

# Wake-up stroke: Dawn of a new era

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## Abstract:

Wake-up stroke or stroke with unclear onset of symptoms is known to occur in one-fourth of ischemic stroke patients. These patients are not considered for thrombolytic therapy based on time designation of their symptom onset as per the current guidelines. Observational studies have investigated the pathophysiology and suggested actual onset of symptoms to be approximate to the awakening time for these patients. Use of advanced imaging modalities in these patients tends to identify favorable patient profiles for thrombolysis. Results of the ongoing trials will likely beckon a seminal juncture in stroke therapy and deliver critical modifications in the current treatment guidelines for thrombolysis in this substantial, yet neglected, group of stroke patients. In this article, we have reviewed the predisposing factors, preferred imaging modalities and various ongoing thrombolytic and endovascular trials to date for patients with unclear time of symptom onset or who wake up with stroke symptoms.

## Key words:

Diffusion-fluid-attenuated inversion recovery mismatch, multimodal imaging, wake-up stroke

## Introduction

Acute ischemic stroke (AIS) has a recurrence rate of 13% by 1 year that accounts for an increasing trend toward elevated global burden of stroke.<sup>[1,2]</sup> Around a quarter of AIS patients notice stroke symptoms on awakening (wake-up stroke [WUS]),<sup>[3,4]</sup> and no clear time of symptom onset could be ascertained in these cases. Use of intravenous tissue plasminogen activator (IV tPA) has been approved within 3 h and can be safely administered up to 4.5 h<sup>[5,6]</sup> while the risk of harm increases beyond 4.5 h.<sup>[7]</sup> Duration of clinical symptoms determines the eligibility for thrombolysis<sup>[8]</sup> while narrow therapeutic window of IV tPA precludes its usage for patients with unknown time last seen well (TLSW) or WUS.<sup>[9,10]</sup> Thrombolysis in this subgroup of patients has been studied in detail although the final consensus on the benefit remains to be unraveled.<sup>[11]</sup>

Obtaining critical data of TLSW has been the primary information that delineates therapeutic management in each AIS case. Investigators in the stroke community have questioned the reliability of TLSW in a hustling emergency department setting, which determines the inclusion or exclusion of patient for IV tPA.<sup>[12]</sup> This concept of relatively arbitrary onset time designation has been implicated as cause of admission delays of AIS patients.<sup>[13]</sup>

Majority of ischemic stroke subtypes have a predilection for early morning onset.<sup>[14]</sup> Similar analogy has been well-studied in WUS patients with a crude dogma that patients likely wake up with their respective clinical symptoms and could very likely be within therapeutic window for IV tPA.<sup>[9]</sup> WUS patients usually present with severe NIH stroke scale (NIHSS), secondary clinical deterioration with prolonged hospital admission, and poor clinical outcomes.<sup>[15]</sup> The rigid time stamp involving TLSW for this subgroup seems to be incongruent due to the dynamic process of ischemia evolution. Poor clinical outcomes further reiterate the focus of stroke community toward this subgroup of stroke patients for consideration of reperfusion therapy.

Recent advancement in neuroimaging, especially with the inclusion of multimodal imaging, has opened up new horizon to further investigate patients with unclear onset of stroke symptoms. Irrespective of the time of symptom onset, various neuroimaging patterns render exquisite details of hemodynamics that guide physicians for thrombolytic therapy. Using Alberta Stroke Program Early CT Score (ASPECTS) for computed tomography (CT) or diffusion-weighted imaging (DWI) for magnetic resonance imaging (MRI), similar early ischemic changes (EICs) have been observed in WUS patients when compared with patients

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presenting within 3 h<sup>[16]</sup> or 6 h<sup>[17]</sup> of symptom onset. In this review, we discuss predisposing factors involved in the pathophysiology of WUS and various neuroimaging modalities available to detect viable tissue that supports therapeutic decisions in the most meticulous time fashion. We have also summarized various clinical trials that are investigating reperfusion therapies in this subclass of stroke population.

### Predisposing Factors for Wake-up Stroke

Various studies have observed stroke incidence during early morning hours with symptom manifestation on awakening or compelling patients to wake up due to symptoms.<sup>[9,18]</sup> Circadian variation plays a major role in the alteration of cerebral blood flow (CBF) and contributes to the pathophysiology of WUS.<sup>[19]</sup> These hemodynamic variations in congruence to any downstream vascular stenosis likely play a critical role in AIS, especially in WUS patients. Kim *et al.* studied the association of ischemic stroke during sleep with clinical outcomes and observed high prevalence of large vessel atherosclerosis in WUS.<sup>[20]</sup>

Several hemodynamic alterations are associated during sleep and are postulated as potential risk factors that predispose cerebral ischemia. Reduction of blood pressure, heart rate, sympathetic and metabolic drive occurs during sleep.<sup>[21]</sup> These hemodynamic alterations potentially contribute toward cerebral ischemia during sleep or WUS.<sup>[22]</sup> Various sleep disorders such as obstructive sleep apnea (OSA) are independently associated with cerebral infarction.<sup>[23]</sup> OSA is chronic disorder with a prevalence of 49% and 23% in men and women, respectively, and the estimated prevalence rate has substantially increased over the last few decades.<sup>[24]</sup> Uncorrected OSA results in frequent hypoxic episodes and generates negative intrathoracic pressure that further increases cardiac afterload.<sup>[22]</sup> OSA also encompasses elevation of systemic blood pressure due to hypoxia, elevated sympathetic nervous system activity, and sleep arousals. These alterations increase cardiac afterload and predispose to cardiac ischemia and arrhythmias. This further reduces the cardiac output and CBF, especially in patients with reduced cerebrovascular reserve due to proximal steno-occlusive carotid disease.<sup>[21]</sup> Transcranial Doppler (TCD) is a noninvasive method to measure blood flow velocities and is an effective tool to detect the presence of patent foramen ovale (PFO).<sup>[25]</sup> Increased prevalence of PFO has been associated with OSA using TCD.<sup>[26]</sup> Recurrent apneic episodes in OSA are associated with elevated right cardiac chamber pressures that tend to increase right-to-left shunting through PFO<sup>[27]</sup> and predispose for paradoxical embolism.

### Commonly used Imaging Sequences in Wake-up Stroke

Neuroimaging is the most critical aspect to assess the viability of cerebral tissue in the therapeutic management of ischemic stroke.<sup>[28]</sup> Cerebral ischemia is a dynamic process that demonstrates heterogeneous imaging patterns in AIS patients. Recent advent of comprehensive imaging techniques, especially multimodal CT or MRI including perfusion and angiography, provides multifaceted critical details of cerebral hemodynamics. Utilization of multimodal imaging has provided substantial

support to physicians to investigate thrombolysis in patients with unclear time of symptom onset.<sup>[29,30]</sup>

Various authors have compared different aspects of patients presenting with unclear onset of symptoms or WUS and patients with accurate time of symptom onset. They have reported similar imaging profiles in both the groups based on either EICs using ASPECTS,<sup>[31]</sup> CT perfusion (CTP) mismatch,<sup>[9]</sup> or diffusion-perfusion-related mismatch<sup>[18]</sup> imaging protocols.

### Noncontrast computed tomography

Noncontrast CT (NCCT) has the benefit of wide availability and easy access in the stroke community. ASPECTS refers to a 10-point grading system that scores EICs in the middle cerebral artery (MCA) territory for AIS patients.<sup>[32]</sup> This scoring system has been shown to be a reliable method to assess EICs using NCCT, with lower scores correlating to poor clinical outcomes. The incidence of EICs was shown to be comparable between WUS patients and patients presenting within 3 h<sup>[16]</sup> or 6 h<sup>[17]</sup> of symptom realization. Other authors have also corroborated with similar NCCT findings in WUS patients and patients who presented with clear onset of symptoms.<sup>[3,33]</sup> This suggests that a favorable percentage of WUS patients might be eligible for thrombolytic benefits. Costa *et al.* recently observed similar clinical severity, neuroimaging findings, and clinical outcomes between WUS patients and those who arrive within therapeutic window of IV tPA.<sup>[34]</sup> However, NCCT provides limited details for EICs and is not a potent tool to determine symptom onset time.

### Computed tomography perfusion

NCCT has recently evolved with the inclusion of new imaging modalities, especially perfusion studies. CTP has been utilized to assess cerebral ischemia in acute, subacute, and chronic phase of AIS [Figure 1]. CTP involves CBF, cerebral blood volume, and mean transit time (MTT) as hemodynamic parameters to recognize critical hypoperfused zone and differentiate from infarct core. Ischemic penumbra is usually interpreted as elevated MTT or time-to-maximum (Tmax) parameters.<sup>[35]</sup> DEFUSE and EPITHET studies defined hypoperfused tissue as Tmax >6 s, i.e., Tmax contrast arrival delay of more than 6 s, delineates penumbral tissue at risk of irreversible injury.<sup>[36]</sup>

Perfusion studies have been studied in small case series involving patients with unclear time of symptom onset and WUS patients. The efficacy and safety of these imaging modalities are being investigated in ongoing randomized controlled trials.<sup>[37,38]</sup> These modalities have extended the scope of off-label use of thrombolysis in WUS patients or patients with unclear symptom onset.<sup>[39]</sup> Despite the wide access and rapidity of NCCT and CTP, the final consensus is still debatable when compared with alternative perfusion imaging modalities.

### Perfusion- and diffusion-weighted magnetic resonance imaging mismatch

Perfusion techniques using MRI similarly delineate salvageable tissue or penumbra and diffusion lesion correlating with infarct core volume. Similar to CT, assessment of optimal threshold values for MR-based ischemic penumbra and infarct core continues to be a challenge.<sup>[40]</sup> Cerebral ischemia is a dynamic process with interplay of various hemodynamic components that influence imaging parameters, especially perfusion studies.

Perfusion-dependent imaging sequences reflect the volume of viable tissue at that specific time point of image acquisition. The risk of further expansion and evolution into infarct core continues to loom,<sup>[41]</sup> with a propensity for infarct evolution.

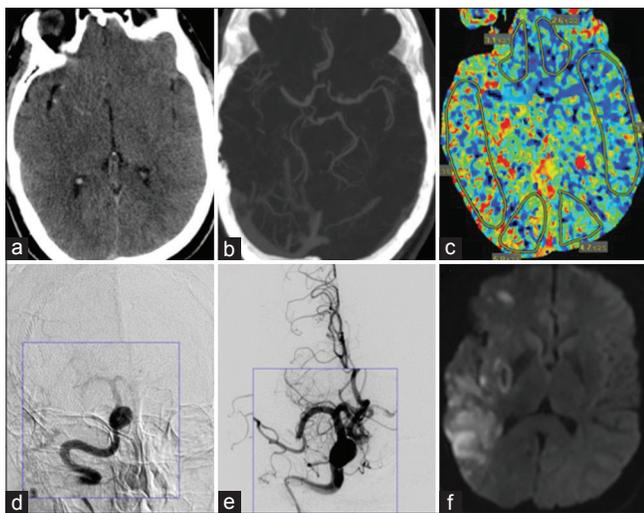
Perfusion-weighted imaging (PWI) and DWI compare the volume of ischemic injury and evaluate the presence of mismatch between these two measures of at-risk tissue versus infarct core, respectively. Clinicians are often faced with the challenge of delineating the size of the infarct core and ischemic penumbra or area at-risk to consider further therapies. Recently, various threshold values have been formulated using software tools that differentiate tissue at-risk from infarct core using color-coded maps.<sup>[42]</sup> Different authors have further refined threshold values of Tmax >6 s and perfusion-diffusion mismatch ratio >1.2 indicating a favorable penumbral pattern while DWI lesion volume >70 cc for infarct core correlating with poor clinical outcome.<sup>[43]</sup> Various pooled studies have shown improvement in clinical outcome for treating such MRI-defined ischemic penumbra with thrombolytics in an extended time window.<sup>[44]</sup> Perfusion-diffusion mismatch has been suggested as a reliable technique to consider thrombolytic decisions in WUS patients.<sup>[45]</sup>

#### Diffusion and fluid-attenuated inversion recovery-defined mismatch

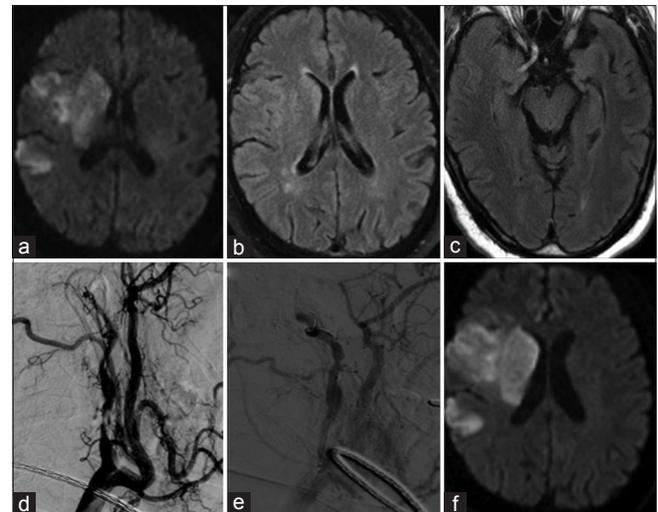
MRI provides various imaging sequences that render exquisite details regarding discrete aspects of cerebral parenchyma. DWI and PWI have remained the primary sequences that differentiate perfusion-dependent tissue from infarct core. Recently, a new concept to assess tissue viability has evolved as a substitute to DWI-PWI

comparative technique that involves comparison of DWI and fluid-attenuated inversion recovery (FLAIR) images [Figure 2]. DWI detects cytotoxic edema due to restriction of permeability of extracellular water within minutes of ischemic onset while FLAIR detects vasogenic edema that develops in the following hours. DWI-FLAIR mismatch estimation tends to assess cerebral tissue viability and thus, supplements PWI-DWI comparative sequences.<sup>[46]</sup>

Ischemic lesions tend to evolve and become conspicuous beyond 3 h from symptom onset using DWI-FLAIR mismatch.<sup>[47]</sup> DWI-FLAIR mismatch estimates the age of an ischemic lesion and tends to identify WUS patients who could be safely administered reperfusion therapies.<sup>[48,49]</sup> FLAIR demonstrates chronological evolution of cerebral ischemia with initial sluggish flow due to large vessel occlusion (LVO) as hyperintense vessels followed by vasogenic edema, thus serves as an image surrogate for time from ischemia onset.<sup>[47]</sup> Clinicians tend to rely on intensity of FLAIR signals to guide them during thrombolytic decision-making. Hyperintense FLAIR signal has been associated with poor clinical outcome at 3 months although these results further need to be confirmed in randomized controlled trials.<sup>[50]</sup> Kufner *et al.* have shown an association of early observation of FLAIR signal hyperintensity with increased hemorrhage risk<sup>[51]</sup> while another group of authors did not find such association in their study.<sup>[52]</sup> DWI-FLAIR comparison has been of paramount significance to estimate the age of ischemic lesion although definite bleeding risk using these sequences remains yet to be determined.



**Figure 1:** A 50-year-old male with a history of hypertension woke up with difficulty walking and left side weakness with a summated NIH stroke scale of 7. (a) Initial noncontrast computed tomography demonstrated hyperdense right middle cerebral artery vessel and early ischemic changes. (b) Computed tomography angiogram demonstrated mid-distal right M1 segment occlusion. (c) Computed tomography perfusion shows perfusion mismatch in right middle cerebral artery territory. (d and e) Digital subtraction angiogram showing right M1 segment occlusion in both pre- and post-endovascular procedure images. (f) Diffusion-weighted imaging sequence showing patchy infarcts in the right middle cerebral artery territory



**Figure 2:** A 61-year-old male with a history of hypertension, diabetes, coronary artery disease woke up with left-sided weakness and numbness. (a) Diffusion-weighted imaging sequence showing acute to subacute infarct in the right middle cerebral artery territory involving caudate head, basal ganglia, and parietal lobe. (b and c) Fluid-attenuated inversion recovery sequence shows subtle hyperintensity suggesting diffusion weighted imaging-fluid attenuated inversion recovery mismatch, distal vascular hyperintensities secondary to slow flow and absence of flow void in proximal, middle cerebral artery segment. (d) Digital subtraction angiogram demonstrating critical stenosis of proximal right internal carotid artery with tandem occlusion of supraclinoid segment. (e) balloon angioplasty of proximal stenosis (f) final evolution of right MCA territory infarct

## Experience with Endovascular Reperfusion Therapy in Wake-up Stroke

Endovascular therapy (ET) has gained paramount attention after the recent success of five randomized controlled trials and is now the standard of care for AIS patients with clear time for symptom onset.<sup>[53-57]</sup> The superior clinical outcomes of these trials were fueled by rapid patient triage, incorporation of multimodal techniques, especially angiography and perfusion studies, and utilization of state-of-the-art stent retriever thrombectomy devices.<sup>[28]</sup> Patients with WUS or unclear symptom onset time were not included in these successful trials. The majority of these trials enrolled patients within 6–8 h of symptom onset, except the ESCAPE trial that enrolled patients within 12 h of symptom onset. However, the vast majority of enrolled subjects were in the earliest time epochs. The ESCAPE trialists set enrollment criteria for patients within 12 h of symptom onset though median time to randomization was 169 min and only small number of patients was enrolled beyond 6 h.<sup>[55]</sup>

Although ET has been investigated for patients with unclear onset of symptoms or WUS patients, its efficacy for this subgroup of patients is yet to be determined. A few case series used intra-arterial urokinase and the MERCI retrieval device for this subgroup of patients, but failed to show any benefit.<sup>[58,59]</sup> Two recent case series failed to convincingly prove better clinical outcomes despite the use of cutting edge stent retrievers in majority of their patients.<sup>[60,61]</sup> Their results also showed high rates of mortality (23% and 37%) and symptomatic intracerebral hemorrhage (sICH) (14% and 21%) in the respective studies. Stampfl *et al.* used stent retrievers in 19 WUS patients and found increased sICH rate with poor clinical outcome at 3 months.<sup>[61]</sup> Although the results of these ET studies have been majorly negative, few authors showed similar clinical outcomes using stent retrievers for patients with known and unknown time of symptom onset.<sup>[59]</sup>

Various neuroimaging modalities have emerged especially multimodal techniques to discern exquisite ischemic details for this subset of patients who might benefit from reperfusion therapies. Many authors have utilized perfusion techniques both CT and MR in patients with unclear time of symptom onset to assess safety and efficacy of mechanical thrombectomy in this subclass of stroke patients.<sup>[59,61]</sup> A few case series have used both CT<sup>[62]</sup> and MR<sup>[63]</sup> perfusion modalities to assess clinical outcomes after using either IV thrombolysis or ET. Cho *et al.* studied the safety and efficacy of thrombolysis and ET using penumbral and DWI-FLAIR mismatch.<sup>[64]</sup> This preliminary concept was further studied in a multicenter trial that included 19.3% of patients with unclear time of symptom who were treated in similar fashion with either IV thrombolysis or intra-arterial revascularization.<sup>[45]</sup> Various ongoing endovascular reperfusion trials are currently underway that will guide future therapeutic management in this subclass of stroke patients.

### Clinical Implications in Wake-up Stroke

It has been well-studied in the literature that onset of hemodynamic changes or symptom onset in patients with unclear-onset stroke or WUS approximates with the time of patient awakening.<sup>[16]</sup> Patients with unclear onset of symptoms

usually are a part of broad subgroup that involves WUS patients or daytime-unwitnessed stroke (DUS) patients. DUS patients are similar to WUS patients and are excluded from potential benefits of thrombolysis. A recent study comparing WUS and DUS patients observed more frequent diffusion-FLAIR and diffusion-perfusion mismatch patterns in DUS patients.<sup>[65]</sup> The authors also observed that DUS patients arrived earlier to seek medical attention and have higher likelihood to receive reperfusion therapy as compared to WUS patients. This analogy concluded time of symptom recognition as a more valuable tool than TLSW for patients with unclear time of symptom onset or WUS patients.

Reperfusion of a hypoperfused zone, either through IV tPA or through ET, has been shown to reduce final infarct core volume and is associated with better clinical outcomes.<sup>[66,67]</sup> Investigators have tried to extend the thrombolytic benefits beyond the narrow therapeutic window of 3–4.5 h, but majorly have been studded with risk/benefit assessment in these patients. Patients with indefinite or unclear onset of symptoms usually present with large volume of ischemic zone that is prone to increased hemorrhagic risk from thrombolysis and worse clinical outcomes.<sup>[68]</sup>

Various CT or MR sequences have been utilized to extend and study clinical implications with thrombolysis in patients with unclear time onset or presenting as WUS. Similar rates of sICH have been found in WUS or patients with clear symptom onset when treated with IV tPA.<sup>[62]</sup> On the contrary, AbESTT-II was a randomized controlled trial that used abciximab in WUS patients and found increased hemorrhagic transformation rate when compared to patients with definite time of symptom onset.<sup>[69]</sup> Similarly, many other studies have failed to show similar results and have been futile in their efforts. Despite these confounding results, physicians tend to arrive at a clinical equipoise by assessing multimodal images and determine risk/benefit ratio for each individual case separately.

Multimodal imaging techniques have emerged as a boon to stroke community that renders multifaceted refined data during emergent settings. Use of these novel imaging techniques has been a topic of diagnostic pursuit in WUS patients and those with unclear time of symptom onset. These techniques are being utilized in majority of the stroke centers to assess the size of salvageable penumbral tissue with a risk to evolve into infarct core. Although these imaging modalities seem to be an appealing concept in this subgroup of patients, interpreting subtle FLAIR and perfusion signals are studded with drawbacks of inter-observer variability and reliability. Recent trials have utilized automated softwares for perfusion and infarct volume analysis such as RAPID software,<sup>[42]</sup> but their validity is yet to be confirmed. However, certain issues including threshold values for FLAIR intensity, inter-observer discrepancies, and generalizability of automated softwares need to be figured out before its applicability in clinical practice for WUS patients.

### Trials of Intravenous Thrombolysis using Penumbral Imaging

#### EXTEND

EXTending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) is a randomized, double-blinded,

multicenter, placebo-controlled, phase III trial.<sup>[37]</sup> It compares the efficacy of IV tPA (0.9 or 0.6 mg/kg) and placebo for AIS patients with penumbral mismatch pattern presenting at 3–4.5 h (depending on guidelines followed by participating center) up to 9 h post symptom onset or who wake up with symptoms. For WUS, the investigators selected midpoint from sleep onset and time of awakening to be  $\leq 9$  h. Diffusion-perfusion mismatch (MRI) or CTP is used to assess the penumbral pattern with  $T_{max} > 6$  s for perfusion lesion and DWI-MRI or CBF-CT to define infarct core volume. Various neuroimaging threshold values used as inclusion criteria comprise infarct core volume  $\leq 70$  cc, ratio of hypoperfusion to infarct core volume  $> 1.2$ , and an absolute mismatch difference  $> 10$  cc. The investigators intend to enroll 400 patients in different centers across Australia along with other concomitant international centers (EXTEND international). In addition, there is another European study in progress (ECASS-4: EXTEND) that intends to enroll patients based on the design of EXTEND trial, except patients will receive 0.9 mg/kg dose of IV tPA using MRI only.

### **Trials of Intravenous Thrombolysis using Magnetic Resonance Estimates of Lesion Age**

#### **WAKE-UP**

Efficacy and safety of MRI-based thrombolysis in WUS (WAKE-UP) is a randomized, double-blinded controlled trial currently recruiting patients across ~60 European centers.<sup>[70]</sup> Investigators plan to enroll 800 AIS patients with unknown time of symptom onset including WUS patients. Investigators evaluate the safety and efficacy of MRI-based thrombolysis with 0.9 mg/kg dose of IV tPA utilizing the novel approach of diffusion-FLAIR mismatch as an indicator of lesion age  $< 4.5$  h. Primary efficacy end-point is favorable clinical outcome defined as modified Rankin scale (mRS) 0–1 at 3 months and mortality as a tool for primary safety end-point. The enrollment was started in October 2012 and is expected to complete by December 2016.

#### **THAWS**

Thrombolysis for Acute Wake-up and unclear-onset Strokes with Alteplase at 0.6 mg/kg Trial (THAWS) is a randomized, single-blinded controlled trial conducted across Japan.<sup>[71]</sup> THAWS trial is the Asian counterpart of WAKE-UP trial<sup>[70]</sup> that intends to enroll 300 patients and study MRI-based thrombolysis in patients with unknown symptom onset time or who present as WUS. The investigators are using 0.6 mg/kg dose of IV tPA that has been shown to be safe, efficacious, and a licensed dose in Japanese AIS patient population. The trial includes patients with last well known  $> 4.5$  h, DWI-ASPECTS score  $\geq 5$ , and absence of FLAIR signal hyperintensity. The enrollment started in May 2014 and the trial was expected to complete by March 2017. THAWS trial, if successful, could trigger more studies to test the efficacy of lower dose of IV tPA using MRI-based thrombolysis in AIS patients who present with unclear time of symptom onset.

#### **NOR-TEST**

The Norwegian tenecteplase stroke trial is an ongoing prospective, randomized, open-label, blinded, multicenter trial to establish the safety and efficacy of tenecteplase versus alteplase in AIS patients.<sup>[72]</sup> The trial compares 0.4 mg/kg tenecteplase (single bolus IV dose) with standard 0.9-mg/kg

dose of alteplase (10% bolus followed by 90% of infusion over 60 min) in AIS patients. Investigators are enrolling three groups of patients: (a) Arriving with known symptom onset in  $\leq 4.5$  h, (b) undergoing ET within 6 h of symptoms onset, (c) WUS patients presenting within 4.5 h. For WUS subgroup, diffusion-FLAIR mismatch was used as imaging inclusion criteria. Primary efficacy end-point is mRS 0–1 at 3 months while secondary end-points include clinical improvement and bleeding complications. The trial began in September 2012 with a plan to enroll 954 patients and is expected to finish by March 2017.

### **Trials of Endovascular Stroke Treatment in Unknown Time Window**

There are four endovascular intervention trials that target to observe clinical outcomes for patients with unknown symptom onset or presenting as WUS.

#### **DAWN trial**

DWI or computerized tomography perfusion Assessment with clinical mismatch in the triage of Wake-up and late presenting strokes undergoing Neurointervention (DAWN) trial was a randomized, multicenter, controlled trial.<sup>[38]</sup> The main objective was to assess the safety and efficacy of ET in WUS patients with stroke onset between 7 and 23 h (treatment to be initiated between 8 and 24 h). Neuroimaging inclusion criteria included vessel occlusion in internal carotid artery (ICA) through M1 segment, ASPECTS  $> 7$  on CT or MRI, and penumbral pattern on CT or MR perfusion. Investigators utilized stent retrievers including Solitaire and Trevo devices and assessed primary outcome of mRS  $> 2$  at 90 days. DAWN trial was further heralded by a similar trial that is a prospective, multicenter, phase II/III, adaptive, randomized controlled trial conducted across 50 centers in North America and Europe.<sup>[73]</sup> The objective is to demonstrate the efficacy of Trevo stent retriever with medical management as compared to standard management alone for patients with unknown time for symptom onset or who present as WUS. Investigators randomized AIS patients between 6 and 24 h from the time they were last seen well in either of the two therapeutic arms. Neuroimaging inclusion criteria included (a)  $< 1/3$  MCA territory involvement on CT or MRI, (b) presence of LVO in ICA or M1 segment on CT or MR angiograms, and (c) clinical imaging mismatch involving NIHSS and infarct core volumes using MR-DWI or CT-CBF thresholds. Primary outcome includes weighted mRS and stroke-related mortality at 3 months. The trial was initiated in July 2014 with a plan to enroll 500 patients. There are currently 92 cases enrolled so far and is expected to complete by July 2017.

#### **POSITIVE**

Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy (POSITIVE) is an open-label, randomized controlled clinical trial to assess the safety and efficacy of ET versus standard medical therapy for AIS patients.<sup>[74]</sup> Investigators included AIS patients with TLSW within 12 h with following neuroimaging criteria: (a)  $< 1/3$  MCA territory involvement on CT/MRI (b) LVO between distal ICA through M1 bifurcation, and (c) presence of ischemic penumbra on CT/MRI perfusion. Primary outcome was adjusted by the investigators as shift analysis with a goal mRS of 0–2 at 90 days. The trial was started in September 2013 with

an estimate to enroll 750 patients and has enrolled 24 patients so far.

### RESTORE

REperfusion therapy in unclear-onset Stroke Based on MRI Evaluation (RESTORE) was an observational, prospective, single-arm, multicenter study to assess the efficacy of ERT along with IV thrombolysis in patients with unclear-onset stroke patients arriving within 6 h of symptom detection.<sup>[45]</sup> For thrombolytic therapy, investigators selected any of the three reperfusion therapies: (a) 0.9 mg/kg IV tPA for patients arriving within 3 h of symptom detection without LVO, (b) 0.6 mg/kg of IV tPA + IA therapy for patients arriving within 3 h of symptom detection with LVO, and (c) IA therapy alone for patients arriving within 3–6 h of symptom detection with LVO. MRI-based inclusion criteria involved diffusion-perfusion mismatch >20% and negative-to-subtle FLAIR signal alterations. The study included 83 out of total 430 patients who received reperfusion therapy in the form of IV tPA alone, IV tPA followed by IA therapy or IA therapy alone. The clinical outcome determined by mRS 0–2 at 3 months was observed in 44.6% of patients while sICH-causing change in NIHSS by  $\geq 4$  points occurred in 3.6% of patients. MRI-based reperfusion therapy was found to be safe and feasible for patients with unclear onset of stroke symptoms using diffusion-perfusion and diffusion-FLAIR imaging mismatch criteria.

### MR WITNESS

MR WITNESS: A Phase IIa Safety Study of IV Thrombolysis with Alteplase in MRI-Selected Patients (MR WITNESS) is an observational, open-label, single-arm, safety study conducted across 10 centers in the United States.<sup>[75]</sup> The study intends to assess the safety and efficacy of 0.9 mg/kg IV tPA administered to patients with TLSW within 24 h of triage. Neuroimaging inclusion criterion was diffusion-FLAIR mismatch to estimate the age of the lesion, while the presence of >10 microbleeds on gradient-recalled echo sequence was considered as exclusion criteria. Primary outcome was to assess the safety using IV tPA within 24 h of TLSW based on MR evidence of early ischemia and assess sICH rate in these patients. The study was started in January 2011 with an estimated enrollment of 100 patients, has finished the recruitment phase, and the study results are awaited with completion by December 2016. Another ongoing study called Imaging-WIndow Thrombolysis iN Emergent Stroke Syndromes intends to determine the safety profile of IV tPA for patients with TLSW within 24 h, using both CT or MR neuroimaging techniques to assess tissue viability.

### Conclusion

Almost a quarter of AIS patients wake up with stroke symptoms and are excluded from thrombolysis based on the current guidelines. Various observational studies have laid immense relevance on patient selection in this subgroup based on novel imaging patterns that discern the tissue at risk from infarct core. Multimodal imaging techniques have played a crucial role in selecting WUS patients who might be ideal candidates for thrombolysis based on tissue-rather-time based guidelines. Ongoing prospective trials are investigating distinct penumbral imaging assays that might streamline optimal therapeutic strategies for this neglected group of patients. The results of various trials are expected to provide safety

and efficacy for both IV thrombolysis and ET that might alter current treatment guidelines for patients with unknown time of symptom onset. Patient selection based on exquisite imaging protocols to determine thrombolysis is expected to become the standard of clinical practice in the near future.

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### Conflicts of interest

There are no conflicts of interest.

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