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# **Stroke with unknown time of symptom onset – baseline clinical and MRI data of the first thousand patients in WAKE-UP**

Götz Thomalla, MD<sup>1</sup>, Florent Boutitie, PhD<sup>2</sup>, Jochen B. Fiebach, MD<sup>3</sup>, Claus Z. Simonsen, MD, PhD<sup>4</sup>, Norbert Nighoghossian, MD<sup>5</sup>, Salvador Pedraza, MD<sup>6</sup>, Robin Lemmens, MD<sup>7</sup>, Pascal Roy, MD<sup>2</sup>, Keith W. Muir, MD<sup>8</sup>, Martin Ebinger, MD<sup>3,9</sup>, Ian Ford, PhD<sup>10</sup>, Bastian Cheng, MD<sup>1</sup>, Ivana Galinovic, MD<sup>3</sup>, Tae-Hee Cho, MD<sup>7</sup>, Josep Puig<sup>5</sup>, MD, Vincent Thijs<sup>11</sup>, MD, Matthias Endres, MD<sup>3,9</sup>, Jens Fiehler, MD<sup>12</sup>, Christian Gerloff, MD<sup>1</sup>, on behalf of the WAKE-UP investigators

<sup>1</sup> Klinik und Poliklinik für Neurologie, Kopf- und Neurozentrum, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

<sup>2</sup> Hospices Civils de Lyon, Service de Biostatistique, F-69003 Lyon, France; Université Lyon 1, F-69100 Villeurbanne, France; CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, F-69100 Villeurbanne, France

<sup>3</sup> Centrum für Schlaganfallforschung Berlin (CSB), Charité - Universitätsmedizin Berlin, Berlin, Germany

<sup>4</sup> Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

<sup>5</sup> Department of Neurology, Hospices Civils de Lyon, Lyon, France

<sup>6</sup> Department of Radiology, Institut de Diagnostic per la Image (IDI), Hospital Dr Josep Trueta, Institut d'Investgació Biomèdica de Girona (IDIBGI), Girona, Spain

<sup>7</sup> Department of Neurology, University Hospitals Leuven, Leuven, Belgium

<sup>8</sup> Institute of Neuroscience & Psychology, University of Glasgow, Glasgow, UK

<sup>9</sup> Klinik und Hochschulambulanz für Neurologie, Charité-Universitätsmedizin Berlin, Berlin, Germany

<sup>10</sup> Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK

<sup>11</sup> Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria,

<sup>12</sup> Klinik und Poliklinik für Neuroradiologische Diagnostik und Intervention, Diagnostikzentrum, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

*Corresponding author:*

Götz Thomalla

Kopf- und Neurozentrum, Klinik und Poliklinik für Neurologie

Universitätsklinikum Hamburg-Eppendorf

Martinistraße 52

D-20246 Hamburg

Germany

E-mail: thomalla@uke.de

telephone: +49-40-7410-50137

fax: +49-40-42803-7410-56721

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**Abstract**

*Background and Purpose* – We describe clinical and magnetic resonance imaging characteristics of stroke patients with unknown time of symptom onset potentially eligible for thrombolysis from a large prospective cohort.

*Methods* – We analysed baseline data from WAKE-UP, an investigator-initiated, randomised, placebo-controlled trial of MRI based thrombolysis in stroke patients with unknown time of symptom onset. MRI judgement included assessment of DWI-FLAIR-mismatch.

*Results* – Of 1,005 patients included, DWI-FLAIR-mismatch was present in 479 patients (48.0%). Patients with daytime unwitnessed stroke (n=138, 13.7%) had a shorter delay between symptom recognition and hospital arrival (1.5 vs. 1.8 hours,  $p=0.002$ ), a higher NIHSS on admission (8 vs. 6,  $p<0.001$ ), and more often aphasia (72.5% vs. 34.0%,  $p<0.001$ ) as compared to wake-up stroke patients. Frequency of DWI-FLAIR-mismatch was comparable between both groups (43.7% vs. 48.7%,  $p=0.30$ ).

*Conclusions* – Almost half of the patients with unknown time of symptom onset stroke otherwise eligible for thrombolysis had MRI findings making them likely to be within a time window for safe and effective thrombolysis. Patients with daytime onset unwitnessed stroke differ from wake-up stroke patients with regards to clinical characteristics but are comparable in terms of MRI characteristics of lesion age.

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## Introduction

In a large proportion of stroke patients information on the exact time of symptom onset is not available. This includes the large group of patients waking up with stroke symptoms, the so called “wake-up” stroke, representing around one in five (14-24%) of stroke patients in registries or epidemiological studies.<sup>1,2</sup> Information on time of symptom onset may also be unavailable in unwitnessed stroke at daytime in patients not capable of providing this information themselves. All these patients are currently excluded from reperfusion treatment based on the available evidence.<sup>3</sup>

Magnetic resonance imaging (MRI) has been suggested to select patients with unknown time of symptom onset likely to benefit from acute reperfusion treatment using DWI-FLAIR-mismatch as surrogate marker of lesion age.<sup>4</sup> However, the proportion of patients qualifying for intravenous thrombolysis based on imaging criteria within a population of unknown symptom onset stroke patients otherwise considered eligible is not known. Furthermore, there are findings indicating that patients with wake-up stroke might differ from those with daytime unwitnessed stroke with regards to clinical and imaging characteristics that might affect acute treatment decisions.<sup>5</sup>

We aimed at studying clinical and imaging characteristics of stroke patients with unknown time of symptom onset otherwise considered eligible for treatment with intravenous thrombolysis.

## Methods

We analysed baseline data from WAKE-UP (Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomised, double-blind, placebo-controlled trial), a trial enrolling acute stroke patients with unknown time of symptom onset (Clinicaltrials.gov identifier NCT01525290; EudraCT No.: 2011-005906-32).<sup>6</sup> In this trial, patients are studied with MRI

including DWI and FLAIR, and the presence of a DWI-FLAIR mismatch<sup>4</sup> represents the main imaging criterion for randomization to treatment with Alteplase or placebo. For the present analysis, only baseline information including demographic, clinical, and imaging data was considered. A database export was performed on 01 April 2016. The sample includes all patients enrolled in the trial, i.e. patients with eligibility verified who gave informed consent and were then subjected to screening with MRI. All patients with at least information on date and time of enrolment, informed consent, symptom onset, age and gender were included in the analysis.

MRI judgement was made by local investigators according to image analysis standards provided together with the study protocol. Unwitnessed day-time stroke was compared to night-sleep wake-up stroke.

For group comparison, Fisher's exact test or Chi-square test were used for categorical variables, and Mann-Whitney-U test for continuous variables. SAS software, version 9.3 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

## Results

Overall, 1,005 patients were included in the analysis. In the majority of patients, stroke symptoms were discovered in the morning hours between 06:00 and 10:00 (see figure). Clinical and imaging characteristics are presented in the table. Overall, 793 patients (81.3%) had a visible DWI lesion, while 72 (7.2%) had findings of intracranial haemorrhage. DWI-FLAIR-mismatch was present in 479 patients (48.0%).

Patients with daytime unwitnessed stroke had a shorter delay between symptom recognition and arrival at the hospital (1.5 vs. 1.8 h,  $p=0.002$ ), a higher NIHSS on admission (8 vs. 6,  $p<0.001$ ), and more frequently aphasia (72.5% vs. 34.0%,  $p<0.001$ ). Medical history and presence of vascular risk factors were similar between groups. Groups were also comparable as to baseline imaging findings including the proportion of patients presenting with DWI-FLAIR-mismatch (43.7% vs. 48.7%,  $p=0.30$ ).

## Discussion

In this large prospective sample consisting of the first 1,005 patients enrolled in the multicentre multinational randomized controlled WAKE-UP trial, DWI-FLAIR-mismatch was observed in virtually half of the patients (48.0%). This confirms the notion that a relevant proportion of patients with unknown time of symptom onset has an MRI signature indicative of stroke lesions within the first 4.5 hours of symptom onset. The number is comparable to the 43.7% DWI-FLAIR-mismatch reported in a previous small case series of stroke with unknown time of symptom onset.<sup>7</sup> In another recently published case series, DWI-FLAIR-mismatch was present in only 35.1% of daytime unwitnessed stroke and 21.9% of patients with wake-up stroke.<sup>5</sup> Smaller numbers may result from a longer delay between symptom recognition to hospital arrival as compared to our sample.

Comparing patients waking up from night-sleep to those with daytime unwitnessed stroke revealed some differences. Patients with unknown time of symptom onset at daytime had more severe neurological symptoms reflected by a higher NIHSS on admission, a higher rate of aphasia, and a trend towards a higher rate of disturbed level of consciousness. These results are in line with a recently published retrospective analysis reporting higher mean NIHSS values for and higher rates of aphasia in patients with day-time onset unwitnessed stroke as compared to wake-up stroke.<sup>5</sup> As aphasia and disturbed level of consciousness represent common reasons for the inability of patients with daytime onset stroke to report the time of symptom onset, these findings might at least in part be considered as a bias resulting from the definition of unwitnessed stroke at daytime. On the other hand, there are hints towards pathophysiological differences between strokes occurring at night and those at daytime which may contribute to differences in risk profile, stroke etiology, and symptom severity between groups. A higher risk of newly diagnosed atrial fibrillation was observed in wake-up stroke,<sup>8</sup> that might relate to the well-known circadian variation of occurrence of atrial fibrillation with most frequent occurrence in the early morning hours.<sup>9</sup>

To summarise, in this large prospective cohort of stroke patients with unknown time of symptom onset otherwise considered potential candidates for thrombolysis, almost half of the patients showed a DWI-FLAIR-mismatch, rendering them likely to be within a time window for effective reperfusion treatment. We found no difference in the presence of DWI-FLAIR-mismatch between patients with wake-up stroke and those with daytime unwitnessed stroke, but the analysis was not adequately powered to detect if the observed small absolute difference was statistically significant. When considering reperfusion treatment in patients with unknown time of symptom onset, these considerations should not be restricted to wake-up strokes but also include daytime onset unwitnessed stroke.

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## Tables

Table: Clinical characteristics and imaging findings

	All (n=1005)	Nightsleep wake-up stroke (n=867)	Daytime unwitnessed stroke (n=138)	Group comparison <i>p</i> -value
Age [years], median (IQR)	68.0 (58.0-75.0)	68.0 (58.0-74.0)	68.0 (58.0-74.0)	0.90
Gender = female, n (%)	390 (38.8)	328 (37.8)	62 (44.9)	0.13
Delay between last seen well and symptom recognition [h], median (IQR)	7.7 (5.5-9.5)	7.5 (5.8-9.3)	8.0 (4.0-12.7)	0.33
Delay between symptom recognition and arrival at hospital [h], median (IQR)	1.8 (1.2-2.5)	1.8 (1.2-2.6)	1.5 (1.0-2.1)	0.002
Medical history / risk factors *				
Arterial hypertension, n (%)	472/989 (48.1)	410/837 (48.6)	62/132 (45.3)	0.71
Diabetes mellitus, n (%)	159/967 (16.2)	134/833 (15.9)	25/134 (18.3)	0.45
Hypercholesterolemia, n (%)	275/935 (28.1)	235/819 (27.9)	40/126 (29.2)	0.53
Atrial fibrillation, n (%)	74/959 (7.6)	65/829 (7.7)	9/130 (6.6)	0.86
Ischemic stroke, n (%)	120/973 (12.3)	97/837 (11.5)	23/135 (16.8)	0.09
Transient ischemic attack, n (%)	46/967(4.7)	42/835 (5.0)	4/132 (2.9)	0.39
NIHSS on admission, median (IQR)	6 (4-11)	6 (3-10)	8 (5-14)	<0.001
Aphasia, n (%)	392 (39.3)	292 (34.0)	100 (72.5)	<0.001
Disturbed level of consciousness (NIHSS LOC item >1), n (%)	83 (8.3)	66 (7.7)	17 (12.3)	0.10
MR imaging findings				
Images of sufficient quality, n (%)	960 (98.1)			
Intracranial haemorrhage†, n (%)	72 (7.2)	62 (7.4)	10 (7.6)	0.86
Acute DWI lesion, n (%)	793 (81.3)	689 (83.4)	104 (79.4)	0.26
DWI-FLAIR-mismatch present, n (%)	479 (48.0)	429 (48.7)	59 (43.7)	0.31

\* Percentage calculated with reference to number of patients with information available;

† intracerebral haemorrhage, subarachnoid haemorrhage, intraventricular haemorrhage, hemorrhagic transformation;

IQR = interquartile range; NIHSS = National Institutes of Stroke Scale; LOC = level of consciousness; DWI = diffusion weighted imaging; FLAIR = fluid attenuated inversion recovery

**Figure legends**

*Figure: Timing of Symptom Discovery among Patients with Unwitnessed Onset*

The figure shows the distribution of the time of day at which symptoms were discovered for all patients (available for n=1.003, missing for n=2).

