Intravenous Thrombolysis in Stroke Patients with Unknown Time of Symptom Onset

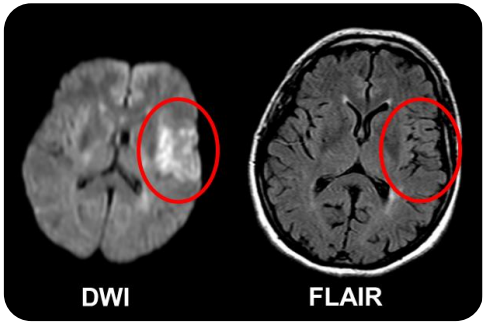
Illustrated imaging manual of the WAKE-UP trial

I. Galinovic, J.B. Fiebach, G. Thomalla, B. Cheng on behalf of the WAKE-UP Investigators

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Thrombolysis in unknown onset stroke?

- Intravenous alteplase is standard of care for acute stroke with clear benefit for treatment ≤4.5 hours of symptom onset
- No approval for alteplase in unknown time of symptom onset
- Unknown onset stroke is a frequent condition: ~20% wake-up strokes, unwitnessed stroke with aphasia or disturbed level of consciousness
- DAWN[1] and DEFUSE-3[2] demonstrated efficacy of thrombectomy in unclear onset stroke from large vessel occlusion
- No proven treatment option exists for the large group of patients with unknown symptom onset stroke without large vessel occlusion
- MRI was suggested as surrogate marker of acute ischemic lesion <4.5 hours of symptom onset: “Mismatch” between an acute lesion on DWI but no clearly visible hyperintensity on FLAIR[3]

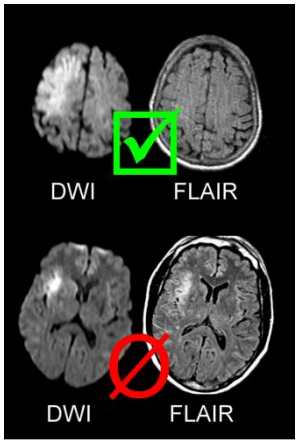


[1] Nogueira et al. N Engl J Med 2018;378:11-21; [2] Albers et al. N Engl J Med. 2018 Feb 22;378(8):708-718; [3]Thomalla et al. 2011 Lancet Neurol;10:978-986

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Aim and Design

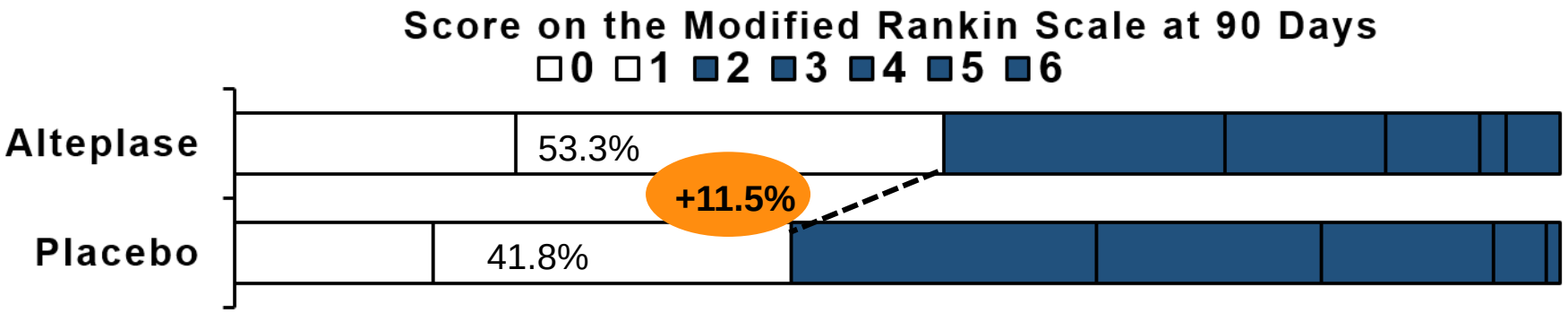
- **Aim**: To prove efficacy and safety of MRI-based thrombolysis in patients with unknown time of symptom onset
- **Design**: randomised, placebo-controlled clinical trial (Alteplase vs. Placebo 1:1)
- **Inclusion criteria**:
  - Acute stroke with unknown symptom onset, disabling neurological deficit
  - Last known well >4.5 hours (ie not eligible for IV alteplase by licence)
  - Age 18-80 years
  - Treatment can be started within 4.5 h of symptom recognition
  - Written informed consent
  - MRI completeted and indicative of lesion age ≤4.5 h: “DWI-FLAIR-mismatch”



- **Exclusion criteria**:
  - Planned thrombectomy
  - Any contradindication against treatment with alteplase (except for unknown time window)
- **Randomization**: 1:1 ratio to alteplase or placebo (alteplase 0.9 mg / kg of body weight (10% as bolus, the remainder by infusion over 60 min) or matching placebo)

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Primary Endpoint

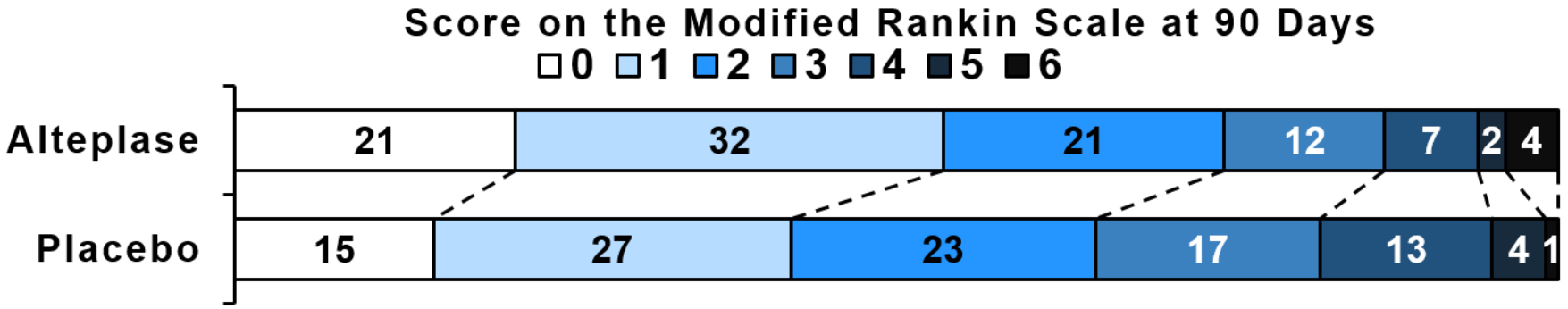


Endpoint	Alteplase (n=254)	Placebo (n=249)	Effect Variable	Adjusted Value (95% CI) *	P-Value
Favorable outcome (mRS 0-1) at 90 days	131/246 (53.3%)	102/244 (41.8%)	Odds ratio	**1.61 (1.09-2.36)**	**0.02**

** Adjusted for age and NIHSS at baseline*

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Secondary Endpoint: mRS „shift analysis“



Endpoint	Alteplase (n=254)	Placebo (n=249)	Effect Variable	Adjusted Value (95% CI) *	P-Value
Median mRS score at 90 days („shift analysis“)	1 (1-3)	2 (1-3)	Common odds ratio	**1.62 (1.17-2.23)**	**0.003**

** Adjusted for age and NIHSS at baseline*

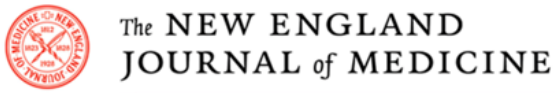
WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Conclusions

- In patients with unknown symptom onset stroke with MRI pattern of DWI-FLAIR-mismatch, treatment with alteplase resulted in better functional outcome than placebo.
- Consistent benefit across all categories of outcome.
- Effect size of MRI-guided thrombolysis in unknown symptom onset stroke is comparable to effect size of thrombolysis <4.5 hours.
- Numerically higher rates of symptomatic intracranial hemorrhage and trend towards higher mortality with alteplase, which might have become significant with larger sample size.
- Paradigm change: first positive trial of intravenous thrombolysis relying on patient selection by advanced brain imaging without information on time of symptom onset.
- MRI-guided intravenous thrombolysis represents an effective treatment option for stroke patients with unknown symptom onset, especially for those with minor or moderate stroke who are not eligible for mechanical thrombectomy.

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Full publication available online



ORIGINAL ARTICLE

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas, J. Fiehler, I. Ford, I. Galinovic, S. Gellissen, A. Golsari, J. Gregori, M. Günther, J. Guibernau, K.G. Häusler, M. Hennerici, A. Kemmling, J. Marstrand, B. Modrau, L. Neeb, N. Perez de la Ossa, J. Puig, P. Ringleb, P. Roy, E. Scheel, W. Schonewille, J. Serena, S. Sunaert, K. Villringer, A. Wouters, V. Thijs, M. Ebinger, M. Endres, J.B. Fiebach, R. Lemmens, K.W. Muir, N. Nighoghossian, S. Pedraza, and C. Gerloff, for the WAKE-UP Investigators*

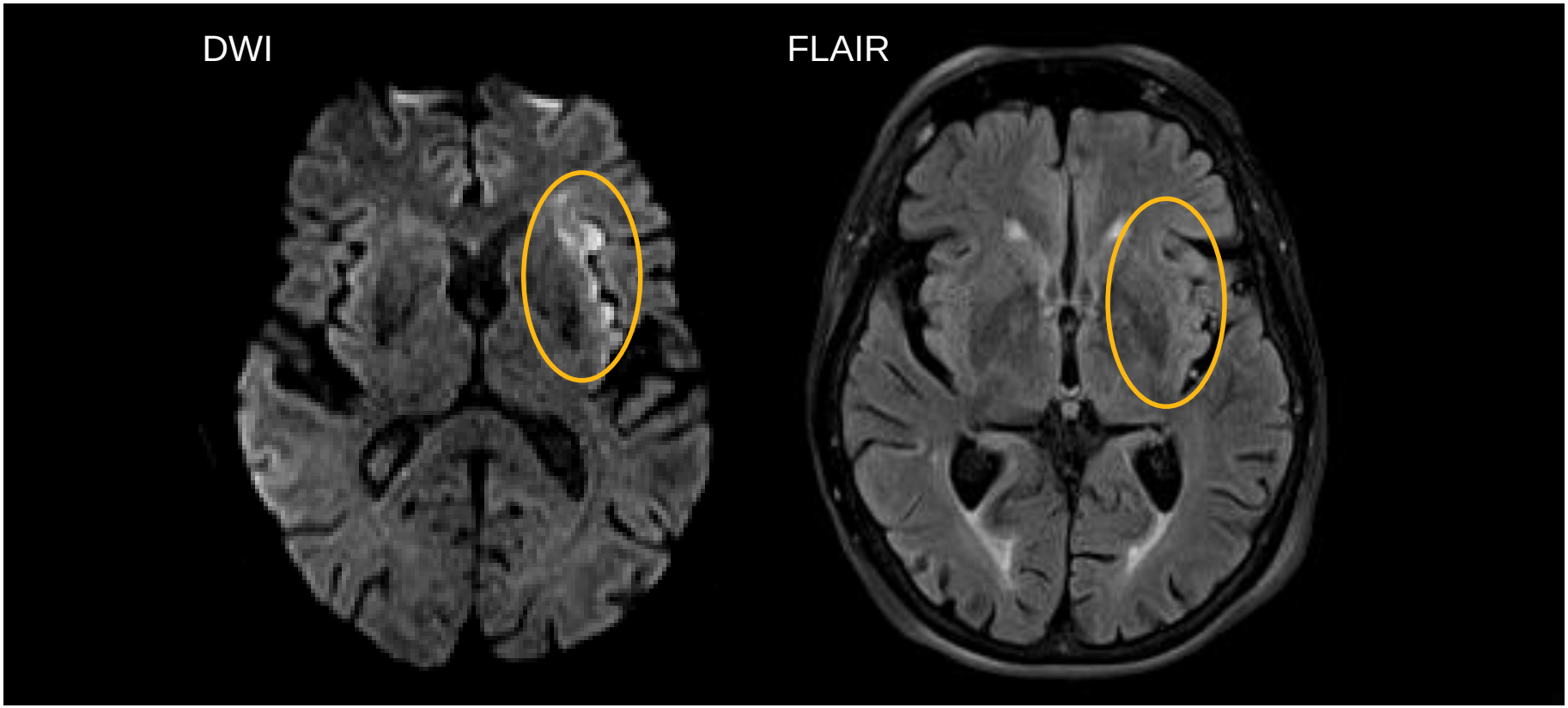
WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Intravenous Thrombolysis in Stroke Patients with Unknown Time of Symptom Onset

Introduction to the main imaging concept / criteria

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

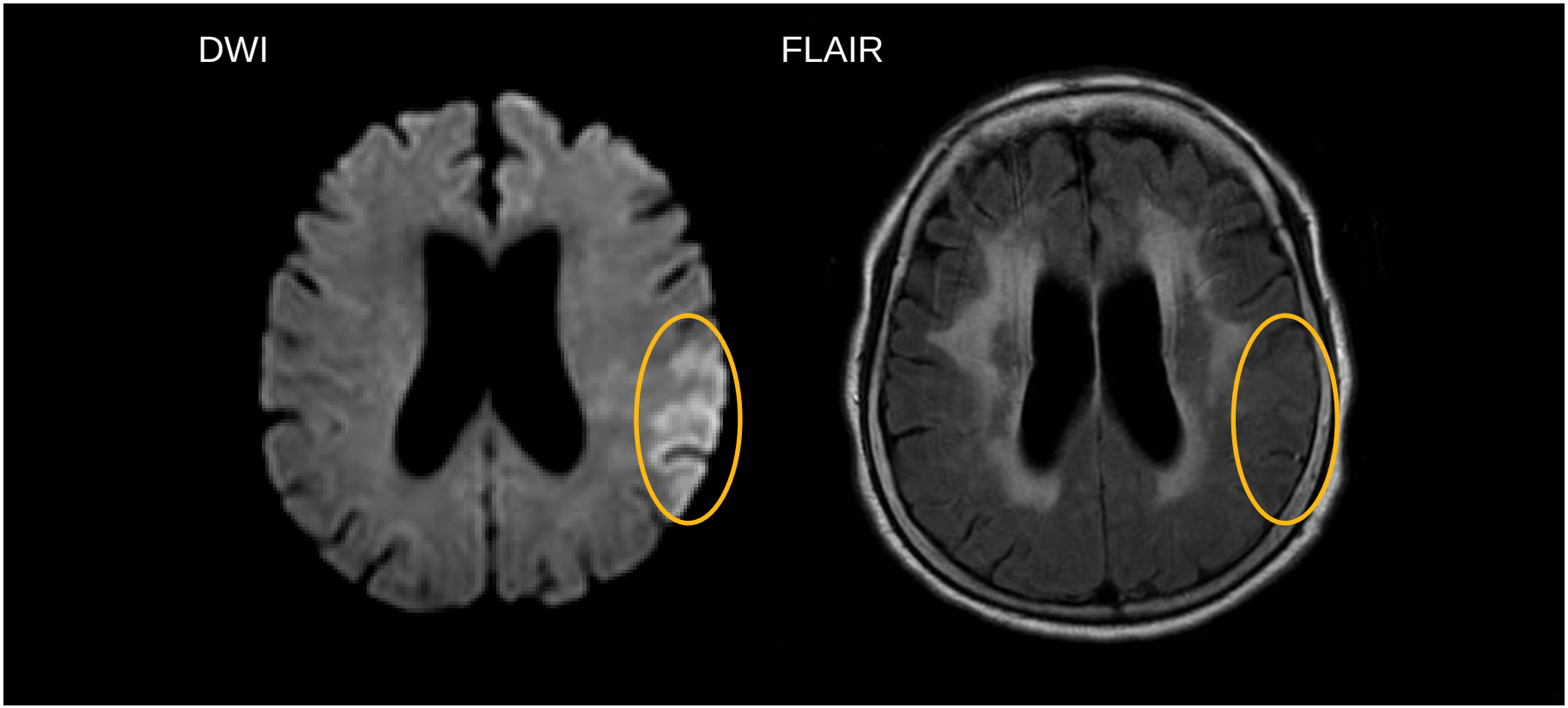
Main imaging concept of the study



- Main imaging question of the WAKE-UP study:
- Is a diffusion restriction (left image) already visible in the FLAIR (right image)?

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

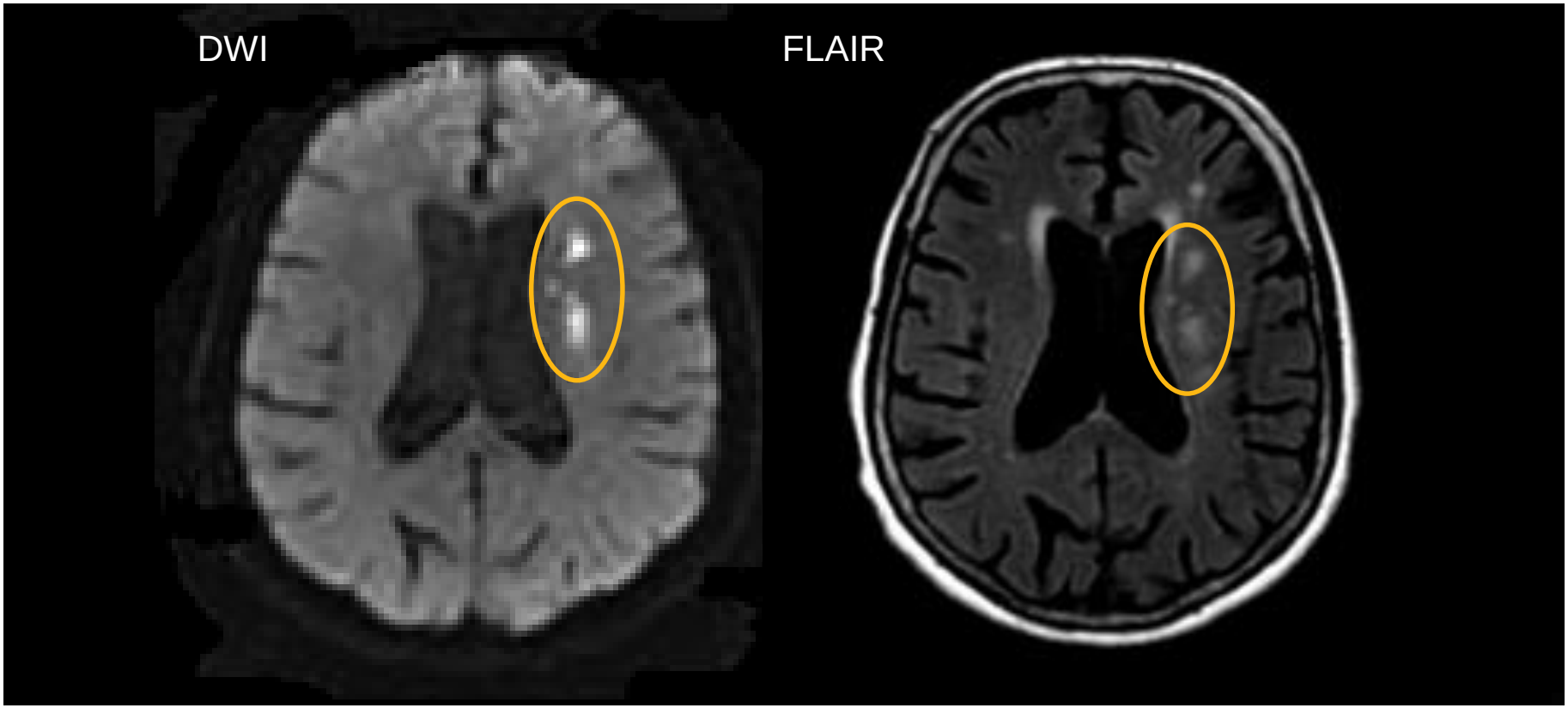
DWI-FLAIR Match or Mismatch



- The diffusion restriction (left image) <u>is not</u> already visible in the FLAIR (right image), giving the patient a verdict of a „DWI-FLAIR mismatch“
- <u>Suitable for treatment with alteplase</u>

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

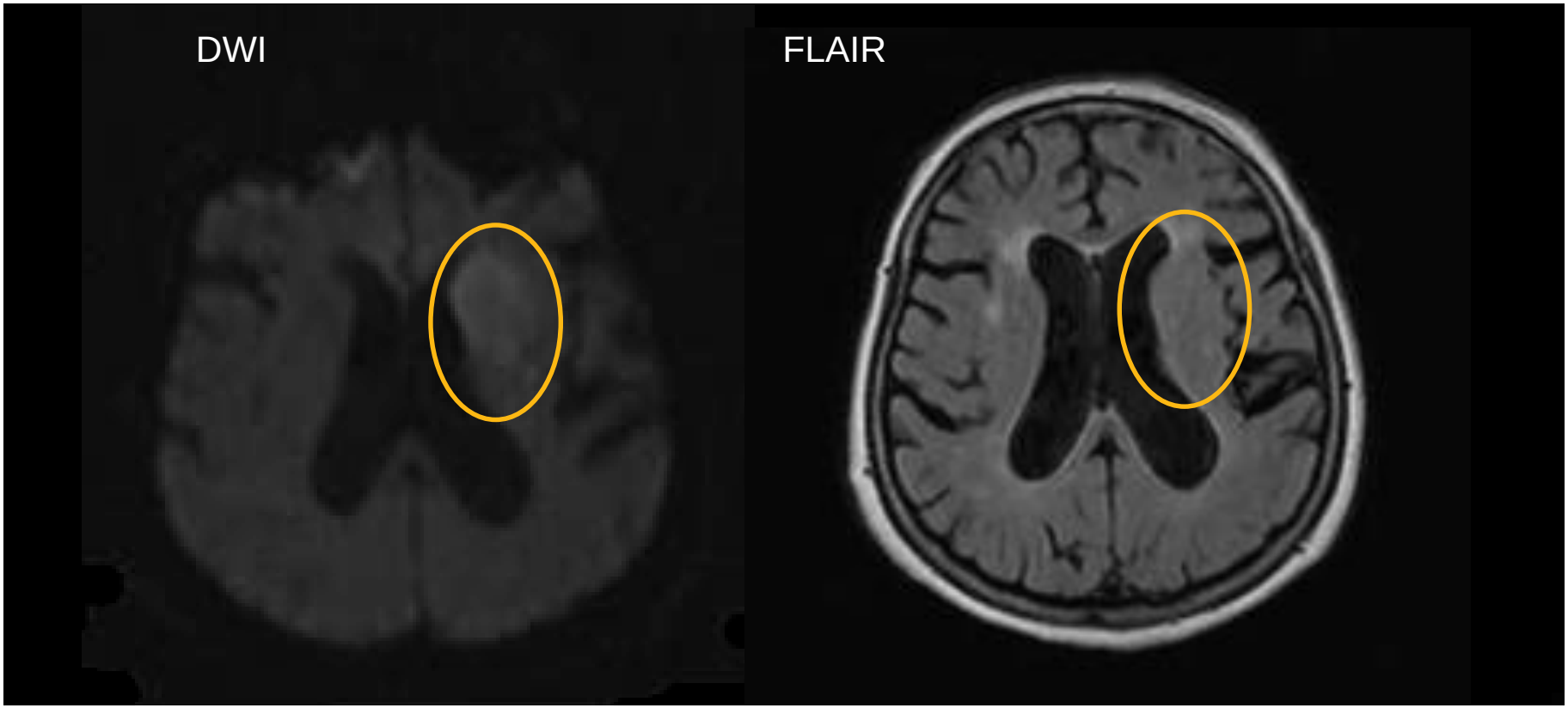
DWI-FLAIR Match or Mismatch



- The diffusion restriction (left image) is already visible in the FLAIR (right image), giving the patient a verdict of a „DWI-FLAIR match“
- Not suitable for treatment with alteplase

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

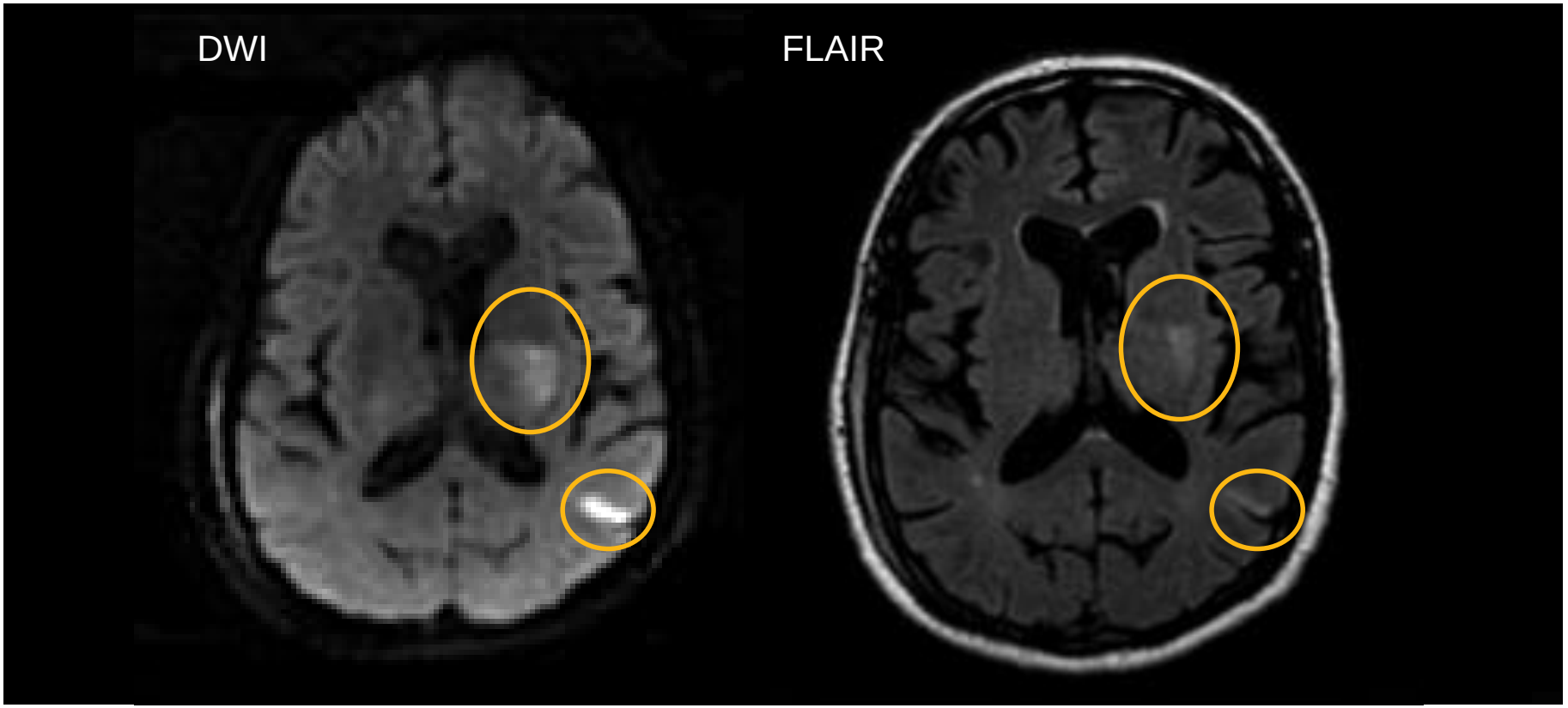
DWI-FLAIR Match or Mismatch



- The diffusion restriction (left image) is not already visible in the FLAIR (right image), giving the patient a „DWI-FLAIR mismatch“
- Suitable for treatment with alteplase

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

DWI-FLAIR Match or Mismatch



- The diffusion restriction (left image) is already visible in the FLAIR (right image), giving the patient a„DWI-FLAIR match“
- <u>Not suitable for treatment with alteplase</u>

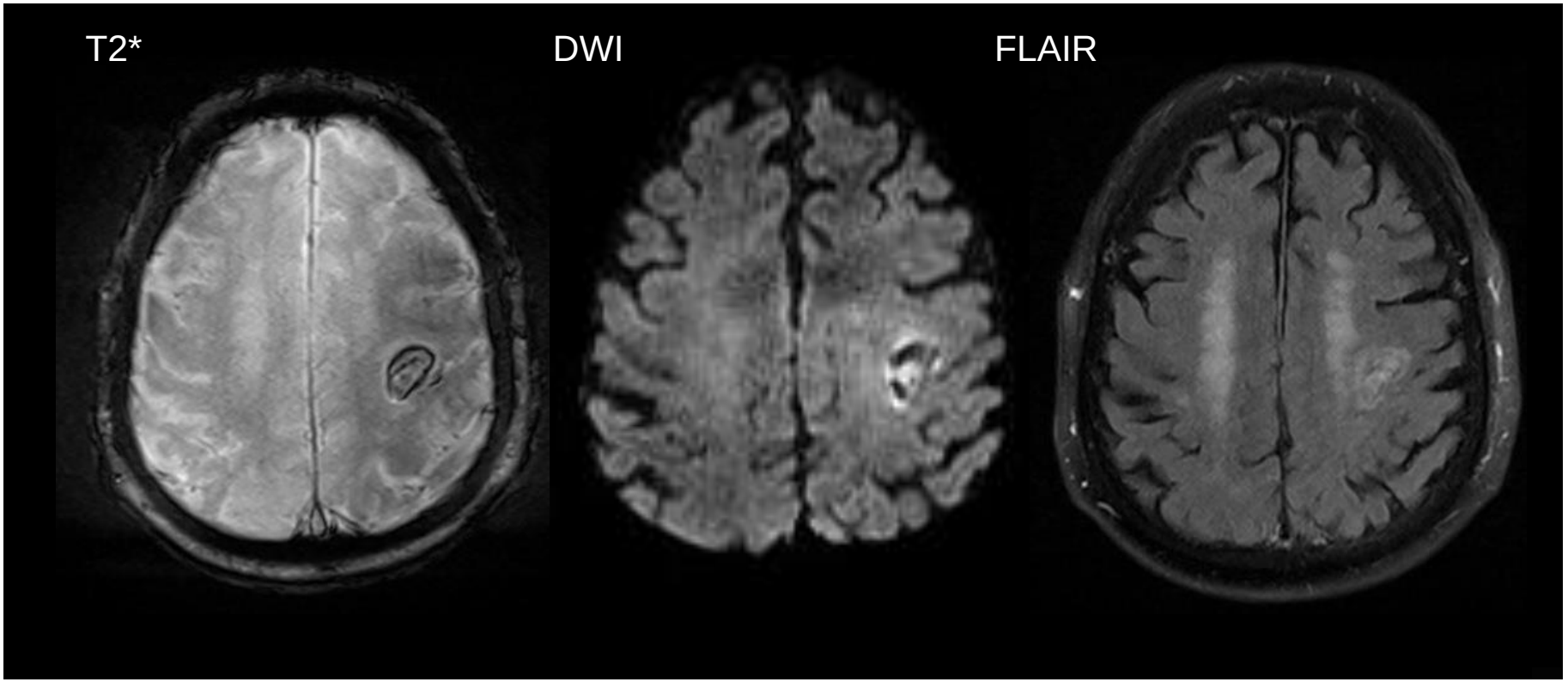
WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Intravenous Thrombolysis in Stroke Patients with Unknown Time of Symptom Onset

Further inclusion and exclusion criteria

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

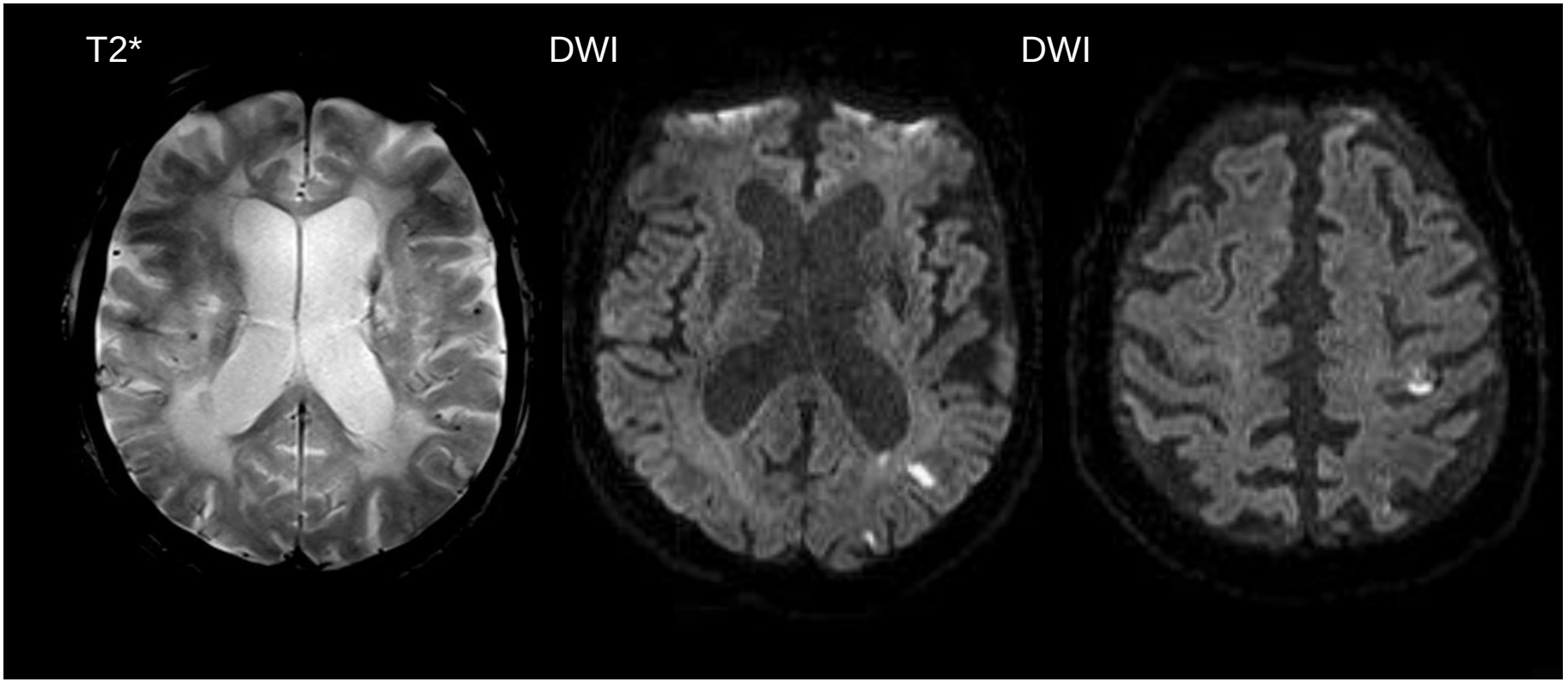
Hemorrhage



- Hemorrhagic stroke (primary bleed instead of an ischemic stroke) left frontal lobe.
- Exclusion criterion for tPA and therefore not suitable for treatment with alteplase.

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

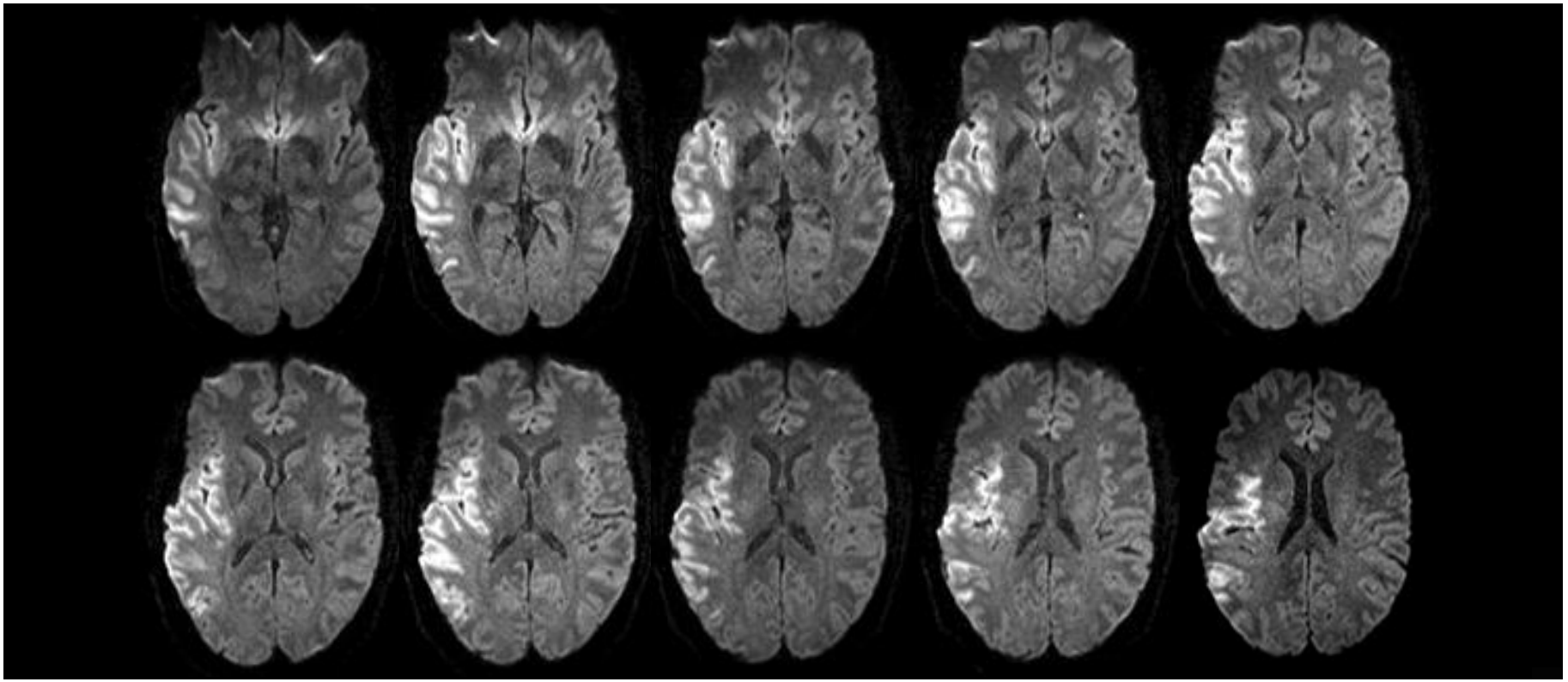
Hemorrhage



- Scattered left MCA-territory ischemic stroke
- multiple microbleeds seen on the T2* image are not necessarily an exclusion criterion for tPA
- Such patients were suitable for randomization in the WAKE-UP trial

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Large hemispheric stroke

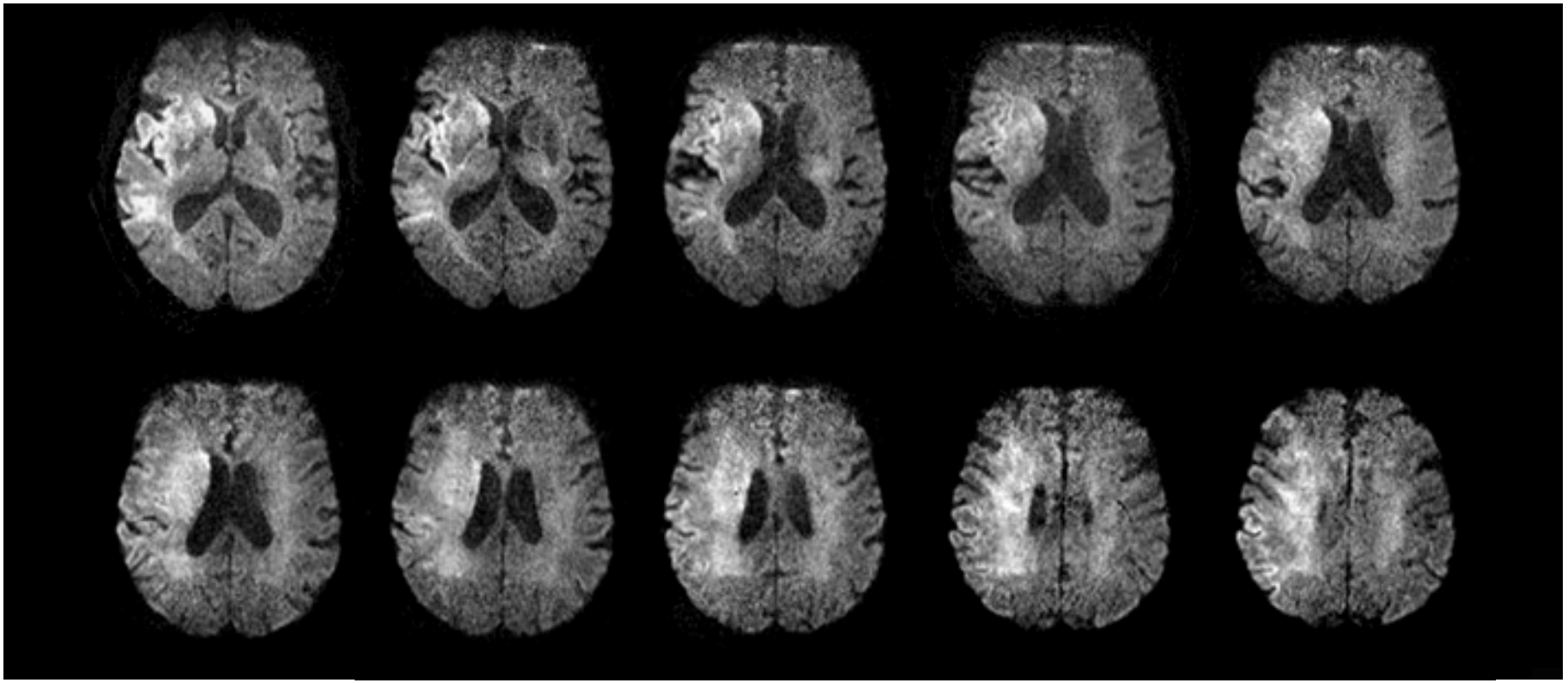


- DWI lesion is mainly cortical yet encompassing more than 1/3 of the MCA-territory*
- Such patients were not randomized in the WAKE-UP trial

* *This exclusion criterion also applies to strokes covering more than 1/2 ACA or 1/2 PCA vessel territory*

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Large hemispheric stroke

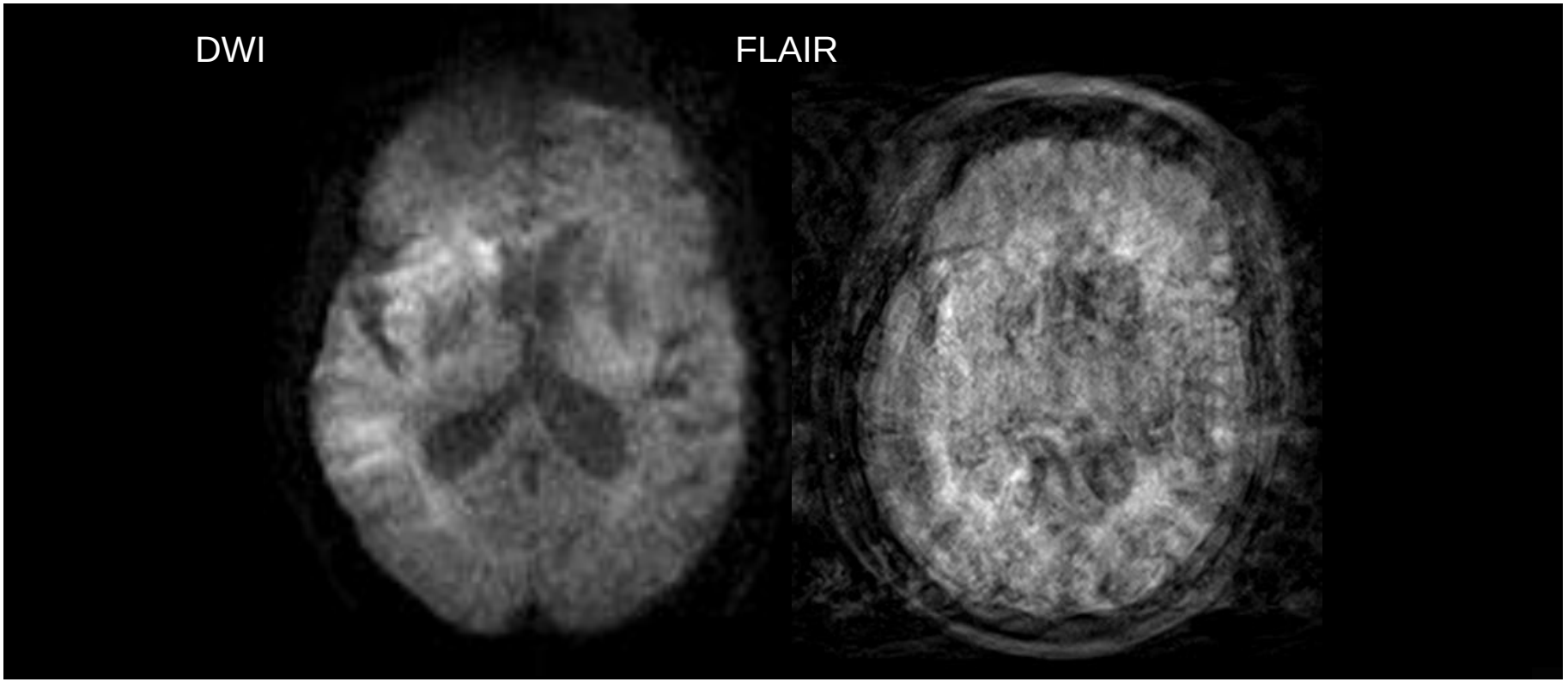


- Bad quality images due to patient movement, however DWI lesion covering much more than 1/3 of the MCA-territory
- Such patients were not randomized in the WAKE-UP trial

***** *This exclusion criterion also applies to strokes covering more than 1/2 ACA or 1/2 PCA vessel territory*

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

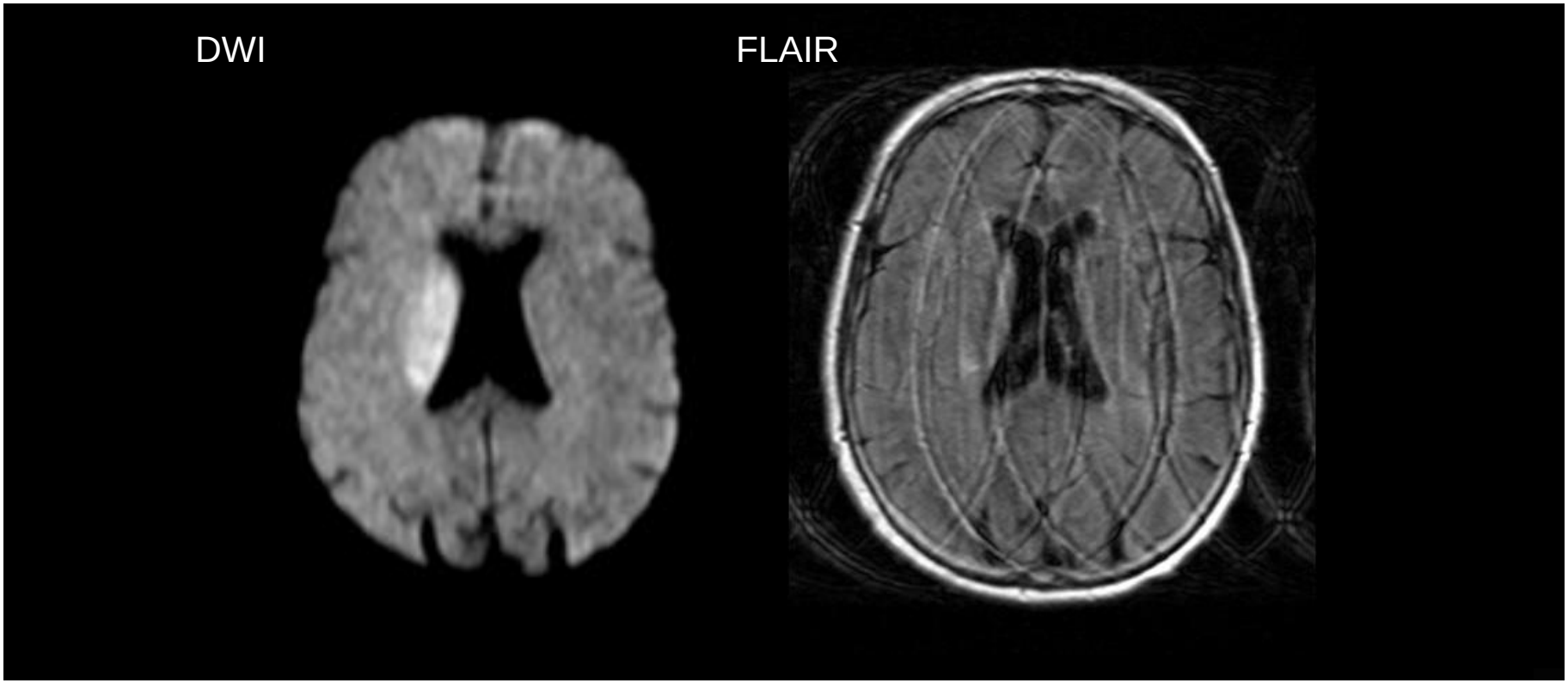
Image quality



- Right-sided MCA-territory ischemic stroke
- Bad quality images (both DWI and FLAIR) due to patient movement
- Not suitable for assessment of lesion visibility on FLAIR hence not randomized in the WAKE-UP trial

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

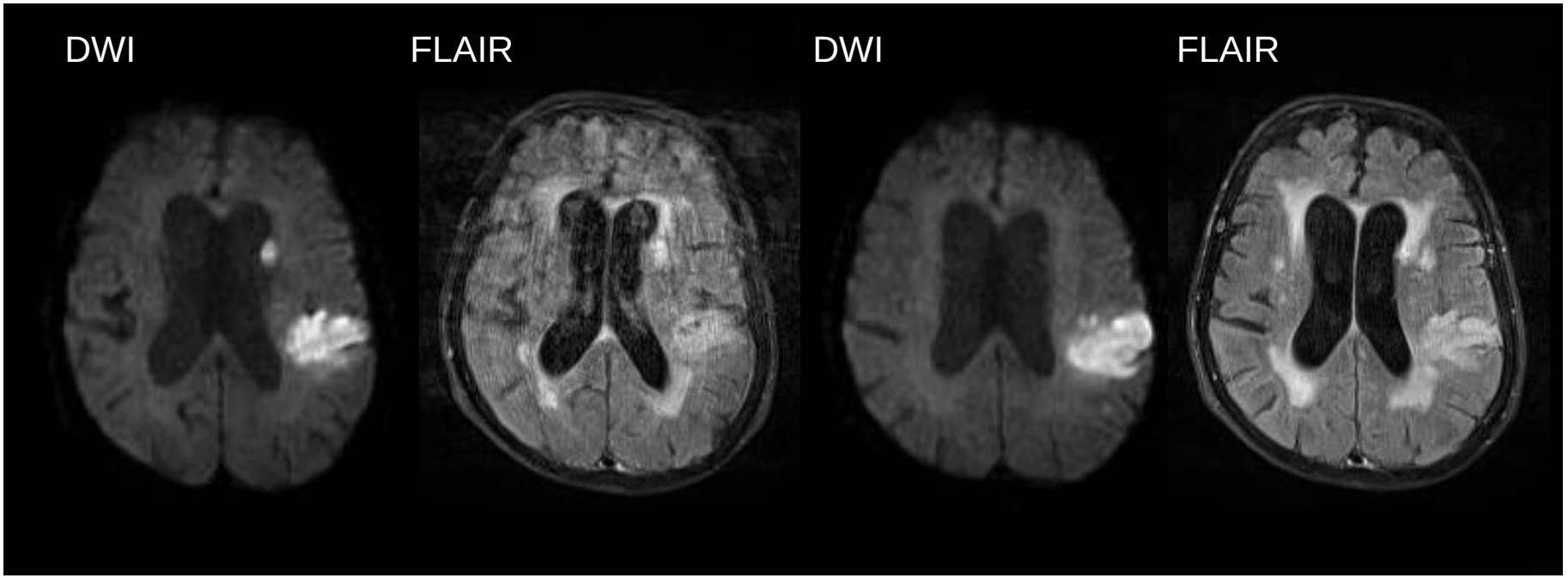
Image quality



- Right-sided, basal ganglia and corona radiata (MCA-territory) ischemic stroke
- DWI lesions appear in the area of extensive artifacts on the FLAIR image, making visibility difficult to judge in a reliable fashion
- Not suitable for assessment of lesion visibility on FLAIR hence not randomized in the WAKE-UP trial

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

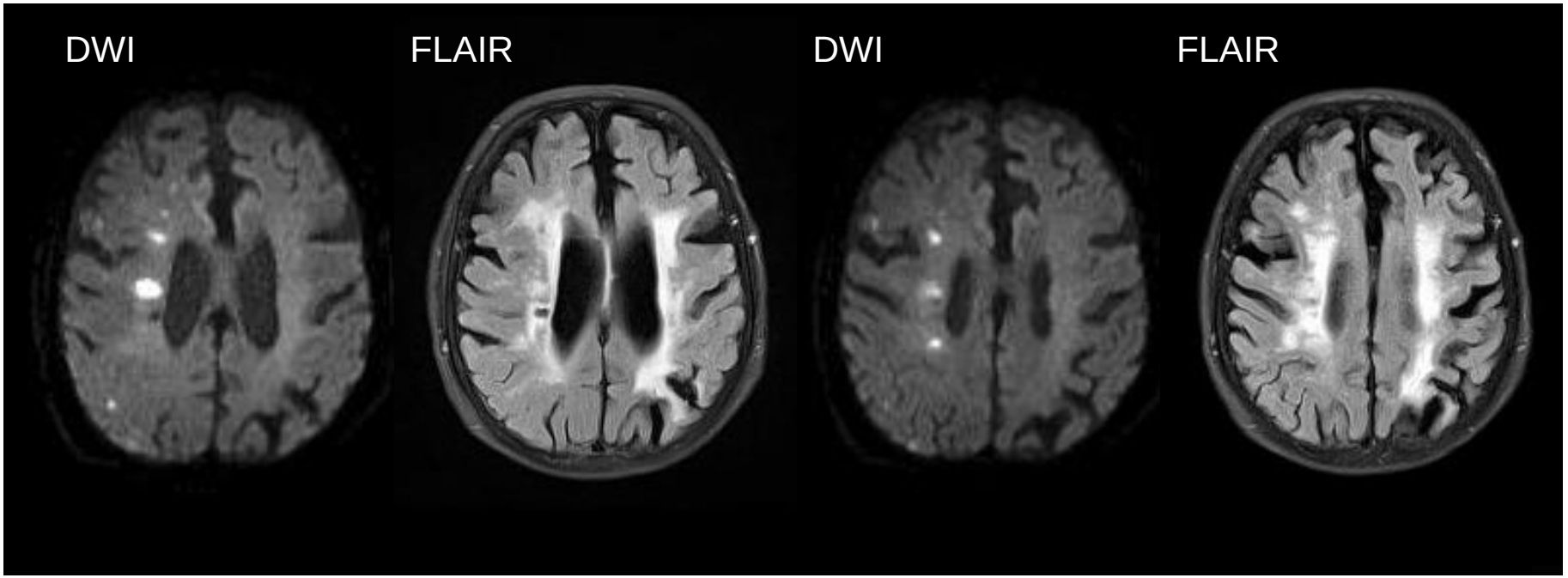
Image quality



- Left-sided, MCA-territory ischemic stroke including the basal ganglia
- Despite motion artifacts in the area of the DWI lesions, these are clearly visible on the FLAIR image.
- Suitable for assessment of lesion visibility on FLAIR, not randomized due to a„DWI-FLAIR match“
-

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

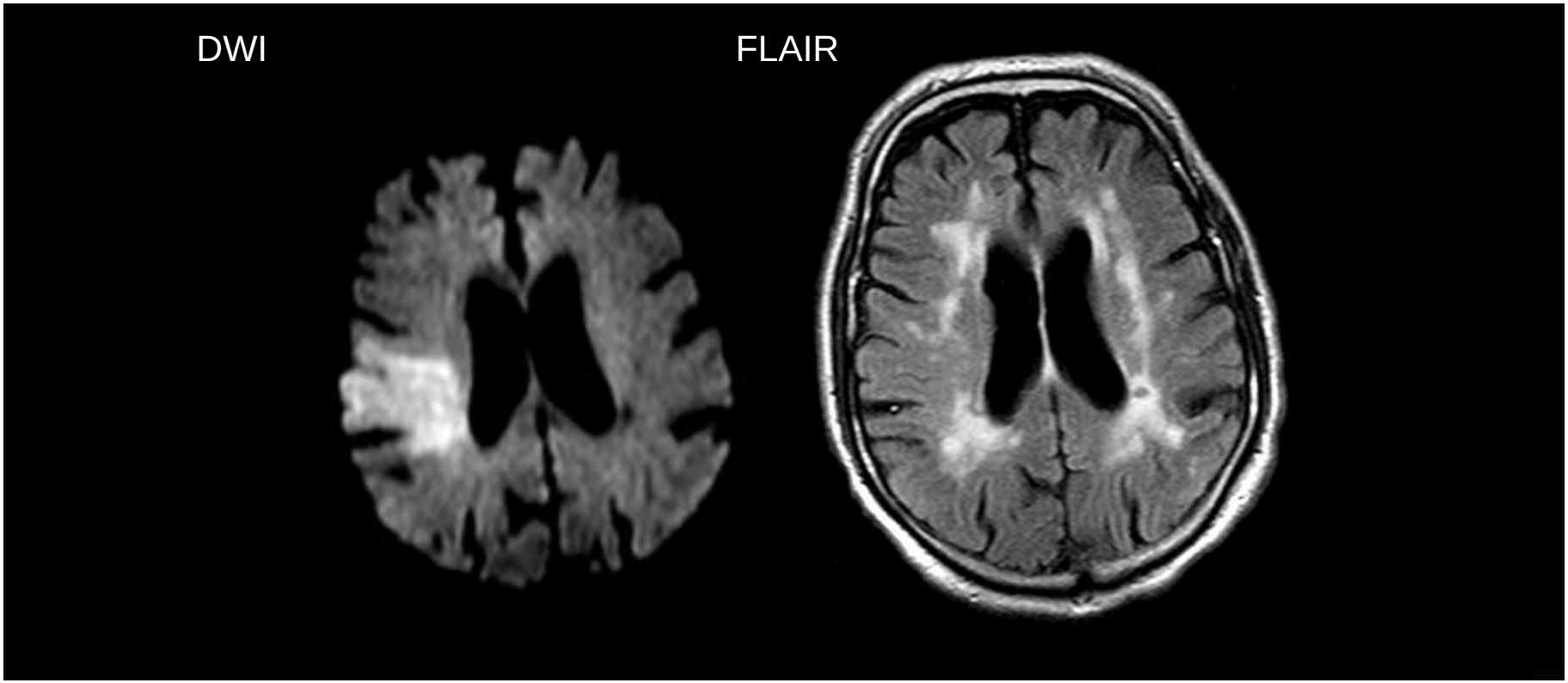
Leukoaraiosis



- Scattered right, mostly subcortical MCA-territory ischemic stroke
- DWI lesions appear in the area of extensive leukaraiosis and an old lacunar stroke, making visibility difficult to judge in a reliable fashion
- Not suitable for assessment of lesion visibility on FLAIR hence not randomized in the WAKE-UP trial

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Leukoaraiosis



- Right-sided MCA-territory ischemic stroke
- Although the DWI lesion is partially in the area of leukaraiosis, large portions of the lesion are outside the white matter changes making FLAIR visibility reliable to judge
- Suitable for assessment of lesion visibility on FLAIR and randomization in the WAKE-UP trial (due to a „DWI-FLAIR mismatch“)

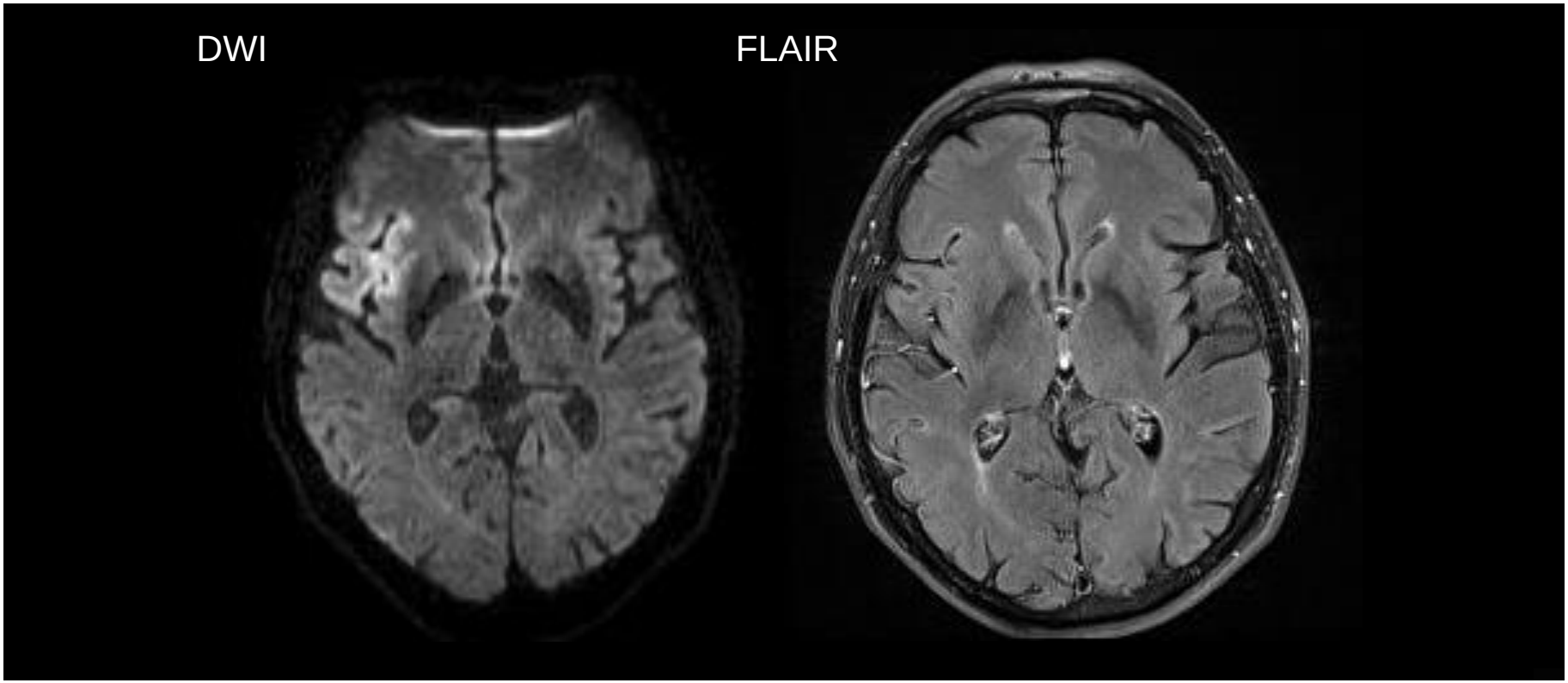
WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Intravenous Thrombolysis in Stroke Patients with Unknown Time of Symptom Onset

Further examples of the main imaging criteria

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

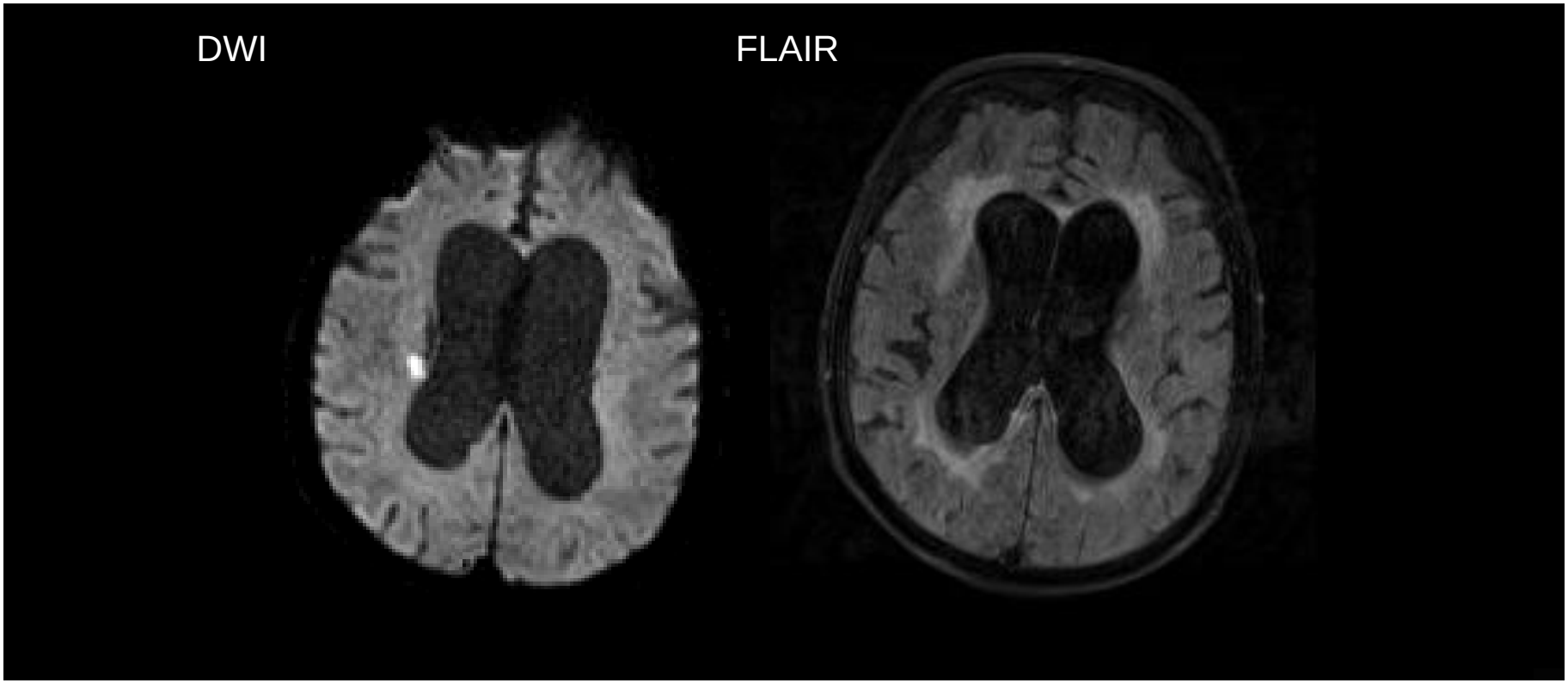
DWI-FLAIR Match or Mismatch



- Right-sided, mostly cortical MCA-territory ischemic stroke
- The tissue signal in the right operculum and insula appears exactly the same as contralateral, no lesion visibility on the FLAIR images
- <u>Suitable for treatment with alteplase</u>

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

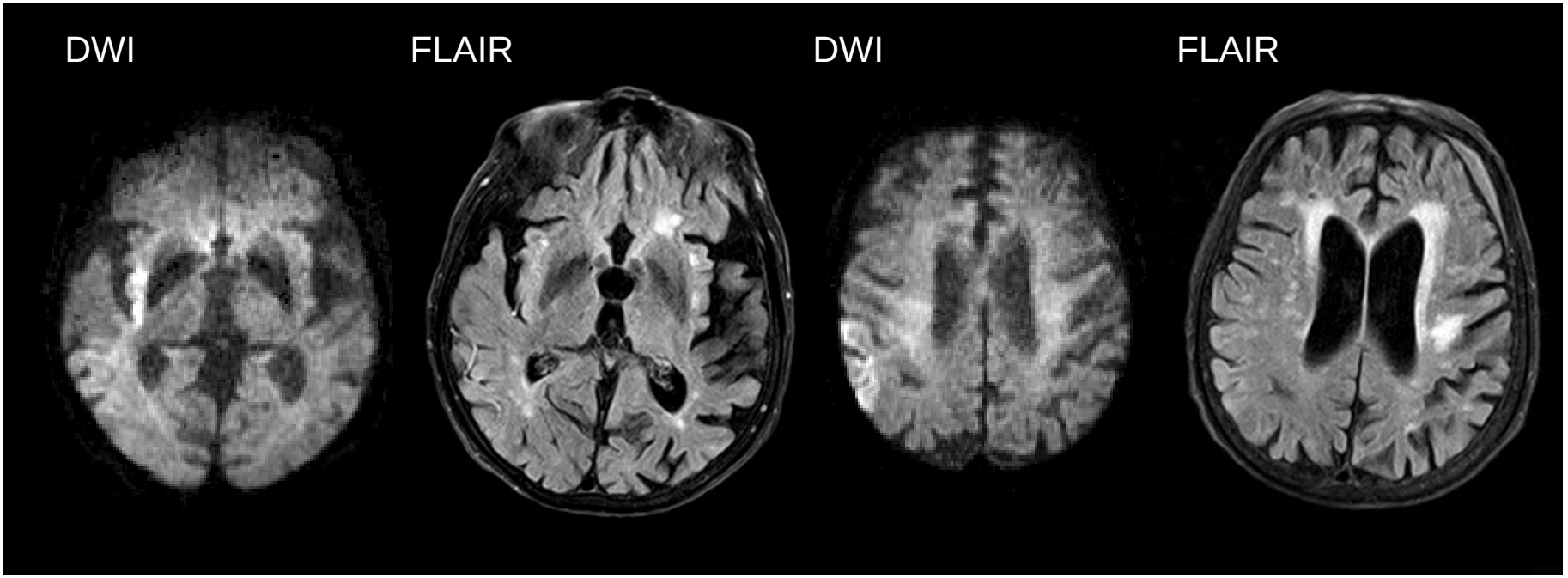
DWI-FLAIR Match or Mismatch



- Right-sided, purely subcortical MCA-territory ischemic stroke, not visible in the FLAIR
- Suitable for treatment with alteplase

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

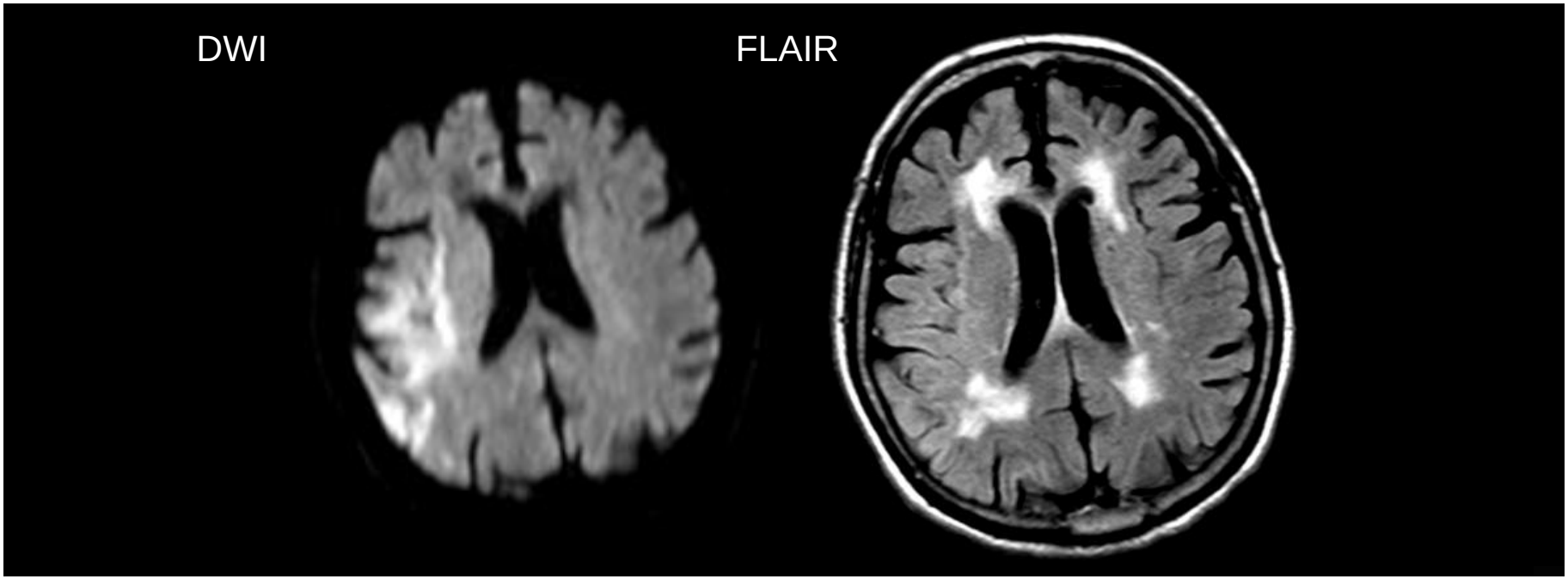
DWI-FLAIR Match or Mismatch



- With enough contrasting many lesions can become subtly visible in the FLAIR. WAKE-UP imaging criteria discouraged aggressive contrasting. Under the current contrast settings, there is no lesion visibility on the FLAIR in this right-sided MCA stroke.
- Suitable for treatment with alteplase

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

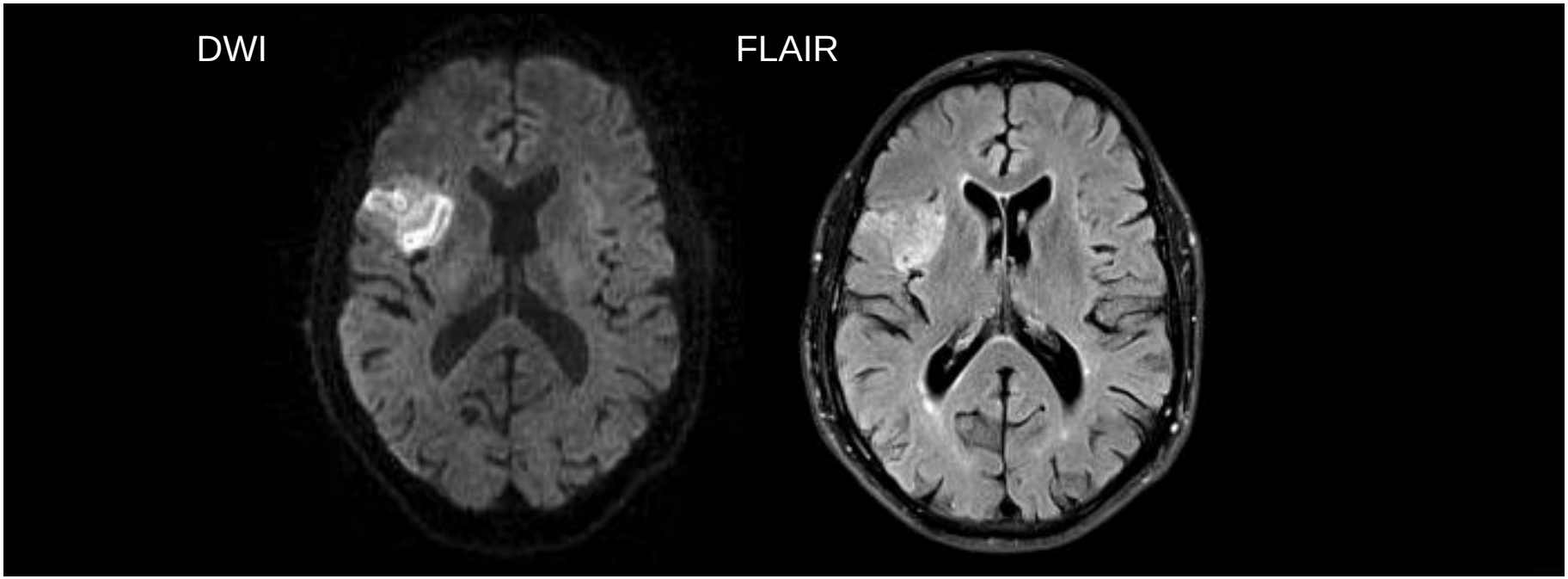
DWI-FLAIR Match or Mismatch



- Right-sided MCA-territory ischemic stroke
- With enough contrasting the insular ribbon becomes subtly visible in the FLAIR. However, without aggressive contrasting, there is no clear lesion visibility on the FLAIR
- <u>Suitable for treatment with alteplase</u>

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

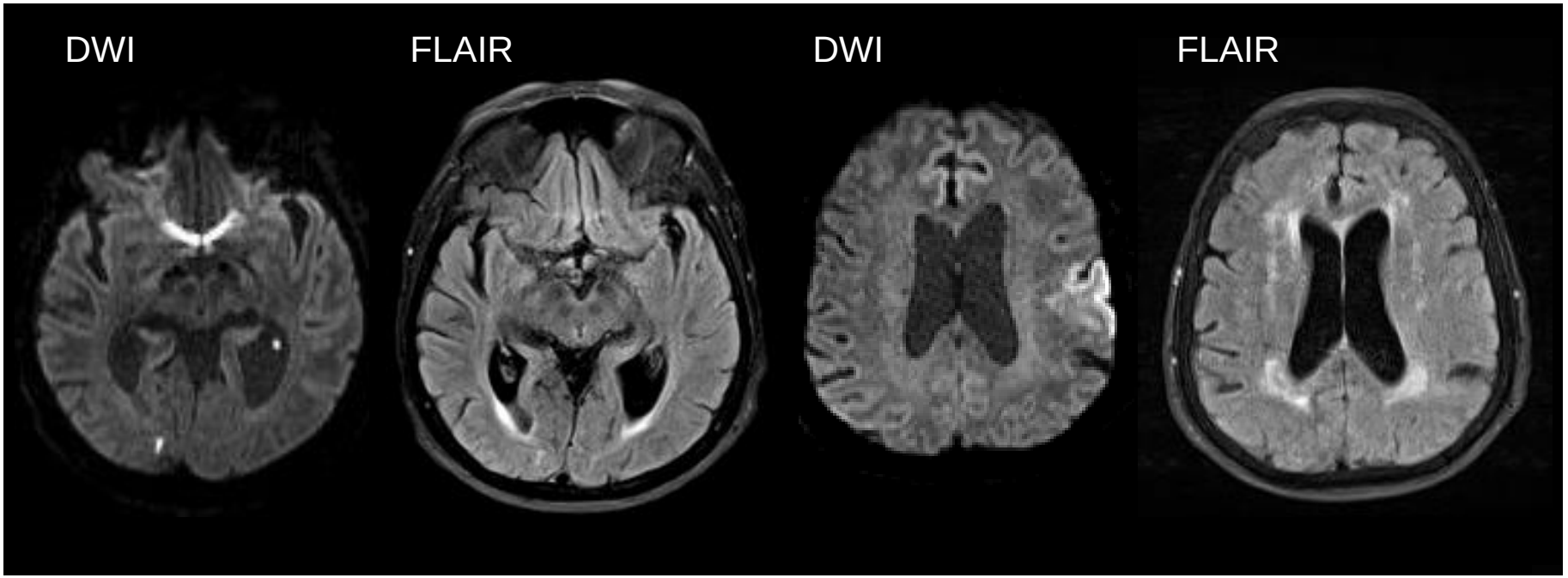
DWI-FLAIR Match or Mismatch



- Right-sided MCA-territory ischemic stroke
- Even with very mild contrasting the DWI lesion is visible in the FLAIR.
- Not suitable for treatment with alteplase

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

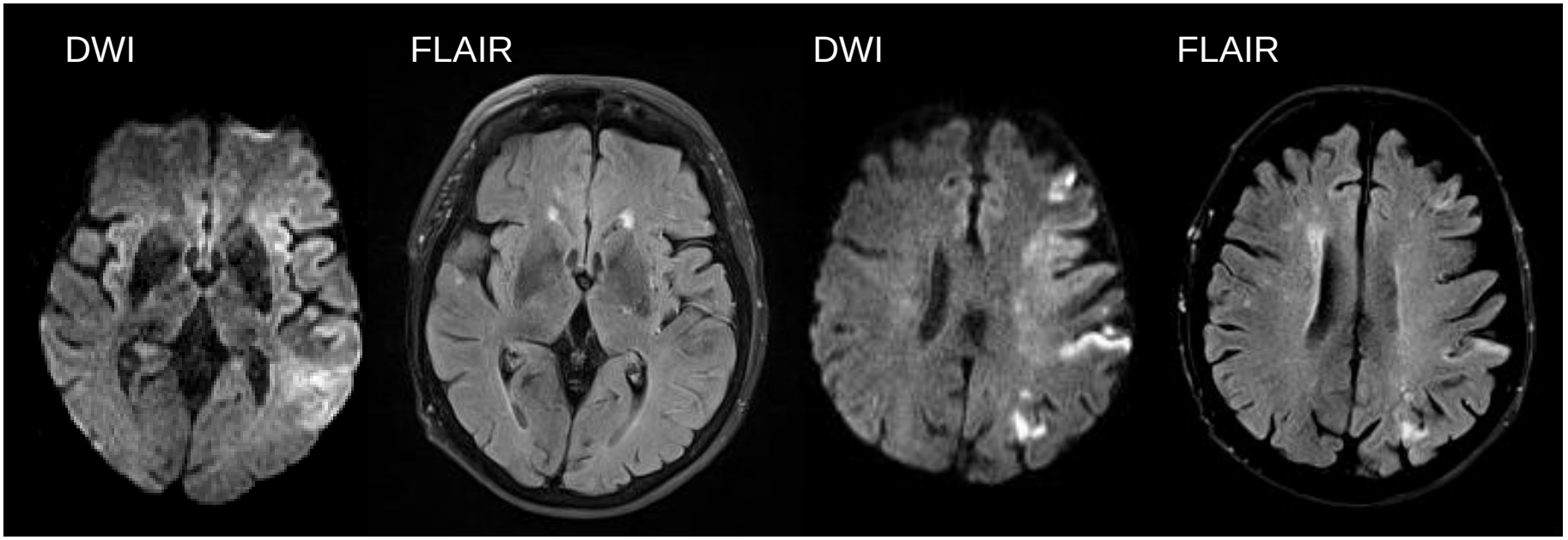
DWI-FLAIR Match or Mismatch



- Right PCA-territory stroke (visible in the FLAIR) and left-sided MCA-territory stroke (not visible in the FLAIR) signaling that this is a time distributed event
- If any acute ischemic lesion is visible in the FLAIR, it represents a „DWI-FLAIR match“
- Not suitable for randomization in the WAKE UP trial

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

DWI-FLAIR Match or Mismatch



- Higher slices show lesions of the left MCA stroke which are visible in the FLAIR whereas on lower slices they are yet invisible, signaling that this is a time distributed event
- If any segment of the acute ischemic lesion is visible in the FLAIR, it represents a „DWI-FLAIR match“
- <u>Not suitable for randomization in the WAKE UP trial</u>

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.

Prof. Jochen B. Fiebach
Head of CSB Neuroradiology
Center for Stroke Research Berlin (CSB)
Charité - Universitätsmedizin Berlin
Campus Benjamin Franklin
Hindenburgdamm 30
D 12200 Berlin
Tel. +49 (0)30 450 560 662
Email. jochen.fiebach@charite.de

Ivana Galinovic PhD MD
CSB Neuroradiology
Center for Stroke Research Berlin (CSB)
Charité – Universitätsmedizin Berlin
Campus Benjamin Franklin
Hindenburgdamm 30
D 12200 Berlin
Tel. +49 (0)30 450 560 717
Email. ivana.galinovic@charite.de

WAKE-UP has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 278276.