a small randomized pilot study on the feasibility of using CTP to randomize stroke patients with unknown time of symptom onset, median door to needle time was even 113 (interquartile range, 75–205) minutes, a finding which the authors explain by the need for reconstruction of CTP images, and the procedures of informed consent and randomization in this trial.

**Endovascular Treatment of Wake-Up Stroke**

Just recently a series of trials has convincingly demonstrated that endovascular treatment mainly using stent retriever devices in addition to standard treatment improves outcome of acute ischemic stroke from large vessel occlusion. However, patients with wake-up stroke or stroke with unknown time of symptom onset were not included in any
of the recent positive trials of endovascular stroke treatment. In the Canadian ESCAPE trial, enrollment was allowed ≤12 hours of symptom onset. However, median stroke onset to randomization time was 169 minutes in the intervention group, and only a small number of patients (n=49) underwent randomization >6 hours. Thus, no conclusions can be drawn as to the efficacy of endovascular stroke treatment beyond 6 hours of symptom onset.

There are several reports of endovascular stroke treatment in patients with unknown time of symptom onset together with intravenous tPA or alone. In 2 case series, decision to perform intravenous tPA or endovascular treatment was made by the treating physician mainly based on noncontrast CT, which later in time was amended by CTP or MRI. One pilot study used penumbral MRI together with the exclusion of a marked FLAIR hyperintensity to select patients for intravenous tPA or endovascular reperfusion treatment. This study was followed by the observational prospective multicenter Reperfusion Therapy in Unclear-Onset Stroke Based on MRI Evaluation (RESTORE) study from the same group applying the same imaging criteria. In this study, 83 of 430 patients (19.3%) with unknown onset stroke were treated by intravenous tPA, by intravenous tPA followed by intra-arterial treatment, or by intra-arterial treatment alone.

Recent case series have added to the literature on endovascular treatment of stroke with unknown onset, so there are 5 further reports of endovascular treatment alone without intravenous tPA. Penumbral imaging using CTP or MRI was used in all these case series as far as reported. Reported case numbers range between 19 and 83 with mean or median National Institutes of Health Stroke Scale values of 13 to 17. For all reports involving endovascular stroke treatment, rates of good outcome range between 11% and 50%, whereas mortality lies between 10% and 37%. Rates of symptomatic intracranial hemorrhage were substantially higher than for intravenous tPA in most cases, ranging between 4% and 21%.

<table>
<thead>
<tr>
<th>References</th>
<th>Sample Size*</th>
<th>Treatment</th>
<th>Imaging Concept</th>
<th>Exclusion of Large Infarct Lesions</th>
<th>Exclusion by Estimation of Lesion Age</th>
<th>Median NIHSS o.a.</th>
<th>mRS 0–2 at Day 90</th>
<th>Mortality at Day 90</th>
<th>SICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoki et al26</td>
<td>10</td>
<td>IV tPA</td>
<td>DWI–FLAIR mismatch</td>
<td>Yes</td>
<td>Yes</td>
<td>14</td>
<td>40%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Bai et al27</td>
<td>48</td>
<td>IV tPA</td>
<td>DWI–FLAIR mismatch</td>
<td>Yes</td>
<td>Yes</td>
<td>11†</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
</tr>
<tr>
<td>Breuer et al28</td>
<td>10</td>
<td>IV tPA</td>
<td>Penumbral: MRI</td>
<td>Yes</td>
<td>Yes</td>
<td>10.5</td>
<td>50%</td>
<td>n.a.</td>
<td>0%</td>
</tr>
<tr>
<td>Ebinger et al29</td>
<td>17</td>
<td>IV tPA</td>
<td>n.s. (MRI was used in all patients)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>13</td>
<td>35.3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Manawadu et al30</td>
<td>68</td>
<td>IV tPA</td>
<td>NCCT</td>
<td>Yes</td>
<td>No</td>
<td>11.5</td>
<td>36.8%</td>
<td>14.7%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Michel et al31</td>
<td>6</td>
<td>IV tPA</td>
<td>Penumbral: CTP</td>
<td>Yes</td>
<td>No</td>
<td>17</td>
<td>66.7%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>IV tPA+endovascular treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barreto et al32</td>
<td>46</td>
<td>IV tPA/endovascular</td>
<td>Individual decision, mainly NCCT</td>
<td>Yes</td>
<td>No</td>
<td>16</td>
<td>28%</td>
<td>15%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Cho et al33</td>
<td>32</td>
<td>IV tPA/endovascular</td>
<td>Penumbral: MRI</td>
<td>Yes</td>
<td>Yes</td>
<td>14.5</td>
<td>50%</td>
<td>n.a.</td>
<td>6.3%</td>
</tr>
<tr>
<td>Kang et al34</td>
<td>83</td>
<td>IV tPA/endovascular</td>
<td>Penumbral: MRI</td>
<td>Yes</td>
<td>Yes</td>
<td>14</td>
<td>44.6%</td>
<td>n.a.</td>
<td>3.6%</td>
</tr>
<tr>
<td>Kim et al35</td>
<td>29</td>
<td>IV tPA/endovascular</td>
<td>NCCT</td>
<td>Yes</td>
<td>No</td>
<td>13</td>
<td>44.8%</td>
<td>10.3%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Endovascular treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aghaebrahim et al36</td>
<td>78</td>
<td>Endovascular (several)</td>
<td>Penumbral: MRI or CTP</td>
<td>Individual decision</td>
<td>No</td>
<td>15†</td>
<td>43%</td>
<td>21%</td>
<td>n.a.</td>
</tr>
<tr>
<td>Jung et al37</td>
<td>55</td>
<td>Endovascular (several)</td>
<td>Penumbral: MRI (penumbral: MRI in 58%)</td>
<td>Individual decision</td>
<td>Yes</td>
<td>15</td>
<td>37%</td>
<td>25.9%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Mokin et al38</td>
<td>52</td>
<td>Endovascular (MT+aspiration)</td>
<td>Penumbral: CTP</td>
<td>Yes</td>
<td>No</td>
<td>…</td>
<td>48.1%</td>
<td>23.8%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Natarajan et al39</td>
<td>21</td>
<td>Endovascular (several)</td>
<td>Penumbral: CTP</td>
<td>Individual decision</td>
<td>No</td>
<td>14†</td>
<td>42.9%</td>
<td>n.a.</td>
<td>14.3%</td>
</tr>
<tr>
<td>Stampfl et al40</td>
<td>19</td>
<td>Endovascular (MT only)</td>
<td>Penumbral: MRI or CTP</td>
<td>Yes</td>
<td>No</td>
<td>17</td>
<td>10.5%</td>
<td>36.8%</td>
<td>21.1%</td>
</tr>
</tbody>
</table>

Only case reports with >5 patients are presented. CTP indicates perfusion computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; IV, intravenous; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; MT, mechanical thrombectomy; n.a., not available; NCCT, noncontrast-enhanced computed tomography; o.a., on admission; SICH, symptomatic intracranial hemorrhage; and tPA, tissue-type plasminogen activator.

*No. of patients with stroke with unknown time of symptom onset.
†Mean is given instead of median.
‡No data given as inconsistent numbers are reported.
Although previous case series of endovascular stroke treatment in unknown onset stroke mostly used out-of-fashion approaches, such as intra-arterial Urokinase or the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device, in two recent reports stent retriever devices were used for treatment the majority of cases. For both case series, overall results are not compelling with high mortality (23% and 37%) and high rates of symptomatic intracranial hemorrhage (14% and 21%) for both studies, while with regard to good outcome (mRS, 0–2 at day 90), the results were different with 48%. in one case series and only 11% in the other case series.

The majority of reports do not provide information on the timing of interventions. In 1 study, median door to needle time for intravenous thrombolysis that was performed before intra-arterial treatment was 154 minutes, which was significantly longer than in a comparison group of patients with known onset stroke screened by the same imaging approach (94 minutes). In RESTORE, median door to treatment time was almost identical (155 minutes), showing the same delay as compared with standard stroke thrombolysis. However, both reports do not provide information on the timing of intra-arterial treatment.

### Ongoing Clinical Trials of Reperfusion Treatment in Wake-Up Stroke

At present, several clinical trials are running that either focus on patients with unknown symptom onset stroke or include these patients as a subgroup in the target population (Table 2).

#### Trials of Intravenous Thrombolysis Using MRI Estimates of Lesion Age (DWI–FLAIR Mismatch)

Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke: A Randomized, Double-Blind, Placebo-Controlled trial (WAKE-UP) is a randomized controlled clinical trial set up to test efficacy and safety of standard dose intravenous thrombolysis (0.9 mg/kg alteplase) in patients with unknown time of symptom onset with MRI signatures of ischemic lesion within 4.5 hours of symptom onset, that is, DWI–FLAIR mismatch. WAKE-UP only enrolls patients with unknown time of symptom onset that otherwise seem eligible for intravenous tPA treatment. The presence of DWI–FLAIR mismatch is assessed visually, although signal intensity measurement at the scanner may be used in addition in cases of doubt. Large DWI lesions are excluded (ie, DWI >100 mL or >1/3 middle

### Table 2. Ongoing Trials Enrolling Stroke Patients With Unknown Onset

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Study Population</th>
<th>Investigational Treatment</th>
<th>Comparator</th>
<th>Imaging Concept</th>
<th>Further Imaging Exclusion Criteria</th>
<th>Planned Sample Size</th>
<th>Trial Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAWN</td>
<td>Late onset stroke incl. unknown time of symptom onset</td>
<td>Endovascular (Trevo thrombectomy procedure) + IV tPA</td>
<td>Standard of care</td>
<td>Proximal occlusion; clinical-imaging mismatch: high NIHSS score with small DWI/CTP-rCBF lesion</td>
<td>Large ischemic lesion &gt;1/3 MCA</td>
<td>500</td>
<td>NCT02142283</td>
</tr>
<tr>
<td>ECASS-4:EXTEND</td>
<td>Stroke onset 4.5–9 h incl. unknown time of symptom onset</td>
<td>IV tPA (Alteplase 0.9 mg/kg)</td>
<td>Placebo</td>
<td>Penumbral: MRI</td>
<td>DWI lesion &gt;1/3 MCA/ &gt;100 mL</td>
<td>264</td>
<td>EudraCT no. 2012-003609-80</td>
</tr>
<tr>
<td>EXTEND</td>
<td>Stroke onset 4.5–9 h incl. unknown time of symptom onset</td>
<td>IV tPA (Alteplase 0.9 or 0.6 mg/kg)</td>
<td>Placebo</td>
<td>Penumbral: MRI or CTP</td>
<td>Infarct core &gt;1/3 MCA/ &gt;70 mL</td>
<td>400</td>
<td>NCT00887328</td>
</tr>
<tr>
<td>MR WITNESS</td>
<td>Unknown time of symptom onset</td>
<td>IV tPA (Alteplase 0.9 mg/kg)</td>
<td>n.a.</td>
<td>Estimation of lesion age: DWI–FLAIR mismatch</td>
<td>&gt;10 microbleeds</td>
<td>80</td>
<td>NCT01282242</td>
</tr>
<tr>
<td>NORTES</td>
<td>Eligible for IV tPA-subgroup &lt;4.5 h after symptom recognition</td>
<td>Intravenous TNK 0.4 mg/kg</td>
<td>IV tPA (Alteplase 0.9 mg/kg)</td>
<td>For wake-up stroke: estimation of lesion age: DWI–FLAIR mismatch</td>
<td>n.a.</td>
<td>954</td>
<td>NCT01949948</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>Stroke onset &lt;12 h incl. unknown time of symptom onset</td>
<td>Endovascular (aspiration, stent retriever)</td>
<td>Standard of care</td>
<td>Proximal occlusion; penumbral: MRI or CTP (by local practice)</td>
<td>Infarct on CT &gt;1/3 MCA or ASPECTS &lt;7</td>
<td>750</td>
<td>NCT01852201</td>
</tr>
<tr>
<td>THAWS</td>
<td>Unknown time of symptom onset</td>
<td>IV tPA (Alteplase 0.6 mg/kg)</td>
<td>Placebo</td>
<td>Estimation of lesion age: DWI–FLAIR mismatch</td>
<td>DWI ASPECTS &lt;5</td>
<td>300</td>
<td>NCT02002325</td>
</tr>
<tr>
<td>WAKE-UP</td>
<td>Unknown time of symptom onset</td>
<td>IV tPA (Alteplase 0.9 mg/kg)</td>
<td>Placebo</td>
<td>Estimation of lesion age: DWI–FLAIR mismatch</td>
<td>DWI lesion &gt;1/3 MCA/ &gt;100 mL</td>
<td>800</td>
<td>NCT01525290</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT score; CT, computed tomography; CTP, perfusion CT; DAWN, Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention; DWI, diffusion-weighted imaging; ECASS-4:EXTEND, European Cooperative Acute Stroke Study-4: Extending the Time for Thrombolysis in Emergency Neurological Deficits; FLAIR, fluid-attenuated inversion recovery; IV, intravenous; MCA, middle cerebral artery; MRI, magnetic resonance imaging; MR WITNESS, A Phase IIa Safety Study of Intravenous Thrombolysis With Alteplase in MRI-Selected Patients; n.a., not available; NIHSS, National Institutes of Health Stroke Scale; NORTES, Norwegian Tenecteplase Stroke Trial; POSITIVE, Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy; rCBF, relative cerebral blood flow; THAWS, Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes; TNK, tenecteplase; tPA, tissue-type plasminogen activator; and WAKE-UP, Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke: A Randomized, Double-Blind, Placebo-Controlled trial.
cerebral artery territory). Besides the unknown time window and patient selection by MRI, the trial largely follows the licensing criteria for alteplase in Europe, including the upper age limit of 80 years. WAKE-UP plans to enroll 800 patients in ≥60 sites in Europe. Primary end point is favorable outcome defined by an mRS of 0 to 1 at 3 months. The trial is running since October 2012, interim safety analysis after randomization of >200 patients has not brought up any safety issues of concern. Final results are expected by the end of 2016.

The Norwegian Tenecteplase Stroke Trial (NORTEST) differs from the other ongoing stroke trials in that it is a RCT of tenecteplase versus alteplase in acute ischemic stroke.38 Enrollment of patients with wake-up stroke is allowed if the midpoint between last known well (eg, onset of sleep) and symptom recognition (eg, the time of waking) is <9 hours before treatment. Penumbral imaging with MRI or CTP is used to select patients for randomization by a penumbral pattern defined as a penumbra:core ratio of >1.2 and an absolute difference >10 mL (where a \( T_{\text{max}} \) delay >6 s defines the perfusion and DWI or CT-CBF defines the core lesion). Patients with large ischemic core (>70 mL) are excluded. The dose of alteplase is 0.6 or 0.9 mg/kg depending on the local practice, as the trial is conducted in Australia and Asia. Planned sample size is 400, primary end point is mRS 0 to 1 at 3 months. European Cooperative Acute Stroke Study-4: Extending the Time for Thrombolysis in Emergency Neurological Deficits (ECASS-4:EXTEND) is the European counterpart of EXTEND and largely follows its design except for some minor differences. In ECASS-4:EXTEND, only MRI is used as imaging method and as the trial is conducted in Europe, only 0.9 mg/kg alteplase is used. Moreover, the primary end point is a categorical shift in the mRS at 3 months. Estimated sample size is 264 patients. As toward wake-up stroke, the same algorithm to enroll patients as in EXTEND is applied.

**Trials of Endovascular Stroke Treatment in Late and Unknown Time Window**

There are 2 ongoing endovascular stroke trials that also allow for enrollment of patients with unknown time of symptom onset. Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) is a prospective, randomized, multicenter, phase II/III, adaptive, controlled trial, designed to demonstrate that mechanical thrombectomy with the Trevo Retriever is superior to standard treatment in patients with unknown time of symptom onset and proximal vessel occlusion in the anterior circulation. The time window for treatment is 6 to 24 hours after symptom onset or last seen well, respectively. Patients are selected by a clinical imaging mismatch, that is, National Institutes of Health Stroke Scale values above given thresholds for different infarct core volumes defined by MRI or CTP. Estimated enrollment is 500 patients, and primary outcomes are weight mRS score and stroke-related mortality at day 90. The trial started in 2014, completion is expected in 2017.

Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy (POSITIVE) is designed to test safety and efficacy of mechanical thrombectomy versus standard treatment for stroke patients with large intracranial vessel occlusion ineligible for intravenous tPA within 12 hours of symptom onset. Patients are further selected by the presence of a penumbral pattern in perfusion MRI or CT. Inclusion of patients with unknown time of symptom onset is allowed if last known well lies within 12 hours. Enrollment of 750 patients is planned. Primary outcome measure is the overall distribution of mRS by shift analysis combined with at least 5% difference in the proportion of subjects achieving functional independence defined as an mRS score of 0 to 2. The trial was started in 2013.

**Trials of Intravenous Thrombolysis Using Penumbral Imaging (MRI or CTP)**

There are 2 companion trials using penumbral imaging to identify patients likely to benefit from intravenous thrombolysis ≤9 hours of stroke onset, including wake-up strokes. The EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) trial is a randomized, multicentre, double-blinded, placebo-controlled trial comparing intravenous tPA with placebo in patients with ischemic stroke outside the time window of thrombolysis (eg, >3 or 4.5 hours, depending on local practice) ≤9 hours of symptom onset.39 Enrollment of patients with wake-up stroke is allowed if the midpoint between last known well (eg, onset of sleep) and symptom recognition (eg, the time of waking) is <9 hours before treatment. Penumbral imaging with MRI or CTP is used to select patients for randomization by a penumbral pattern defined as a penumbra:core ratio of >1.2 and an absolute difference >10 mL (where a \( T_{\text{max}} \) delay >6 s defines the perfusion and DWI or CT-CBF defines the core lesion). Patients with large ischemic core (>70 mL) are excluded. The dose of alteplase is 0.6 or 0.9 mg/kg depending on the local practice, as the trial is conducted in Australia and Asia. Planned sample size is 400, primary end point is mRS 0 to 1 at 3 months. European Cooperative Acute Stroke Study-4: Extending the Time for Thrombolysis in Emergency Neurological Deficits (ECASS-4:EXTEND) is the European counterpart of EXTEND and largely follows its design except for some minor differences. In ECASS-4:EXTEND, only MRI is used as imaging method and as the trial is conducted in Europe, only 0.9 mg/kg alteplase is used. Moreover, the primary end point is a categorical shift in the mRS at 3 months. Estimated sample size is 264 patients. As toward wake-up stroke, the same algorithm to enroll patients as in EXTEND is applied.

There are 2 ongoing endovascular stroke trials that also allow for enrollment of patients with unknown time of symptom onset. Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) is a prospective, randomized, multicenter, phase II/III, adaptive, controlled trial, designed to demonstrate that mechanical thrombectomy with the Trevo Retriever is superior to standard treatment in patients with unknown time of symptom onset and proximal vessel occlusion in the anterior circulation. The time window for treatment is 6 to 24 hours after symptom onset or last seen well, respectively. Patients are selected by a clinical imaging mismatch, that is, National Institutes of Health Stroke Scale values above given thresholds for different infarct core volumes defined by MRI or CTP. Estimated enrollment is 500 patients, and primary outcomes are weight mRS score and stroke-related mortality at day 90. The trial started in 2014, completion is expected in 2017.
Conclusions and Future Perspective
To summarize, stroke with unknown time of symptom onset represents a relevant health problem and an unresolved challenge for stroke clinicians and researchers. There is still no evidence from clinical trials to guide recommendations for clinical practice of reperfusion treatment in these patients. New imaging approaches have been suggested to select stroke patients with unknown symptom onset likely to benefit from reperfusion treatment, either (1) based on the identification of tissue at risk of infarction by penumbral imaging or (2) relying on the identification of patients within the approved time window for thrombolysis by using MRI as a surrogate marker of lesion age. There is also a growing number of case series and observational studies of both intravenous and endovascular reperfusion treatment demonstrating that advanced imaging for selection of patients under such circumstances is feasible, and that reperfusion treatment may probably be safe and potentially effective in these patients.

However, reported outcomes of both intravenous thrombolysis and endovascular treatment of patients with unknown time of symptom onset are inconsistent and overall not compelling. Thus, available evidence does not suffice to justify a general recommendation for intravenous thrombolysis or endovascular treatment of patients with unknown time of symptom onset, including wake-up strokes. Evidence from large RCTs is needed which demonstrates efficacy and safety of the suggested approaches to guide reperfusion treatment in these patients. Both, trials of intravenous thrombolysis and trials of mechanical thrombectomy in patients with unknown time of symptom onset are underway. These trials rely on extended imaging to enroll patients by either penumbral imaging or the estimation of lesion age by the DWI−FLAIR mismatch concept. Both the diagnostic approaches indicate a strategic change, away from observed and reported time windows toward tissue imaging. Given the lack of evidence and the carefully designed ongoing clinical trials, enrollment of patients with unknown time of symptom onset in RCTs of reperfusion treatment is strongly recommended. In the near future, the results of these trials will hopefully provide the desired proof of efficacy and safety of both intravenous thrombolysis and endovascular reperfusion treatment for patients with unknown time of symptom onset and by this make effective treatment accessible to a large group of patients with stroke that is currently excluded from reperfusion treatment.

Sources of Funding
Dr Thomalla receives funding from the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement no. 278276 (WAKE-UP) and no. 634809 (PRECIOUS) and from the German Research Foundation (DFG), SFB 936 Multi-site Communication in the Brain (Project C2). Dr Gerloff receives funding from the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement no. 278276 (WAKE-UP) and from the German Research Foundation (DFG), SFB 936 Multi-site Communication in the Brain (Project C1, Z1, and ZZ) and Ge844/4-1 (Neuroregeneration Enhanced by Transcranial Direct Current Stimulation in Stroke [NETS] trial).

Disclosures
Dr Thomalla is the coordinating investigator of the WAKE-UP project. He has received fees as consultant or lecturer from Bayer Vital, Boehringer Ingelheim, Glaxo Smith Kline, Lundbeck, Pfizer, Sanofi Aventis, UCB, Merck Serono, EBS technologies, and Silk Road Medical.

References


KEY WORDS: magnetic resonance imaging • perfusion imaging • randomized clinical trials • reperfusion • stroke • thrombolysis
Treatment Concepts for Wake-Up Stroke and Stroke With Unknown Time of Symptom Onset
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Stroke. 2015;46:2707-2713; originally published online August 4, 2015;
doi: 10.1161/STROKEAHA.115.009701

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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