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INTRAVENOUS THROMBOLYTIC THERAPIES IN THE MANAGEMENT OF UNKNOWN ONSET AND WAKEUP STROKES: A SCOPING REVIEW

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ABSTRACT

Background: The efficacy and safety of intravenous recombinant tissue plasminogen activator (IV rt-PA) for the management of unknown time onset stroke (UTOS) and wake-up stroke (WUS) are in a debate.

Objective: The objective of this review is to discuss the UTOS and its management with intravenous thrombolytic therapies.

Data Sources: Databases searched included PubMed and Cochrane electronic databases and manual search. Study Selection and Data Extraction: 45 articles of potential relevance were selected.

Results: 14 relevant papers were included. Most of studies including recent trials using Magnetic resonance imaging diffusion-weighted imaging fluid-attenuated inversion recovery (MRIDWI FLAIR) mismatch or Computed tomography perfusion (CTP) based selection showed favorable outcome modified Rankin scale (mRS) of 0 to 2 at 90 days in range of 44.6% to 53%. While Symptomatic intracranial hemorrhage (SIH) was observed in 1.3% to3.6%. Patients selected with significant ischemic penumbra using visual assessment of MRI DWI perfusion weighted images (PWI) mismatch did not showed a significant benefit in clinical outcome. OR: 1.2; 95%CI 0.63-2.27, p = 0.5. While use of RAPID software for automated penumbral image processing with median time from "last seen well" 9.9 hours showed favorable outcome in IV rt-PA group with no significant difference in in mortality.(OR, 1.44; 95% CI, 1.01 to 2.06; P=0.04).

Conclusions: The penumbral mismatch in UTOS is a cogent method to recognize the patients for thrombolytic therapy without significant risk, but the appropriate neuroimaging criteria to maximize the efficacy and minimize hemorrhagic complications of thrombolytic treatment still has to be fully defined.

Keywords: Intravenous thrombolysis, Unknown time onset stroke, Magnetic Resonance Imaging, Perfusion Imaging, delayed presentation.

INTRODUCTION

Acute ischemic stroke (AIS) is among the foremost causes of disability and death in worldwide.[1] Thrombolytic therapy with intravenous recombinant tissue plasminogen activator (IV rt-PA) and mechanical thrombectomy are the evidence-based safe and effective treatment for AIS.[2] In approximately 25 to 30% of AIS patients' time of onset is not known.[3] Clinical evidence suggests that thrombolytic and other recanalization therapies if given within the time window may restore perfusion and improve clinical outcomes in AIS patients.[4] Despite this fact, only 5% to 10% of AIS patients receive thrombolytic therapy worldwide, and this small percentage is mainly due to the narrow therapeutic time window for thrombolytic therapy.[5] Among them unknown time onset stroke (UTOS) constitute 25% of causes of non-administration of IV rt-PA.[6] Patients with UTOS are usually having large volume of the ischemic zone with increase hemorrhagic risk from thrombolysis, so IV rt-PA therapy is not recommended in these patients.[7]

The group of UTOS patients may include a subgroup of patients in whom the stroke occurred within the 4.5 hours window. Many clinical and imaging studies have found that a considerable number of patients with wake-up stroke (WUS) are having stroke onset near to time of awakening, so that many of these patients may still have potentially salvageable penumbral tissue and may respond better to IVrtPA.[8] Recently stroke related

MRI findings with DWI restriction and absence of marked hyperintensity in FLAIR sequence were proposed to act as a 'brain clock 'indicating the stroke occurrence within 3–4•5 hours.[9] A study found that if the time of arrival was not considered as a factor then 35.9% of WUS patients could have been eligible for thrombolysis[10]

This scoping review is written to discuss the UTOS and WUS and to summarize the available literature regarding the clinical and imaging based criteria for management of these patients with thrombolytic therapies.

Definition of the stroke of unknown onset stroke
UTOS is defined as stroke with unwitnessed symptom onset. (Figure 1). This includes both WUS and daytime unwitnessed stroke (DUS) patients.[11]

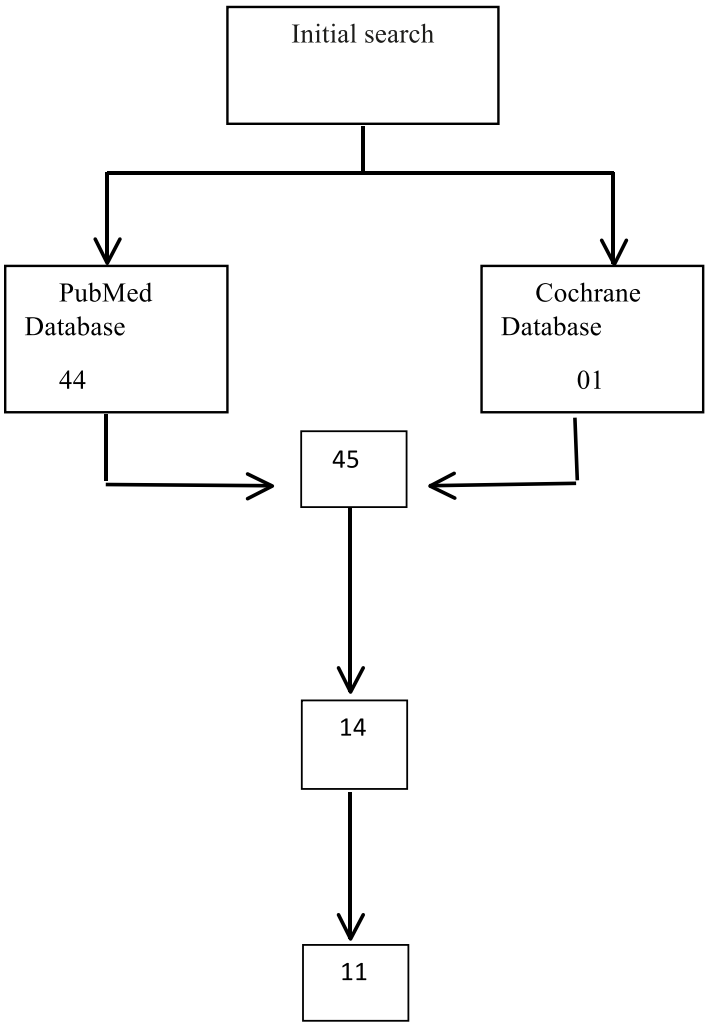


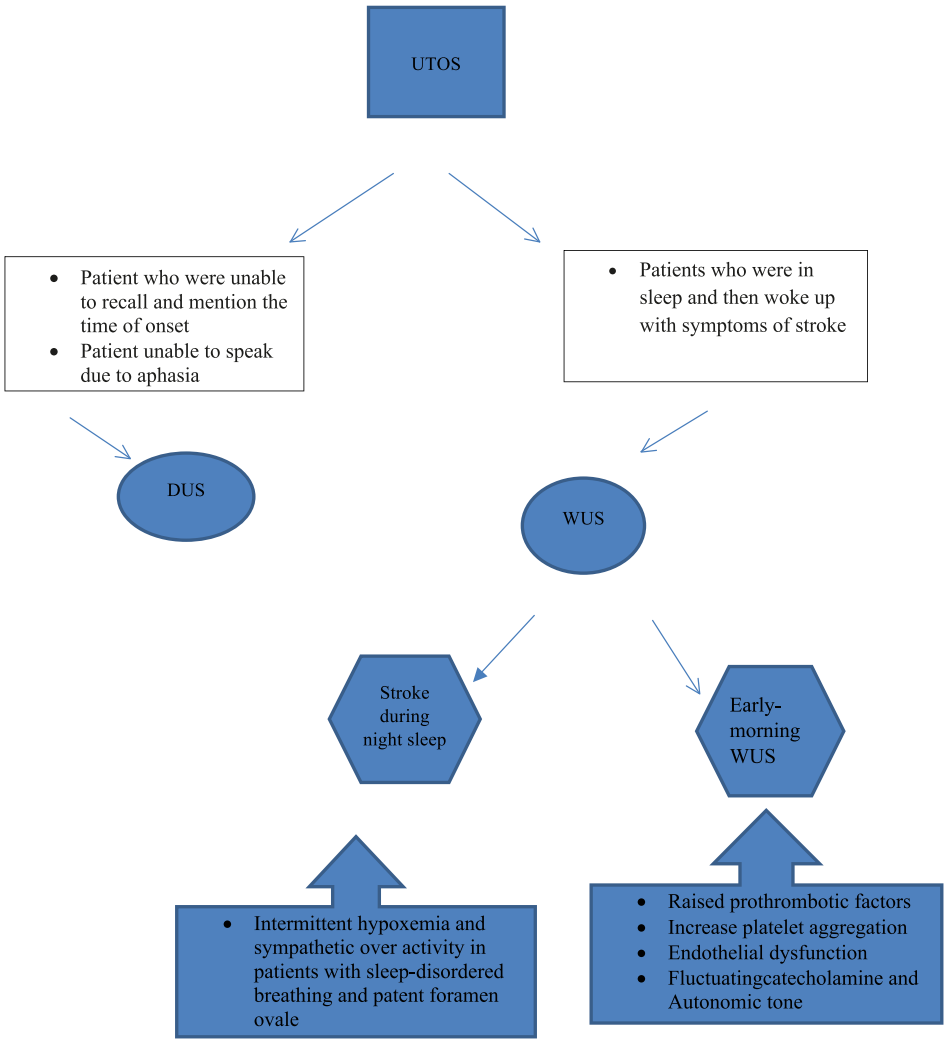
Figure 1: Search strategy followed in this review

Epidemiology
UTOS is not rare comprising approximately 25 to 30% of patients with AIS. Out of them, more than half of these patients are presenting as WUS.[8] There is more than 50% rise in the early morning stroke when compared to the nighttime onset.[12] An estimated prevalence of WUS is 26/ 100,000 population.[10]

Mechanism and physiology of wake-up strokes
In UTOS patients, a large proportion is comprises of WUS where onset might be closer to awakening, as there seems to be an early morning peak of AIS. The mechanism of high incidence of early-morning AIS and WUS is related to underlying endogenous factors. These factors include a peak in prothrombotic factors,

an increase in platelet aggregation and endothelial dysfunction, while fluctuating serum catecholamine levels and autonomic tone with an increase in blood pressure (BP), a "morning serge" are also thought to be contributing.[13] Other suggested factors like intermittent hypoxemia, sympathetic over activity associated with sleep-disordered breathing, and patent foramen ovale increase the risk of WUS and cardiovascular diseases.[14] Figure 2

Figure 2: UTOS types and possible mechanism



UTOS=unknown time of stroke onset;**DUS**= Daytime unwitnessed stroke **WUS**=wake-up stroke; **PFO**=Patent foramen ovale

Clinical and Radiological characteristics of unknown onset stroke

A population-based study found no significant clinical difference in baseline clinical characteristics among all UTOS patients including both WUS and DUS group, except the patients with WUS were older and he had a high baseline national Institute of health stroke scale (NIHSS).[10]

Data from the International Stroke Trial (IST) showed no significant differences regarding age, gender, and average BP. Although other parameters like atrial fibrillation, impaired conscious level were more in these patients. Other than that, lacunar syndromes and less total anterior circulation syndrome were also observed in these groups of patients. However, despite these differences outcomes were not changed.[15] A study related to the effects of diabetes, sedentary lifestyle and WUS showed high frequencies of these parameters in patients with WUS. These patients showed excessive daytime sleepiness that was related to heavy drinking and sedentary lifestyle.[1] Similarly, in another study it was found that hypertension and smoking were related to more severe WUS, however there was no difference

in fatality among WUS and non-WUS patients.[17] A hospital-based comparative study on WUS and non-WUS wake-up stroke showed high frequency of thalamic hemorrhagic stroke in these patients while clinical improvement in deficits were more appreciated in non-WUS patients.[18] There are several non-contrast computed tomography (CT)-based comparative studies about early ischemic changes on CT brain between UTOS and WUS patients has been published. These studies showed no significant difference in early CT changes among these groups within 3 hours or 6 hours.[19] In a study, comparing DUS and WUS patients showed that DUS patients presented earlier to emergency services and showed more frequent diffusion FLAIR and diffusion-perfusion mismatch patterns in brain imaging when compared to WUS patients.[20]

Role of diagnostic imaging modalities

Diagnostic imaging plays an important role in evaluating a patient with UTOS and WUS. Different neuroimaging modalities have been evaluated in several studies to find them as a surrogate marker of cerebral ischemia.

Computed tomography perfusion

CTP helps to predict brain tissue ischemia in acute, sub-acute, and chronic phase of AIS through different hemodynamic parameters (see Figure 3 and 4). These parameters include cerebral blood flow (CBF), mean transit time (MTT) delay time (Tmax) and cerebral blood volume (CBV) These are helpful in recognizing critical hypo perfused zone and differentiate from infarct core. The ischemic core is a region with markedly reduced CBV or CBF combined with prolonged MTT orTmax. Ischemic penumbra is usually interpreted as elevated MTT or time to maximum (Tmax) parameters.[21] Tissue at risk has been defined with different thresholds and variety of definitions have been proposed.[22] Although real consensus on these parameters and threshold are yet to be decided for critical hypoperfusion and core identification. Literature suggests that relative CBF is important and far better to define infarct core followed by CBV,[23] however more recent evidence suggests a threshold of CT-Tmax of >6s to define the tissue at risk.[24]

CT combined with CTP is a widely used technique that may help decide eligibility of thrombolysis in patients with UTOS. [25]

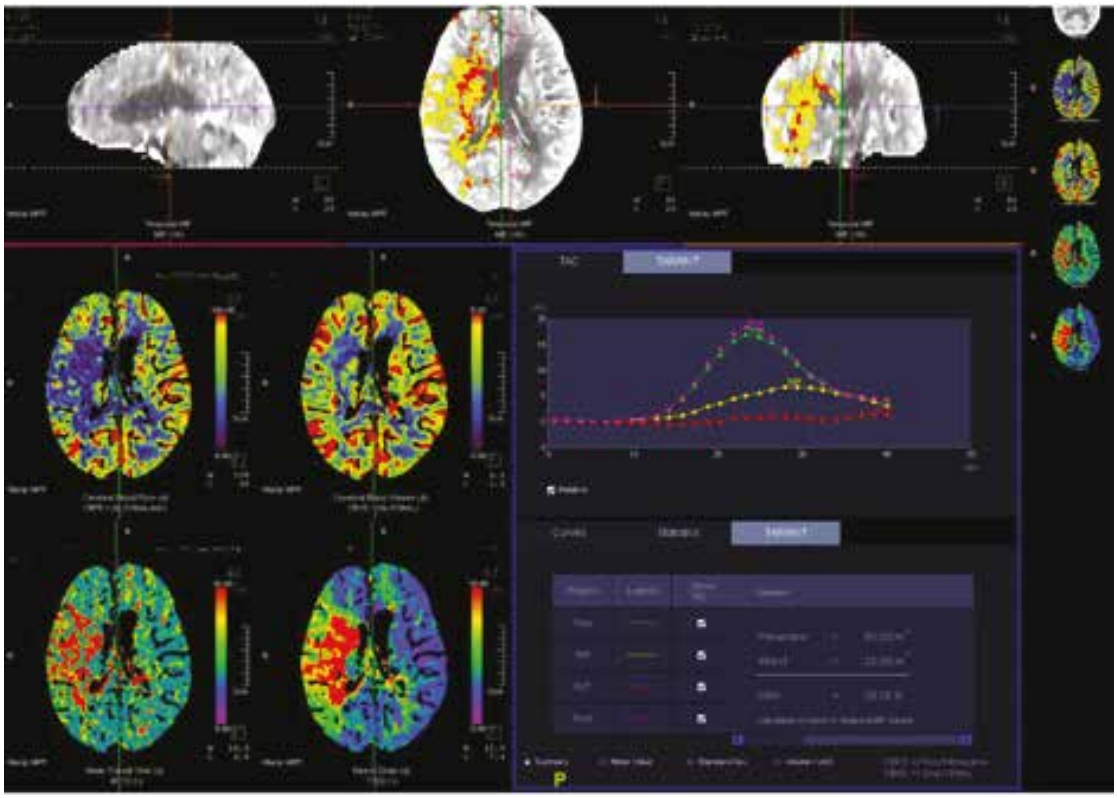


Figure 3: CTP of a 70-year-old female with multiple risk factors presented with acute left-sided weakness at early morning time off on onset was unknown. CTP showed prolonged mean transient time and reduced blood flow indicating a good volume penumbra in right MCA distribution.

CTP= computerized tomography perfusion; MCA=Middle cerebral artery

Figure 4: 57 years old male presented with left sided weakness of unknown onset. CTP showed reduced blood flow and decrease blood volume indicating a core infarction in right MCA distribution.

CTP= computerized tomography perfusion; MCA=Middle cerebral artery

MRI diffusion FLAIR mismatch

In AIS patients high intense T2 weighted MRI signals together with hyperintensity in FLAIR sequence often came positive within in 3–4•5 hours after stroke onset,[26] While DWI can depict cytotoxic edema caused by ischemia within minutes of a AIS.[27] (Figure 5). Thus DWI-FLAIR mismatch has been founded as an indicator of AIS onset of less than 4.5 hours, It can be utilized a well suited surrogate marker of lesion age in patients with UTOS, One study reported a DWI-FLAIR mismatch in 44% of patients with WUS.[28]

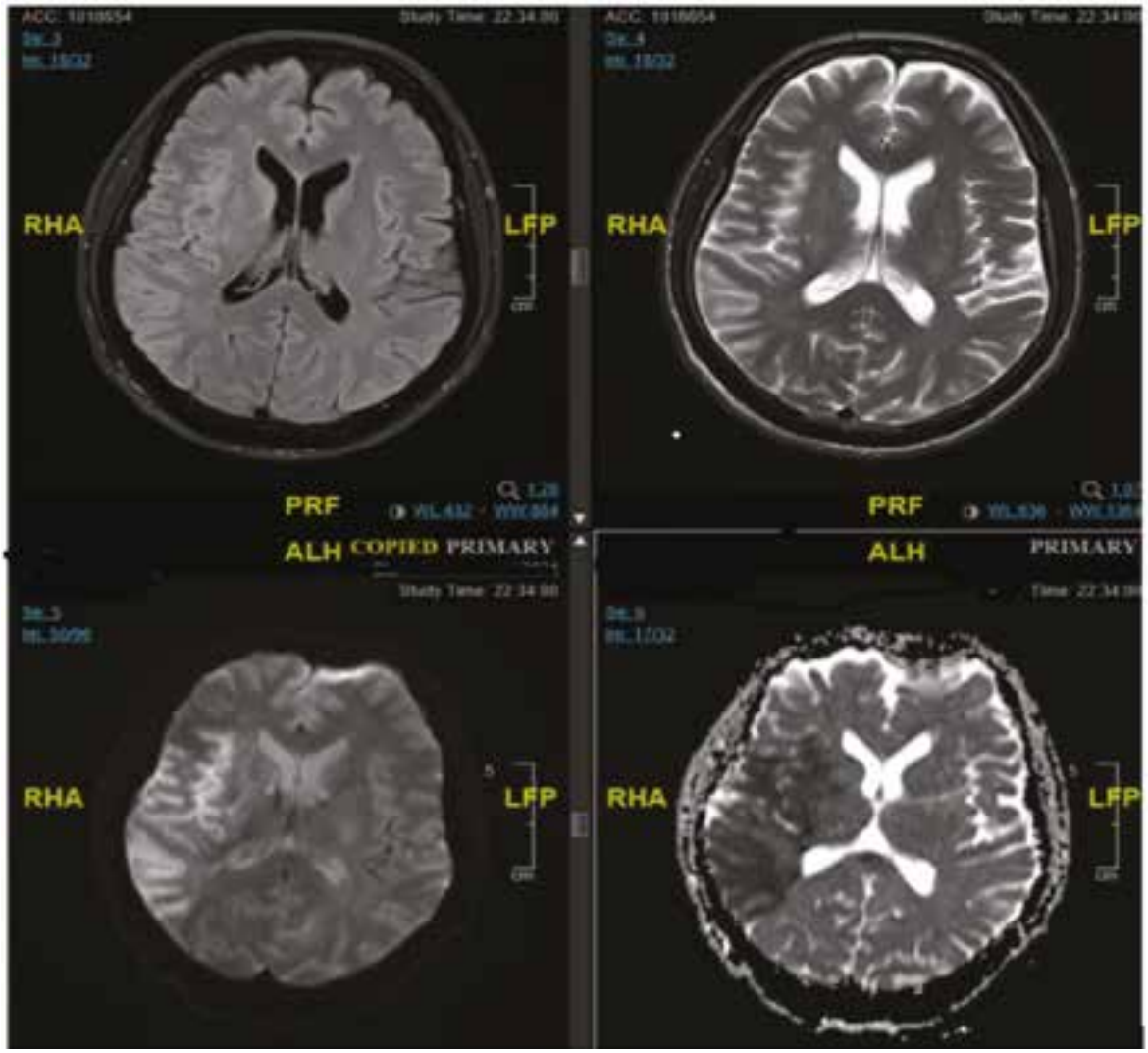


Figure 5: MRI FLAIR diffusion mismatch in a 55-year-old male with left sided weakness. MRI DWI showed evidence of diffusion restriction within the large diffusion restriction on DWI/ADC sequences with no clear-cut t2/flair high signal intensity in corresponding region.

MRI flair= magnetic resonance imaging fluid attenuated recovery; DWI= diffusion weighted imaging; ADC=apparent diffusion coefficient

MRI perfusion /diffusion mismatch

DWI and PWI have been considered the prevailing sequences to differentiate the perfusion dependent tissue from the infarct core. These sequences have been advocated as advanced and strong parameters for detection and differentiation of the ischemic penumbra from ischemic core tissue and can be used as an ideal imaging method for selection of the patient in UTOS. Thus, DWI FLAIR mismatch can be supplemented by PWI-DWI comparative sequences, to estimate and assess cerebral tissue viability.[29] As with CTP, there are obstacles of consensus on the determination of the optimal thresholds to differentiate salvageable brain tissue from ischemic core.[30] However a fair assessment of the ischemic core with apparent diffusion coefficient (ADC) sequence, taking ADC-threshold of 600x106 mm2/s seems to look are a reasonable parameter for prediction of ischemic core tissue. Recent trials have utilized automated softwares for perfusion and infarct volume determination such as RAPID software.[33]

Other techniques

Other advanced radiological techniques for defining tissue at risk, like SPECT or FDG-PET, are not much patently used in current clinical practice.

Role of thrombolytic therapies in UTOS

It has been evident that sometimes in an ischemic penumbra a potentially viable brain tissue can be persistent up to 48 hours after onset of symptoms in ischemic stroke.[32] Based on this evidence a substantial group of the UTOS patients might be eligible for thrombolytic therapy.

METHODS

Data Sources: The literature search was conducted using the search terms {(Intravenous thrombolysis)} AND {(Unknown time onset stroke)} in pub med and Intravenous thrombolysis *, Unknown time onset stroke *in Cochrane. Databases searched included PubMed and Cochrane electronic databases complemented with a manual search.

Study Selection: The initial search revealed 45 articles of potential relevance. Figure 1

Data Extraction: Author in details to obtain clinical information relevant to meeting the objectives of the review analyzed the studies. Articles containing relevant information direct to the question include 1 was literature reviews, 1 was systemic reviews, 1 SITS-ISTR registry-analysis, 5 Multicenter Randomized control trial, 3 comparative cohorts, 1 open labelled pilot study, 2 retrospective analysis 1 case series and 1 was case report.

Data Synthesis: The information was analyzed, tabulated and discussed in narration.

RESULT

From 14 relevant papers, critical appraisal was done on two Retrospective observational, two case control, one pilot study, one old RESTORE trial and five recent RCTs. Key results of the selected retrospective observational and case control, studies are summarized in Table 1. These studies either used, MRI DWI- FLAIR mismatch or CTP based criteria. [33,34,35] Some of these studies have selected the patients as UTOS as WUS and non-WOS, A few studies used low dose IV rt-PA 0.6mg/kg.[36]

Table 1: Selected studies on efficacy and safety of intravenous thrombolytic therapies in the management of UTOS and WUS

Ref.	Study type	Study drug	Imaging modality used	Pt group and intervention	Key results	Outcomes
Dorado et al., 2017	Retrospective based on SITS-ISTR	IV alteplase, 0.9mg/kg	CT ,MRI	N=502 AIS with UTOS	**primary endpoint** **(median mRS) at 90 days** was available for only 359 patients Functionally independent =168 Functionally dependent =111 **Mortality** =80 deaths	Unfavorable
Ebinger et al., 2012	Retrospective, off-label, observational	IV alteplase, 0.9mg/kg	DWI- FLAIR mismatch	N=148 Cases:17 AIS with UTOS Controls: 131	**primary endpoint** **(mRS 0-2) at 90 days** Cases 35.3% vs. Controls 49.6%, **SIH** UTOS group =None **Mortality** Cases 0% vs. Controls 15.3%	Favorable in patients with . DWI- FLAIR mismatch
Aoki et al., 2016	Case-control	IV alteplase, 0.6mg/kg	MRI FLAIR	N=52 Cases:24 AIS with UTOS Controls: 28	**primary endpoint** **NIHSS at day 7** (10-point reduction in score or NIHSS score of 0-1) IV-tPA group = 46% Control group = 18%	Favorable in patients with negative FLAIR MRI finding.
Aoki et al., 2013	Case-control	IV alteplase, 0.6mg/kg for cases and 0.9mg/kg dose for controls	MRI FLAIR	N=80 Cases:20 UTOS with negative FLAIR Controls:60	**primary endpoint** **(mRS 0-1)** at 90 days Negative FLAIR group = 47% Control group =33% (p = 0.365). **SIH** Negative FLAIR group = None Control group = 1 (2%).	Favorable and safe in patients with negative FLAIR MRI finding.
Morelli et al., 2015	Non-randomized, open-label, pilot study	IV alteplase, 0.9mg/kg	CTP	N=170 NWUS: 143 WUS: 27	**primary endpoint** **(mRS ≤1)** = 35.8 % NWUS: 36.4 % WUS 33.3 %; **SIH** NWUS=3.4 % WUS (p = 0.32)	Favorable in CTP based selected group of patients.

AIS=acute ischemic stroke; **CTP**=computed tomography perfusion**; FLAIR**=fluid-attenuated inversion recovery; **IV-tPA**=Intravenous thrombolysis with recombinant tissue plasminogen activator; **MRI**=magnetic resonance imaging; **mRS**= modified Rankin scale;

NIHSS= National Institutes of Health Stroke Scale; **NWUS=**Non-wake-up stroke; **SITS-ISTR**=Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry; **SIH**=symptomatic intracranial hemorrhage; **UTOS**=unknown time of stroke onset; **WUS**=wake-up stroke;

RESTORE trial was first prospective multicenter study for safety and feasibility of MRI-based reperfusion therapy in patients with UTOS showed favorable outcome in 37 patients (44.6%) achieved modified Rankin scale (mRs)of 0 to 2, and 24 (28.9%) had mRsof 0 to 1.[37] Symptomatic intracranial hemorrhage (SIH) was observed in 03 patients (3.6%). After this trial A Study of Intravenous Thrombolysis with Alteplase in MRI-Selected Patients (MR WITNESS) trial, A small phase II a trial of IV thrombolysis in UTOS selected by DWI FLAIR mismatch showed 39% of subjects achieved a favorable outcome at 90 days with SIH was observed in 1.3%.[38] Later on another study named Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE UP) Study showed 53% of patients achieved a favorable outcome at 90 days, defined as a score of zero or 1 on mRS of neurologic disability, while favorable outcome was observed in 42 percent of patients in the placebo group. The IV rt-PA group included 10 deaths, compared to 3 deaths in the placebo group.[39]

While European Cooperative Acute Stroke Study-4 (ECASS-4) did not showed a significant benefit in clinical outcome when compared with placebo.(OR: 1.2; 95%CI 0.63-2.27, p = 0.5).[40] Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND TRIAL) , for extended time window used RAPID software for automated penumbral image processing.[41]The median time from "last seen well" to IV rt-PA was 9.9 hours vs 8.9 hours for placebo. In this study 51% of patients in the IV rt-PA group showed favorable outcome with no significant difference in mortality at 90 days when compared to placebo group (OR, 1.44; 95% CI, 1.01 to 2.06; P=0.04). Ratio of SIH was similar as with other thrombolytic therapy trials.(OR,7.22; 95% CI, 0.97 to 53.5; P=0.05).

Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes With Alteplase at 0.6 mg/kg (The THAWS TRIAL),[42] a Japanese trial of low-dose thrombolysis IV rt tPA 0.6mg/kg) in patients with UTOS, who were selected with imaging patterns suggesting recent onset, study showed no evidence of either benefit or harm with use of the 0.6mg/kg dose of IV rt-PA. Alteplase group=59% Control group =60% OR, 0.97; p = 0.86. Main results of these trials are summarized in Table 2.

Table 2: Randomized controlled trials on efficacy and safety of intravenous thrombolytic therapies in the management of unknown onset and wakeup stroke

Reference	Study type	Study drug	Imaging modality used	Pt group and intervention	Key results	Outcome
Koga et al., 2014 **THAWS TRIAL** Results announced in **May 2019**	Phase III Randomized control trial	IV alteplase, 0.6mg/kg	DWI-FLAIR mismatch	N= 131 AIS with UTOS	**primary endpoint (mRS 0-1)** at 90 days. Alteplase group=59% Control group =60% odds ratio, 0.97; p = .862. **SIH at 22–36 h,** occurred in one patient in alteplase group = 01 control group= none (p = 1.0). **Mortality at 90 days.** Alteplase group=02 Control group =02 (p = 1.0).	Unfavorable Showed no evidence of benefit but also no evidence of harm.
Ringleb et al., 2019 **ECASS-4 TRIAL** **2019**	Randomized, multi-center, double-blind, placebo-controlled phase III trial	IV alteplase, 0.9mg/kg	MRI PWI-DWI mismatch	N=119 alteplase group :61 placebo:58	**primary endpoint (mRS 0-1)** OR: 1.2;95%CI 0.63-2.27, p = 0.5 **SIH** alteplase group=01 patient **Mortality rate** alteplase group =11.5 Placebo =6.8 p =0.53	Unfavorable in patients with 4.5 to 9 hrs
Ma H, et al., 2019 **EXTEND TRIAL** **2019**	Multicenter, double-blind, placebo-controlled phase III trial	IV alteplase, 0.9mg/kg	MRI PWI-DWI mismatch	N=225 3 Groups: 4.5 to 6 hours; 6 to 9 hours; and "WUS" where the	**primary endpoint (mRs 0-1)** Alteplase group =37% Placebo group=29% **Secondary outcome (mRs 0-2 at 90 days)** Alteplase group=51%	Favorable in patients who presented within 9 hours or with WUS selected with automated perfusion imaging

				precise time of the stroke is unknown. 112 received placebo and 113 received thrombolysis	Placebo group=43% **SIH** at 36 hours Alteplase group=6% Placebo group=1% **Mortality rate at 90 days** Alteplase group= 11.1% Placebo group=9.5%	
Thomalla et al., 2018b **WAKEUP TRIAL** **2018 AUG**	Multicenter randomized, double-blind, placebo-controlled clinical trial	IV alteplase, 0.9mg/kg	DWI-FLAIR mismatch	N=503 patients with UTOS Alteplase group:254 placebo:249	**primary endpoint (Median mRs)** Alteplase group=01 Placebo group= 02 **Secondary outcome (mRs at 90 days)** Alteplase group = 131(53.3%) Placebo group = 102(41.8%) **SIH** Alteplase group = 2.0% Placebo group =0.4% **Mortality** Alteplase group = 10 deaths (4.1%) Placebo group = 3 deaths (1.2%)	Favorable in functional outcome but numerically more SIH than with placebo at 90 days.
Schwamm et al., 2018 **MR WITNESS 2018**	Randomized, multicenter, phase IIa open label trial	IV alteplase, 0.9mg/kg	DWI-FLAIR mismatch SIR <1.15	N=80 AIS with UTOS at 4.5 to 24 hrs.	**primary endpoint (mRs 0-1)** at 90 days 39% of subjects achieved mRs = 0-1 **SIH** 1 patient (1.3%) **Symptomatic edema** 3 patients (3.8%)	Favorable in patients Selected by DWI-FLAIR mismatch. .
Kang et al., 2012 **RESTORE TRIAL 2012**	Prospective multicenter single-arm study	IV alteplase 0.9mg/kg Intra-arterial therapy, or a combination.	MRI PWI-DWI mismatch >20% and negative or subtle FLAIR	N=83 UTOS patients, received reperfusion therapy	**primary endpoint (mRs 0-2) at 90 days** 37 patients (44.6%) achieved **mRs** of 0 to 2, and 24 (28.9%) had **mRs** of 0 to 1. **SIH** 03 patients (3.6%).	Favorable and safe in patients with MRI PWI-DWI mismatch

AIS=acute ischemic stroke; **DWI**=diffusion-weighted imaging; **FLAIR**=fluid-attenuated inversion recovery; **MR**I=magnetic resonance imaging; **mRs**= modified Rankin scale; **PWI**=perfusion-weighted imaging; **SIH**=symptomatic intracranial hemorrhage; **SIR**= signal intensity ratio; **UTOS**=unknown time of stroke onset.

DISCUSSION

Most of the studies concerning the efficacy and safety of IV rt-PA in the management of UTOS are either retrospective observational studies, stroke registry based or case-control and open-labeled pilot studies with a small number of patients.[43,44] Few retrospective studies of stroke patients and case reports with UTOS treated with IV thrombolysis found that IV rt-PA may be safely administered in a select subgroup with imaging findings consistent with an early stroke.[45,46] The first positive multicenter single-arm trial for safety and feasibility of MRI-based reperfusion therapy in patients with UTOS, RESTORE, was published in 2012.Since then many phase II a and phase III trials attempting to establish the efficacy and safety of thrombolytic therapy in UTOS or WUS have been conducted.[47] MR WITNESS trial, A small phase II a trial of IV thrombolysis in UTOS selected by DWI FLAIR mismatch was published in favor of IV thrombolysis safety and efficacy recently, After this phase II a trial WAKE-UP trial, a potentially important RCT was the first to demonstrate the efficacy of IV thrombolysis beyond

4.5 hours using MRI perfusion for patient selection. This trial was stopped early due to favorable outcomes and discontinuation of funding, so 503 of patients were enrolled than 800 planned subjects. Furthermore, interpretation of safety was also limited. On the other hand another phase III Trial ECASS-4 of AIS patients selected with significant ischemic penumbra using visual assessment of MRI PWI-DWI mismatch, when treated with IV rt-PA at 4.5 -9 hrs after onset of stroke did not show a significant benefit in clinical outcome when compared with placebo. This trial was also stopped early due to decrease in recruitment after positive trials of thrombectomy in 6-24 hours' time window. EXTEND TRIAL, for extended time window used RAPID software for automated penumbral image processing was used. The median time from "last seen well" to IV rt-PAwas 9.9 hours vs 8.9 hours for placebo. EXTEND TRIAL trial also restricted its recruitment after 225 of the planned 310 patients, after the result of the WAKE-UP trial so did not reach to calculated sample size. Regarding low dose thrombolysis ,The THAWS,A Japanese trial of low-dose thrombolysis IV rt tPA 0.6mg/kg) in patients with UTOS, who were selected with imaging patterns suggesting recent onset, study showed no evidence of either benefit or harm with use of the 0.6mg/kg dose of IV rt-PA. This trial was also stopped early after recruitment of 131 patients of 200 planned enrollment due to the positive results of the WAKE-UP trial, which showed better outcomes with 0.9mg/kg dose of IV rt-PA in AIS patients with UTOS also identified by suitable imaging. The positive late thrombectomy trials also affected THAWS trial candidates, and they were considered for thrombectomy and received different doses of IV rt-PA used.

Results of all these recent RCTs using a tissue-based collection of patients are promising and time window to administer IV rt-PA may be extended in certain patients. In the future, thrombolytic therapy may become move toward tissue-based selection, although all these RCTs on UTOS and WUS are based on the use of advanced imaging modalities such as MRI DWI/FLAIR mismatch or CT/MRI penumbral mismatch for selection of participants. Apparently, these imaging modalities are promising in this subgroup of patients; Observations on these modalities are biased due to inter observer variability and reliability for interpretation, so the consensus on an inter-observer agreement for MRI DWI/FLAIR mismatch is moderate, and the sensitivity and negative predictive value is low to moderate.[48] A recent meta-analysis of ECASS4-EXTEND and EPITHET have emphasized the benefit of thrombolysis up to 9 hours after onset of AIS or in cases of WUS, for selected patients with identified potentially salvageable brain tissue, by mismatch on CTP imaging.[49]

Results of few ongoing phase III RCTs including TWIST TRIAL are still awaited.[50] TWIST trial is an ongoing CT based RCT of tenecteplase (TNKtPA) in patients who wake up with AIS. TNKtPA seems to be as effective as alteplase, and safe. Administration is easier. This trial is designed to assess use of TNKtPA given <4.5 hours from wake-up to see improvement in functional outcome at 3 months. If this trial showed patients benefit from I/V thrombolytic treatment up to 4.5 hours after awakening this will substantially increase the proportion of patients who can be treated

CONCLUSION

UTOS is not uncommon, clinical studies have been conducted to find a place for the therapeutic optimism in UTOS patients. Up to now no definite clinical and radiographic pattern has been established to select UTOS and WUS patients for efficacious and safe reperfusion therapy. Although results of recent RCTs using a tissue-based selection of patients are in favor of extending the time window to administer IV rt-PA in a certain group of UTOS patients, still there is insufficient evidence to produce a recommendation of IV thrombolytic therapies for UTOS. Further larger-scale RCTs with completed data and good selection of cases without selection bias, along with use of advance sensitive imaging modalities without discrepancy in selection criteria for imaging to prove its safety and efficacy are needed. There is a dire need to establish a consensus on the interpretation of predictive value, including threshold values for FLAIR intensity. Issues of inter observer discrepancies for visual and semi-quantitative analysis of CT perfusion, FLAIR DWI mismatch, PWI–DWI mismatch and generalizability of automated software also needed to figure out.

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