Wake-Up Strokes: Advanced Imaging Solutions for Time-Sensitive Neurological Emergencies

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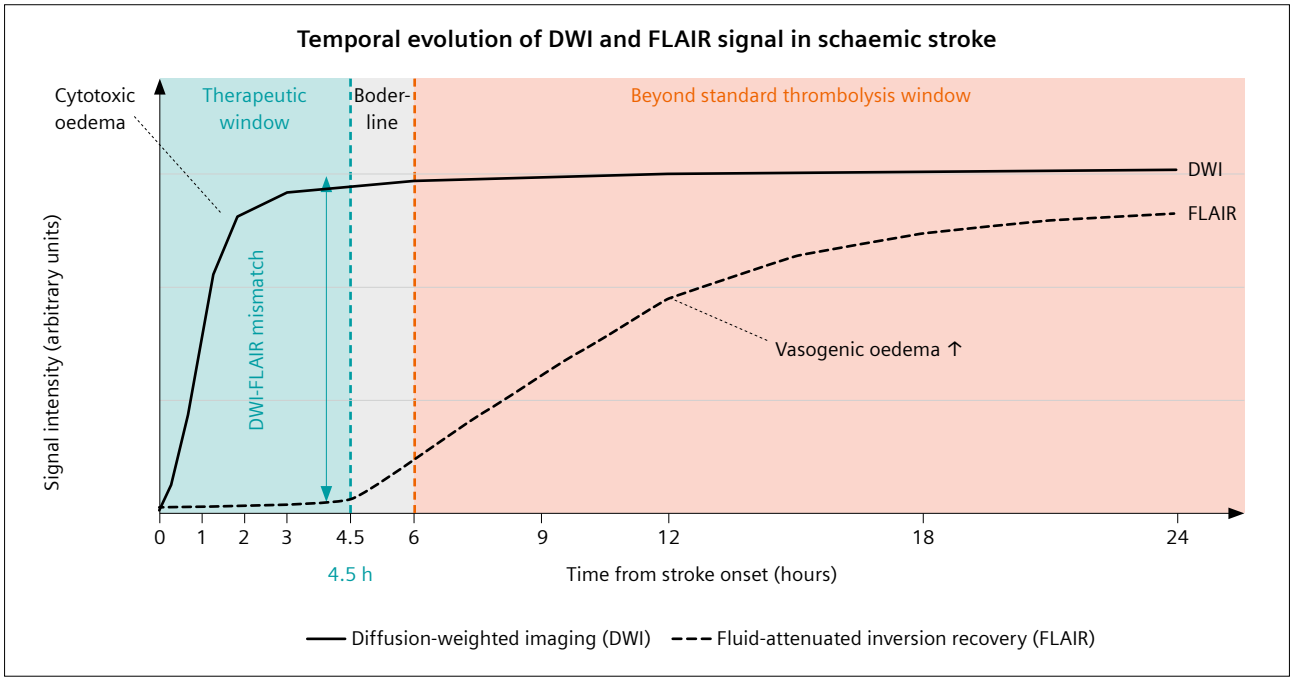
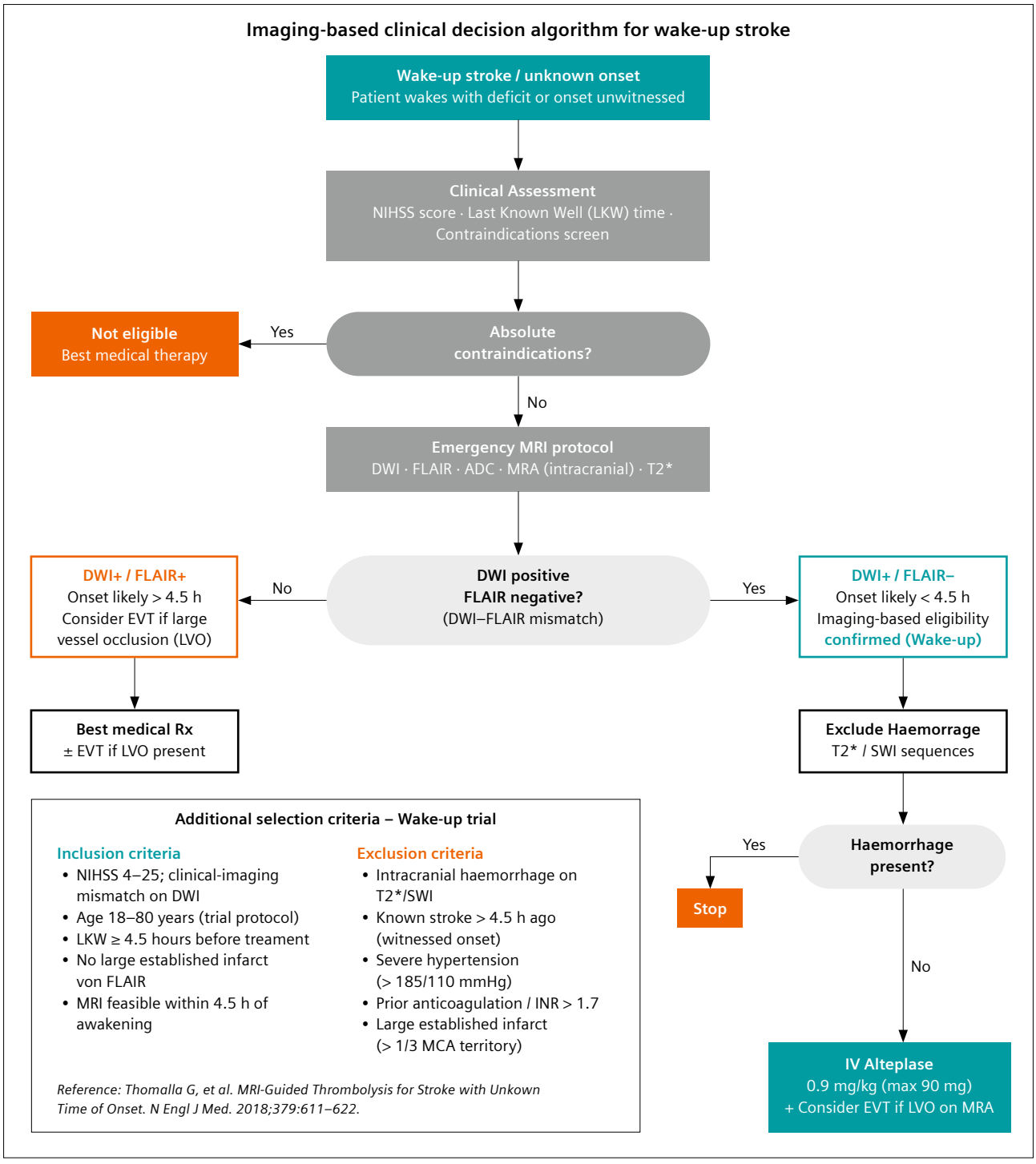
Wake-up strokes, which account for 14%–28% of all ischemic strokes, present a unique diagnostic challenge [1]: In wake-up stroke, patients first notice neurological deficits when they awaken, making it impossible to precisely determine the onset time of the stroke. This uncertainty has historically excluded these patients from thrombolytic therapy, as traditional protocols required confirmed symptom onset within 4.5 hours [3]. However, advanced neuroimaging has revolutionized treatment paradigms, enabling tissue-based rather than time-based treatment decisions [4, 5].

The clinical challenge

Wake-up strokes are when individuals go to sleep neurologically intact and awaken with established deficits. The last-known normal time is bedtime, but the actual time of stroke onset remains unknown. Traditional stroke management follows the principle that time is brain — every minute of ischemia destroys approximately 1.9 million neurons [2]. Alteplase, a tissue plasminogen activator, offers benefit only within narrow time windows. This creates an impossible situation for wake-up stroke patients, who, even with rapid emergency response, fall outside traditional eligibility criteria due to the unknown onset time [3].



1 **Temporal evolution of DWI and FLAIR signal intensity following acute ischemic stroke onset.** Schematic graph illustrating the divergent time courses of diffusion-weighted imaging (DWI; solid line) and fluid-attenuated inversion recovery (FLAIR; dashed line) signal intensity following ischemic stroke onset. DWI signal rises rapidly within minutes of onset as cytotoxic oedema — driven by failure of the Na^+/K^+-ATPase and subsequent intracellular water accumulation — restricts water diffusion in the infarcted core. FLAIR signal elevation, reflecting vasogenic oedema from blood–brain barrier disruption, is delayed by several hours, typically beyond 3–4.5 hours from onset. The interval during which DWI is positive and FLAIR remains negative (petrol shaded zone) constitutes the DWI–FLAIR mismatch window, underpinning the imaging-based patient selection strategy employed in the WAKE-UP randomized controlled trial. The borderline zone (4.5–6 hours, orange shading) reflects inter-individual variation in the rate of FLAIR signal emergence; treatment decisions in this range require individual risk–benefit evaluation.



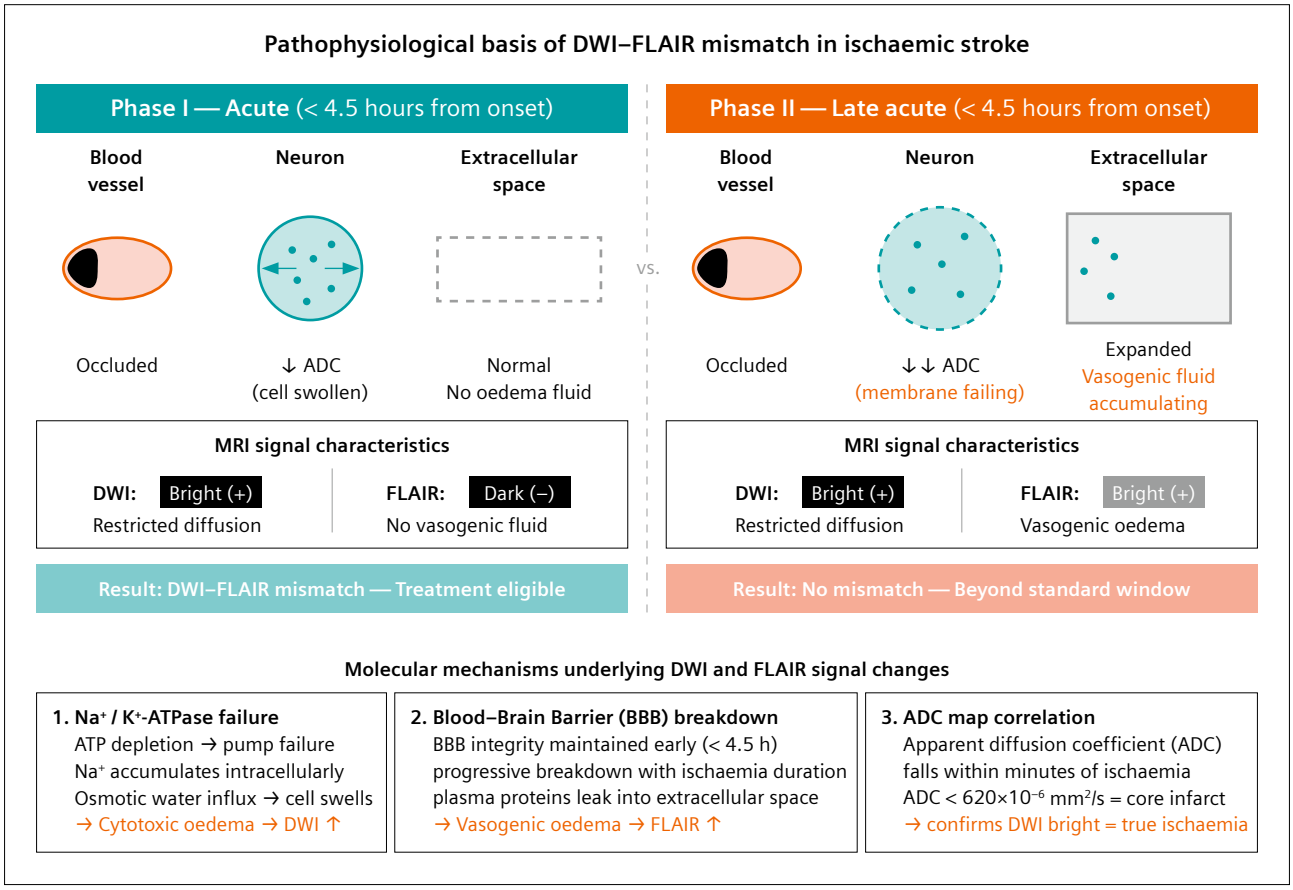
2 **Imaging-guided clinical decision algorithm for acute management of wake-up stroke.**
Stepwise decision algorithm for the management of wake-up and unknown-onset ischemic stroke, based on the imaging selection criteria of the WAKE-UP trial [5]. Following clinical assessment and exclusion of absolute contraindications, emergency MRI is performed (DWI, FLAIR, ADC map, MRA, T2*/susceptibility-weighted imaging). Confirmation of DWI–FLAIR mismatch (DWI-positive, FLAIR-negative) — indicating a high likelihood of onset within 4.5 hours — combined with exclusion of intracranial hemorrhage on T2* sequences, supports eligibility for intravenous alteplase at 0.9 mg/kg (maximum 90 mg). The presence of DWI–FLAIR concordance (both sequences positive) suggests onset beyond the standard window, with management directed toward best medical therapy or endovascular thrombectomy where large vessel occlusion is confirmed on MRA. The inset table summarizes key inclusion and exclusion criteria from the WAKE-UP trial protocol.
Abbreviations: LKW = last known well; NIHSS = National Institutes of Health Stroke Scale; LVO = large vessel occlusion; EVT = endovascular thrombectomy; IV = intravenous; INR = international normalized ratio

MRI-guided treatment selection

With modern magnetic resonance imaging (MRI), clinicians can employ diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences as biological clocks. DWI detects acute ischemic changes within minutes by measuring restricted water diffusion in swollen cells. FLAIR imaging suppresses cerebrospinal fluid signal while highlighting edema, but these changes develop more slowly, typically requiring several hours. When stroke appears bright on DWI but shows no corresponding FLAIR changes, the mismatch indicates recent onset, typically within the therapeutic window [4]. This imaging signature provides the timing information that a clinical history cannot offer.

Clinical evidence and treatment protocols

The landmark WAKE-UP trial (2018) enrolled 503 wake-up stroke patients with DWI-FLAIR mismatch, and randomly assigned them to receive either alteplase or a placebo. The results demonstrated favorable outcomes in 53.3% of the alteplase group, compared to 41.8% in the placebo group, without increased hemorrhagic complications [5]. The EXTEND trial reinforced these findings using perfusion imaging. It showed benefit up to 9 hours from last-known well in selected patients [6]. These studies established that imaging-guided patient selection enables safe, effective thrombolysis regardless of clock time [10].



3 **Pathophysiological basis of DWI–FLAIR mismatch in ischemic stroke.**
Cellular and molecular mechanisms underlying DWI and FLAIR signal changes in early and late acute ischemic stroke. **Phase I (left panel, < 4.5 hours from onset):** ischemia causes rapid depletion of adenosine triphosphate (ATP), leading to failure of the Na^+/K^+-ATPase pump. Sodium accumulates intracellularly, drawing water osmotically into the cell — cytotoxic (intracellular) oedema. Restricted intracellular water diffusion generates DWI hyperintensity and a reduced apparent diffusion coefficient (ADC < 620×10^{-6} mm^2/s). Blood–brain barrier integrity is maintained at this stage, preventing extracellular fluid accumulation; FLAIR signal therefore remains negative. **Phase II (right panel, > 4.5 hours from onset):** progressive ischemic injury disrupts tight junctions of the blood–brain barrier, allowing plasma proteins and fluid to accumulate in the extracellular space (vasogenic oedema). This extracellular water accumulation is detected by FLAIR as hyperintensity, eliminating the DWI–FLAIR mismatch. **Column 3 (lower panel):** the ADC map provides quantitative confirmation of true cytotoxic ischemia and assists in differentiation from T2 shine-through artefact.
Abbreviations: ADC = apparent diffusion coefficient; ATP = adenosine triphosphate; BBB = blood–brain barrier; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery

Contemporary protocols integrate MRI into streamlined workflows. Following rapid neurological assessment and non-contrast CT imaging to exclude hemorrhage [12], patients undergo MRI with DWI and FLAIR sequences. Stroke neurologists and neuroradiologists evaluate mismatch patterns in real time. Positive mismatch without contraindications prompts immediate alteplase administration. Large-vessel occlusions may proceed to mechanical thrombectomy, the window for which has been extended in recent trials to 24 hours for appropriately selected patients [7, 8].

Implementation and technical factors

Successful implementation requires optimized imaging protocols, expert interpretation, and efficient workflows. DWI sequences employ b-values of 1000 s/mm^2 for optimal sensitivity. Both 1.5T and 3T MRI systems can effectively demonstrate mismatch, although 3T offers superior signal-to-noise ratios. Interpretation demands specialized expertise to distinguish acute changes from chronic white-matter disease and to avoid motion artifacts. Leading centers have achieved door-to-MRI times of less than 20 minutes by using dedicated stroke imaging slots, direct ambulance-to-scanner protocols, and immediate notification of radiologists [13].

Patient selection balances treatment benefit against hemorrhage risk. Inclusion criteria typically require a disabling neurological deficit, a last-known normal time between 4.5 and 24 hours prior, confirmed DWI-FLAIR or perfusion-diffusion mismatch, and absence of hemorrhage. Standard contraindications for thrombolysis remain applicable and include recent surgery, active bleeding, uncontrolled hypertension, and a large established infarction exceeding one-third of the middle cerebral artery territory [9, 14].

Current challenges and future directions

Despite remarkable progress, challenges persist. Advanced MRI capabilities remain concentrated in comprehensive stroke centers, creating geographic disparities. Approximately 10% of patients cannot undergo MRI due to pacemakers, defibrillators, or claustrophobia, although CT perfusion imaging offers an alternative [13]. Imaging protocols, mismatch definitions, and treatment thresholds vary across institutions. Artificial intelligence may eventually enable automated mismatch detection, thereby reducing variability and accelerating decision-making [11].

With approximately 180,000 wake-up strokes occurring annually in the United States alone [1], imaging-guided therapy can potentially benefit tens of thousands of patients who were previously excluded from treatment. Public education remains critical — many people believe that waking up with symptoms means treatment is impossible. Healthcare campaigns must emphasize that immediate evaluation is essential, regardless of symptom onset time. This shifts the paradigm from "time is brain" to "tissue is brain," with salvageable tissue mattering more than elapsed clock time [9].

Conclusion

Advanced neuroimaging has transformed wake-up strokes from untreatable conditions to intervention opportunities. The shift from rigid time windows to flexible tissue windows guided by sophisticated MRI techniques exemplifies the power of technology in overcoming clinical barriers. Successful intervention requires integrated emergency response, rapid imaging capabilities, expert interpretation, streamlined protocols, and robust monitoring. Innovations in medical technology — including high-field MRI systems, accelerated sequences, automated analysis software, and algorithms — continue to expand access to evidence-based treatment.

For healthcare systems, investing in advanced imaging infrastructure and specialized teams directly translates into improved outcomes. For patients, stroke symptoms require immediate medical attention regardless of onset time. Wake-up strokes no longer automatically exclude patients from treatment. Through continued collaboration among clinicians, researchers, and medical-technology innovators, the 14%–28% of stroke patients whose symptoms begin during sleep can increasingly receive interventions that preserve brain tissue and function.

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