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What to do With Wake-Up Stroke

Mark N. Rubin, MD[1], and Kevin M. Barrett, MD, MSc[2]

Abstract

Wake-up stroke, defined as the situation where a patient awakens with stroke symptoms that were not present prior to falling asleep, represents roughly 1 in 5 acute ischemic strokes and remains a therapeutic dilemma. Patients with wake-up stroke were excluded from most ischemic stroke treatment trials and are often not eligible for acute reperfusion therapy in clinical practice, leading to poor outcomes. Studies of neuroimaging with standard noncontrast computed tomography (CT), magnetic resonance imaging (MRI), and multimodal perfusion-based CT and MRI suggest wake-up stroke may occur shortly before awakening and may assist in selecting patients for acute reperfusion therapies. Pilot studies of wake-up stroke treatment based on these neuroimaging features are promising but have limited generalizability. Ongoing randomized treatment trials using neuroimaging-based patient selection may identify a subset of patients with wake-up stroke that can safely benefit from acute reperfusion therapies.

Keywords

acute stroke, wake-up stroke, tPA, thrombolysis, hemorrhage, outcome

Introduction

Definition

Acute stroke evaluation and management is fundamentally predicated on time from symptom onset.[1,2] Intravenous tissue plasminogen activator (tPA) remains the only Food and Drug Administration (FDA)-approved nonsurgical reperfusion therapy for acute stroke with evidence-based efficacy, and well-designed, adequately powered studies have consistently shown that efficacy is exquisitely time sensitive.[3-7] That being the case, knowledge of the exact time of symptom onset, or at least the time at which the patient was last known to be normal, is paramount.

Patients who go to sleep normal and awaken with stroke symptoms, a phenomenon known as "wake-up stroke," present a management dilemma for acute stroke providers. Sometimes the period of sleep is short and a patient can still be eligible for tPA based on standard time-based criteria; however, when the time at which the patient was last known to be normal is the night prior to a morning presentation, which is often the case, the acute stroke provider is left without the key time-based data by which one typically makes safe therapeutic decisions for tPA candidacy. This makes for a diagnostic and therapeutic "gray area" in acute stroke practice.

Epidemiology

The wake-up stroke phenomenon is common. Numerous studies of various size and methodological strength through the years have given a sense of actual incidence of wake-up stroke as compared to other stroke presentations. These mostly stroke-registry–based studies range in estimation of wake-up stroke incidence from 8% in California[8] to 33% in a region of France[9] to nearly 39% in Ohio[10] but most typically suggest somewhere in between 15% and 25%.[11-24] Clinical and radiographic characteristics distinguishing wake-up stroke from other modes of stroke onset have been sought, but results have been conflicting. Some older studies have suggested that wake-up strokes seem to be more severe at onset[14,19] and portend a worse outcome overall,[17,19] while others suggested there are no appreciable clinical or radiographic differences between wake-up and "while awake" strokes.[16,22,25-27]

The best estimate of wake-up stroke prevalence comes from a retrospective population-based study of 1854 acute ischemic strokes in the Greater Cincinnati/Northern Kentucky region. In this representative biracial sample, 273 (14.3%) of acute strokes were wake-up strokes, resulting in an adjusted event rate of 26.0/100 000. No clinically significant differences in baseline characteristics were observed between

[1] Department of Neurology, Divisions of Hospital & Vascular Neurology, Mayo Clinic, Scottsdale, AZ, USA
[2] Department of Neurology, Division of Vascular Neurology, Mayo Clinic, Jacksonville, FL, USA

Corresponding Author:
Mark N. Rubin, Department of Neurology, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259, USA.
Email: rubin.mark@mayo.edu

wake-up and nonwake-up strokes; however, patients with wake-up stroke were older (72.3 vs 70.0 years, $P = .01$) and had higher baseline retrospectively calculated National Institutes of Health Stroke Scale (NIHSS) scores (4 vs 3, $P = .004$). Importantly, 98 (35%) patients were otherwise eligible for tPA if time was not a factor.[27]

Overall, in spite of the methodological heterogeneity and different focus of published studies, the common theme is that wake-up stroke is not rare and the clinical features suggest that there is a place for therapeutic optimism; although, no definitive clinical or radiographic paradigm has yet been established to select wake-up stroke candidates for safe and efficacious reperfusion therapy (Table 1).

Pathophysiologic Hypotheses

The wake-up stroke phenomenon is incompletely understood pathophysiologically. What seems clear, though, is that wake-up strokes are not actuarial quirks of evenly spread stroke risk through the course of a day but likely the result of circadian changes in coagulability, serum catecholamine levels, and autonomic tone. Much like cardiac events,[30] there is a preponderance of strokes of all subtypes in the morning as compared to evening onset.[11,31] Several homeostatic and structural factors may contribute to this phenomenon. Proposed factors include sleep-disordered breathing with or without patent foramen ovale,[32-34] overnight changes in autonomic tone affecting blood pressure with morning surges,[35,36] morning increases in platelet aggregation[37,38] relatively refractory to clopidogrel,[39] endothelial dysfunction,[40] blood viscosity,[41] and fluctuating prothrombotic/fibrinolytic factor level balance.[42-44] The circadian blood pressure-related changes behind the morning ''surges,'' which essentially mirror stroke incidence through the course of a day, are a tempting therapeutic target. Given the preponderance of strokes of all types between 0600 and 1200,[31] a treatment trial targeting morning blood pressure changes did not change the distribution of strokes through the course of a day.[45] Lending credence to the contribution of overnight paroxysms of atrial fibrillation,[46] a recent study demonstrated a significant association between wake-up stroke and a new diagnosis of atrial fibrillation.[47] Given the heterogeneity of wake-up stroke subtypes, it is likely that no one factor underlies wake-up stroke but some combination of the aforementioned and other yet undiscovered contributors (Table 2).

Neuroimaging and Wake-Up Stroke

The key feature of wake-up stroke that makes it a therapeutic dilemma is the absence of distinct time of symptom onset, which limits the ability to establish eligibility for acute reperfusion therapies. Diagnostic neuroimaging in a patient with wake-up stroke thereby plays an even stronger role than usual in acute stroke evaluations. Several studies have been conducted to evaluate neuroimaging modalities as a surrogate marker of cerebral ischemia and the so-called ''tissue clock'' to supplant the absent time of onset that starts the strictly clinical ''time clock.''

Several noncontrast computed tomography (CT)-based studies compared early ischemic changes on CT between wake-up stroke and stroke of known onset. Overall, there was no significant difference in early CT changes between wake-up stroke and stroke of known onset within 3 hours[25,28] or 6 hours.[26] These results suggest that the ischemic insult may occur shortly before or at the time of awakening in the absence of early ischemic change.

Perfusion and volume-based imaging with magnetic resonance (MR) or CT-based studies provide more granular physiologic data than noncontrast CT for acute stroke (see Table 3). These advanced neuroimaging techniques estimate the volume of brain tissue potentially at risk for progression to infarction (ie, ischemic penumbra) if recanalization does not occur. The volumetric difference between a surrogate for established infarction and penumbra, if present, is referred to as a ''mismatch'' and represents a rational biomarker for treatment selection (see Figure 1). Studies of advanced neuroimaging techniques have been conducted in patients with wake-up stroke. An MR-based study of diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), imaging surrogates of ischemic, and ''at-risk'' tissue, respectively, found that patients with wake-up stroke and stroke of known onset had similar DWI and PWI lesion volumes as well as a similarly high proportion of DWI-PWI mismatch.[52] A similarly designed CT-based study of mismatch between cerebral blood volume (like DWI, the estimate of infarcted tissue) and cerebral blood flow (like PWI, the at-risk tissue) found no difference between the percentage of mismatch between patients with wake-up stroke and stroke of known onset within a therapeutic window.[20]

Another interesting mismatch approach utilizes DWI and fluid attenuated inversion recovery (FLAIR) sequences of magnetic resonance imaging (MRI) to identify infarcted versus at-risk tissue. Both sequences detect cerebral water changes but in different time sequences (see Figure 2). The DWI sequence is very sensitive to early cerebral water changes; however, the abnormalities noted do not change once they appear after the first several minutes of ischemia, so exact timing of an ischemic injury cannot be made with DWI. The T2-based FLAIR sequence measures the accumulation of cerebral edema as the infarction process proceeds. Thus, in principle, the presence of a DWI lesion and absence of a matched FLAIR abnormality should represent a relatively early infarct. This idea has been studied in several single-center[51,53-56] pilots and a multicenter investigation.[57] Overall, the DWI-FLAIR mismatch was found to very accurately identify ischemic tissue beyond 3 to 6 hours and can

Table 1. Wake-Up Stroke Characteristics by Study.

Authors	Study Design	Total Patients	Wake-Up Stroke #, %	Clinical Differences vs While-Awake Stroke	Outcome Differences vs While-Awake Stroke	Imaging
CASPR group[8]	Retrospective, prospectively collected data, US state registry	374	30 (8)	—	—	—
Michel et al[9]	Retrospective, prospectively collected data, hospital registry	1633	568 (33.1)	—	—	—
Tanimoto et al[10]	Retrospective, prospectively collected data, hospital registry	72	28 (38.9)	WUS: tended to be African American, younger, small vessel mechanism, less severe NIHSS, worse lipid profile	—	—
Marler et al[11]	Retrospective, prospectively collected data, hospital registry	1167	331 (28)	—	—	—
Ricci et al[12]	Retrospective, prospectively collected data, regional registry	375	68 (18.1)	—	—	—
Lago et al[13]	Retrospective, prospectively collected data, hospital registry	1223	309 (25.2)	—	—	—
Bornstein et al[14]	Retrospective, prospectively collected data, national registry	1671	311 (18.6)	WUS more severe	—	—
Chaturvedi et al[15]	Subanalysis of prospective RCT	1272	323 (25.4)	—	—	—
Serena et al[16]	Retrospective, prospectively collected data, national registry	1248	301 (24.1)	None	—	WUS: CT head normal in 39.4% of patients seen within 6 hours of symptom recognition (60% in stroke while awake)
Nadeau et al[17]	Retrospective, prospectively collected data, national registry	2585	349 (13.5)	WUS had higher BP and ischemic stroke subtype	WUS less likely to return home	—
Boode et al[18]	Retrospective, hospital registry	263	48 (18.3)	—	—	—
Jiménez-Conde et al[19]	Retrospective, prospectively collected data, hospital registry	813	127 (15.6)	WUS had more obesity, less AF, and higher initial stroke severity	WUS had worse 3-month outcome	—
Silva et al[20]	Prospective cohort study, hospital registry	676	131 (19.4)	None	None	Similar prevalence of CTP mismatch and arterial occlusion in WUS and known onset groups
Turin et al[21]	Retrospective, prospectively collected data, national registry	897	87 (9.7)	WUS more hypertension and increased initial severity	None	—

(continued)

Table 1. (continued)

Authors	Study Design	Total Patients	Wake-Up Stroke #, %	Clinical Differences vs While-Awake Stroke	Outcome Differences vs While-Awake Stroke	Imaging
Fink et al[22]	Retrospective, prospectively collected data, hospital registry	364	100 (27)	None	—	Similar prevalence of MRI DWI/PWI mismatch
Moradiya et al[23]	Subanalysis of a prospective RCT	17 398	5152 (29.6)	WUS initially less severe	None	—
Koton et al[24]	Retrospective, prospectively collected data, national registry	4408	820 (18.6)	None	None	20%-40% prevalence of penumbra
Todo et al[25]	Retrospective, prospectively collected data, hospital registry	158	17 (10.8)	—	—	CT findings in WUS similar to patients within 3 hours of known symptom onset
Huisa et al[26]	Prospective cohort study, hospital registry	96	28 (29.6)	None	Trend toward favorable (0-1) 90 d mRS in WUS vs 4 hours from symptoms controls (73% vs 45%)	Favorable CT ASPECTS (8-10) similar in WUS and known 4 h from symptoms (89.3% vs 95.6%)
Mackey et al[27]	Population-based registry	1854	273 (14.7)	"Minor differences" in age and rNIHSS (WUS older, higher rNIHSS)	None	—
Roveri et al[28]	Retrospective, prospectively collected data, hospital registry	1531	190 (12.4)	None	Outcome better in controls (patients treated with tPA within 3 hours of symptoms)	Baseline ASPECTS similar in WUS and controls within 3 hours of symptoms and treated with tPA
Manawadu et al[29]	Retrospective, prospectively collected data, hospital registry	1836	193 (10.5)	—	Outcome better in thrombolyzed WUS vs nonthrombolyzed WUS	CT ASPECTS and CTP to select patients for IV tPA

Abbreviations: WUS, wake-up stroke; RCT, randomized controlled trial; CT, computed tomography; CTP, CT perfusion; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; ASPECTS, Alberta Stroke Program Early CT Score; rNIHSS, retrospective National Institutes of Health Stroke Scale; BP, blood pressure; AF, atrial fibrillation.

Table 2. Proposed Pathophysiologic Mechanisms of Wake-Up Stroke.

Structural	• Sleep-disordered breathing[32] and PFO[33]
	• New-onset atrial fibrillation[47]
	• Endothelial dysfunction[40]
Homeostatic	• Morning blood pressure "surge"[31,35,36]
Serological	• Increased viscosity[41]
	• Increased platelet aggregation[37-39]
	• Increased procoagulant factors[42-44]

Abbreviation: PFO, patent foramen ovale.

identify ischemia within the 3- to 4.5-hour window with excellent specificity. The large multicenter study of 543 patients supported the findings of the single-center studies, with DWI-FLAIR mismatch identified in patients within 4.5 hours of stroke onset with a sensitivity of only 62% but a good specificity of 81%, although interrater agreement was less than ideal ($\kappa = .569$). A recent publication sought to increase interrater reliability of DWI-FLAIR mismatch identification by color-coding FLAIR intensity and did just that with a roughly 10% increase in positive predictive value for both observers (85%-95% in one and 72%-82% in the other) once color coding was introduced.[58] A recent small observational study noted a DWI-FLAIR mismatch in 44% of their patients with wake-up stroke.[52] These findings supported the initiation of thrombolysis treatment trials based on the identification of a DWI-FLAIR mismatch, which are ongoing and will be discussed further in a subsequent section.

Emergent neuroimaging is of heightened importance in the setting of wake-up stroke, given the absence of a clear time of symptom onset. Imaging modalities as simple and rapid as noncontrast CT and as sophisticated as multimodal

Table 3. Wake-Up Stroke Imaging Modalities.

Parenchymal imaging	CT	Noncontrast CT	Screen for early ischemic changes	Time to ischemic change: variable; with MCA occlusion as little as 1 hour[48] but often 3+ hours
		Perfusion CT	Screen for infarct/penumbra mismatch (see Figure 1)	Time to ischemic change: variable, depends on patient hemodynamics and CBV threshold for "infarct," but is typically abnormal before clear signs on noncontrast CT
		CBV—total volume of blood in a given volume of brain (mL/100 g)		
		CBF—total volume of blood *moving through* a given volume of brain (mL/100 g)		
		MTT—the average transit time of blood through a brain region		
		TTP—time from contrast arrival-to-peak-intensity flow through a brain region		
	MRI	Routine MRI	Screen for infarct volume, DWI/FLAIR mismatch (see Figure 2)	Time to ischemic change: DWI—3 minutes[49]; T2WI—1-4 hours[50]; FLAIR—3-6 hours[51]
		Perfusion (PWI) MRI	Screen for infarct/penumbra mismatch	
		CBV, CBF, and MTT as defined previously are the basic sequences of a PWI protocol		
Vascular imaging	CT	CT angiography	Screen for large artery occlusion	
	MRI	MR angiography		
	Ultrasound	Complete neurosonology (carotid duplex ultrasonography plus transcranial Doppler)		

Abbreviations: CT, computed tomography; CBV, cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time; TTP, time to peak; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; FLAIR, fluid attenuated inversion recovery.

CT and MRI show promise in identifying patients with acute ischemic stroke who may benefit from systemic thrombolysis. Ongoing randomized treatment trials based on these neuroimaging findings have practice-changing implications.

Treatment Evidence

Currently, there is a lack of a high-level evidence base to support any acute treatment in the setting of wake-up stroke. In the absence of high-level data, there are now many small studies of off-label use of acute reperfusion therapies for wake-up stroke employing various clinical and neuroimaging criteria for inclusion.

The majority of studies conducted so far are small, single-center observational studies of off-label intravenous tPA with or without endovascular reperfusion therapies.[29,59-75] Largermulticenter studies,[76] organized phase II studies,[77] and randomized placebo-controlled treatment trials[78-80] are fewer in number. Of note, the only large, multicenter, randomized placebo-controlled trial studied a glycoprotein IIb/IIIa inhibitor (abciximab) as an adjunct to intravenous tPA and patients with wake-up stroke made up only a small subgroup of the cohort. The individual

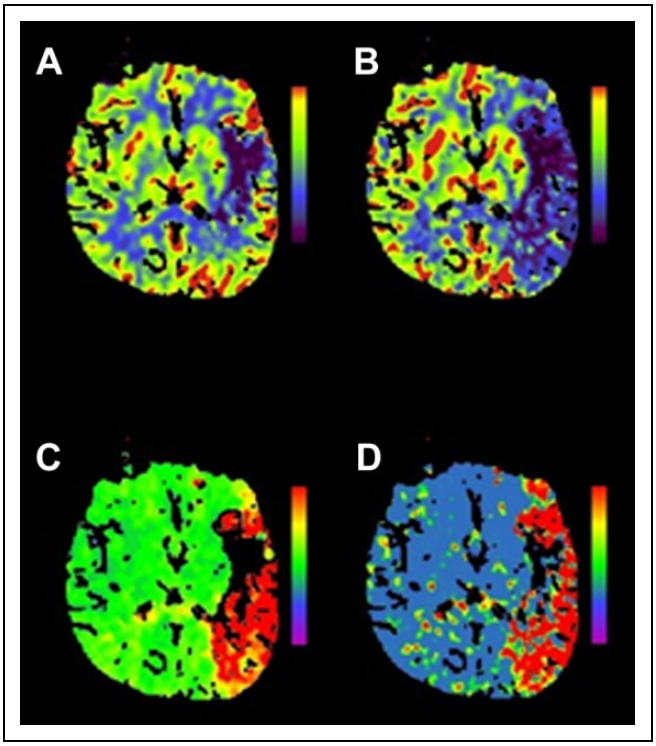

Figure 1. Multimodal CT mismatch (or "penumbra"). Panel (A) is a cerebral blood volume (CBV) map. The dark area noted in the left frontal operculum suggests low contrast volume in the region and is considered a surrogate for infarcted tissue, or the "infarct core." The other maps—cerebral blood flow (CBF) in panel (B), time to peak (TTP) in panel (C), and mean transit time (MTT) in panel (D)—are different measures of contrast movement through cerebral vasculature (see Table 3) and clearly involve much more of the left hemisphere than the CBV map. This discordance is referred to as a multimodal CT mismatch or "penumbra" and may represent tissue at risk of infarction but potentially salvageable by reperfusion therapy. Siemens SOMATOM, syngo perfusion software. CT indicates computed tomography.

characteristics and levels of evidence are detailed in Table 4.

Their inherently biased study designs, small numbers, and marked heterogeneity in inclusion criteria and reported results do not allow for much to be said about acute reperfusion therapy for wake-up stroke other than there seems to be a case for therapeutic optimism and large, randomized, placebo- and sham-controlled studies are justified. Ongoing trials include Efficacy and Safety of MRI-based thrombolysis in Wake Up Stroke (WAKE-UP),[81,82] THrombolysis for Acute Wake-up and Unclear-onset Strokes With Alteplase at 0.6 mg/kg Trial (THAWS),[83] Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND),[84] A Phase IIa Safety Stusdy of Intravenous Thrombolysis With Alteplase in MRI-Selected Patients (MR WITNESS),[85] Safety of Intravenous Thrombolysis for Wake Up Stroke,[86] Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical

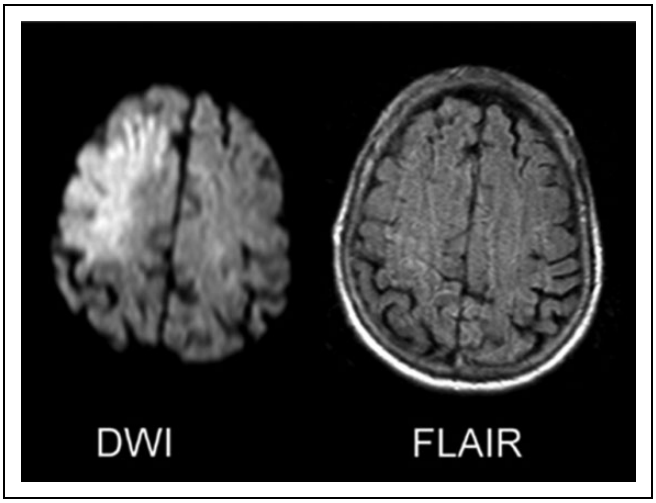

Figure 2. The DWI/FLAIR mismatch. These 2 axial images of the brain at a level just above the lateral ventricles represent the so-called DWI/FLAIR mismatch that can be seen in the early hours after symptom onset when DWI (left) hyperintensity—which can arise in minutes from symptom onset—occurs in the absence of T2-based FLAIR (right) hyperintensity, which takes 3 to 6 hours to develop. DWI indicates diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery.

Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN),[87] Safety of Intravenous Thrombolytics in Stroke on Awakening (SAIL-ON),[88] and Wake Up Symptomatic Stroke in Acute Brain Ischemia (WASSABI; Table 5).[89]

What to do With Wake-Up Stroke

Evaluation

Based on the studies mentioned previously and our own clinical experience, we recommend a wake-up stroke evaluation proceeds as any other acute stroke assessment, with as much clinical detail as possible, an NIHSS examination and basic laboratory studies according to guidelines. This should be followed by multiparametric CT or MRI with noninvasive angiography or fast-track neurosonology (eg, transcranial Doppler and carotid duplex ultrasonography)[90-94] to screen for an infarction/at-risk mismatch and large arterial occlusion, respectively. Even if one is uncomfortable providing treatment recommendations based on the results given the lack of high-level supporting evidence, the diagnostics can serve to inform prognostication.

Treatment

Regarding treatment of wake-up stroke, the authors agree with the sentiment of the recent systematic review of treatment strategies in wake-up stroke[95] that routine treatment of wake-up stroke cannot be offered based on available evidence. Readers are encouraged to participate in clinical trials so that

Table 4. Wake-Up Stroke Treatment Studies and Level of Evidence.

Authors	Study Design	Clinical Inclusion Criteria	Imaging Inclusion Criteria	# Patients With Wake-Up Stroke (Treated)	# Control Patients	Treatment Type	Mean Door to Treatment in WUS	Mean/Median NIHSS of Treated Patients (Control)	Mean Age of Treated Patients (Control)	sICH in WUS, % (Control)	mRS 0-1, % (Control)	mRS 0-2, % (Control)	Level of Evidence[a]
Iosif et al[60]	Case report	"Admitted to hospital rapidly after waking up with stroke"	MRI DWI/PWI and DWI/FLAIR mismatch, MRA occlusion	2 (2)	0	IAT	–	15.5	45	50	At d/c: 100	–	Class IIb level C
Kuruvilla et al[71]	Case report	–	CT	2 (2)	–	IAT	–	16	33	0	–	–	Class IIa level C
Bracco et al[74]	Case report	–	Multimodal CT	1 (1)	–	IAT	–	12	74	0	–	–	Class IIb level C
Sung and Lee[75]	Retrospective review	–	–	10	–	IAT	168 min	19	–	0	–	90 d: 20	Class IIb level C
Stampfl et al[69]	Retrospective review	WUS, NIHSS ≥ 10	CTA occlusion, multimodal MRI mismatch (DWI/PWI)	19	–	IAT	–	11	73.7	21.1	–	10.5	Class IIb level C
Jung et al[70]	Retrospective review	NIHSS >4, symptoms <24 h but >6 h from last normal	Multimodal MRI mismatch (DWI/PWI)	55 (55)	804	IAT	–	16.8 (16.8)	61.9 (62.6)	3.7 (6)	90 d: 16.7 (23.3)	90 d: 37 (39.7)	Class IIa level C
Natarajan et al[68]	Retrospective review	7-23 h from last normal, WUS, mRS ≤ 1, NIHSS 5-22	CT ASPECTS, multimodal CT mismatch	30 (30)	–	IAT	–	13	72	10	–	20	Class IIb level C
Natarajan et al[72]	Retrospective review	WUS within 12 h of noticing symptoms, NIHSS >8	Multimodal CT mismatch, CTA occlusion	25 (25)	–	IAT	–	–	–	14.3[b]	–	42.9[b]	Class IIb level C
Barreto et al[59,c]	Retrospective review	Major deficit from stroke, neurologically normal prior to stroke	No EIC in >1/3 of vascular territory	80 (46)	34/174	IV tPA, IAT, or both	2.4 h/1.2 h	16 (10.5/11)	62 (64/65)	4.3 (0/2.9)	At d/c: 14 (6/48)	At d/c: 28 (13/48)	Class IIb level C
Cho et al[61]	Retrospective review	Present within 6 hours of symptom recognition	Multimodal CT or MRI mismatch	26 (26)	223	IV tPA, IAT or both	154 min (90 min)	14.5 (13)	67.1 (65.8)	6.3 (5.8)	90 d: 37.5 (35)	90 d: 50 (49.3)	Class IIa level C
Breuer et al[62]	Retrospective review	Present within 6 hours of symptom recognition	Multimodal MRI mismatch	45 (10)	35	IV tPA	–	–	–	0 (0)	90 d: 30 (31)	90 d: 50 (60)	Class IIb level C
Kim et al[63]	Retrospective review	Present within 3 hours of symptom recognition	CT ASPECTS, multimodal MRI mismatch	26 (-)	49	IV tPA, IAT or both	–	13 (12)	67 (72)	10.3 (8.2)	90 d: 27.6 (4.1)	90 d: 44.8 (14.3)	Class IIa level C
Manawadu et al[73]	Retrospective case-control	WUS, last normal <12 hours but >4.5 hours	CT ASPECTS, multimodal CT mismatch	122 (68)	54	IV tPA	–	11.5 (9)	73.9 (70.6)	2.9 (0)	90 d: 16.2 (9.3)	90 d: 36.8 (25.9)	Class IIa level C
Aoki et al[64]	Prospective cohort	Unknown onset stroke, "last known normal not consistent with first found abnormal"	MRI DWI/FLAIR mismatch	4 (4)	–	IV tPA	1 hour	15.5	73.25	0	90 d: 25	90 d: 25	Class IIb level C
Ebinger et al[54,65]	Trial substudy, observational cohort	European guideline, "disregarding the contraindication of unknown time of onset"	Multimodal MRI mismatch	13 (13)	131	IV tPA	86 min[d] (60 min)	13[d]	81[d]	0 (3.1)	90 d: 29.4[d] (38.9)	90 d: 35.3[d] (49.6)	Class IIb level C

(continued)

Table 4. (continued)

Authors	Study Design	Clinical Inclusion Criteria	Imaging Inclusion Criteria	# Patients With Wake-Up Stroke (Treated)	# Control Patients	Treatment Type	Mean Door to Treatment in WUS	Mean/Median NIHSS of Treated Patients (Control)	Mean Age of Treated Patients (Control)	sICH in WUS, % (Control)	mRS 0-1, % (Control)	mRS 0-2, % (Control)	Level of Evidence[a]
Manawadu et al[66]	Prospective case-control	WUS, last normal <12 hours but >4.5 hours vs controls within 4.5 hours symptom onset	CT ASPECTS	68 (68)	326	IV tPA	73 min (60 min)	12 (13)	73.9 (72.8)	2.9 (3.4)	90 d: 16 (24)	90 d: 37 (38)	Class IIa level C
Bai et al[67]	Prospective case—control	WUS and all patients with ischemic stroke within 12 h of symptom onset	Multimodal MRI mismatch (DWI/FLAIR)	68 (48)	172	IV tPA	–	–	–	2 (2)	90 d: 77 (76)	–	Class IIa level C
Kang et al[76]	Prospective multicenter observational	Last normal and symptom awareness times discordant, in emergency department within 6 hours of symptom awareness	Multimodal MRI mismatch (DWI/PWI and DWI/FLAIR)	63 (63)	156	IV tPA, IAT or both	155 min	14 (12)	67 (70)	3.2 (-)	90 d: 28.6 (-)	90 d: 46 (-)	Class IIa level B
Hill et al[77]	Prospective observational	Last normal <12 hours, WUS, "disabling stroke"	Arterial occlusion, ASPECTS >5	89 (20)	–	IV tPA	148 min (awakening to treatment)	13	75	0	45	–	Class IIa level C
Adams et al[78,79]	Subanalysis of RCT	WUS within 3 hours of symptom awareness	CT	43 (43; 22 tPA + abciximab, 21 tPA only)	758	IV tPA + abciximab or placebo	–	10 (8)	69.5 (68.9)	18.2 (4.8)	–	90 d: 9.3 (29.2)	Class III harm level B
Michel et al[9,80]	Pilot RCT	Supratentorial stroke, too late for standard tPA but not more than 24 hours or WUS	Multimodal CT	9 (4)	5	IV tPA	109.5 min (113 min)	17 (14.5)	69.5 (49)	0 (0)	-[e]	-[e]	Class IIa level C

Abbreviations: sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale; CT, computed tomography; MRI, magnetic resonance imaging; CTP, CT perfusion; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; IAT, intra-arterial therapy; IV tPA, intravenous tissue plasminogen activator; d/c, discharge; ASPECTS, Alberta Stroke Program Early CT Score; WUS, wake-up stroke; EIC, early ischemic change; NIHSS, National Institutes of Health Stroke Scale; d, day.

[a]Classification schema from the American Heart Association/American Stroke Association.

[b]Anterior circulation WUS only.

[c]Two control groups: control 1 = untreated WUS and control 2 = treated patients within 3 hours of known symptom onset (control 1/control 2).

[d]Investigators combined WUS with unknown onset strokes, so exact proportions of WUS alone is unknown.

[e]Mean mRS at 90 d was 1.5 in the treatment group, 3 in placebo.

Table 5. Ongoing Wake-Up Stroke Treatment Trials.

- WAKE-UP[81,82]
- THAWS[83]
- EXTEND[84]
- MR WITNESS[85]
- Safety of Intravenous Thrombolysis for Wake Up Stroke[86]
- DAWN[87]
- SAIL-ON[88]
- WASSABI[89]

Abbreviations: DAWN, Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; MR WITNESS, A Phase IIa Safety Study of Intravenous Thrombolysis With Alteplase in MRI-Selected Patients; SAIL-ON, Safety of Intravenous Thrombolytics in Stroke on Awakening; WASSABI, Wake Up Symptomatic Stroke in Acute Brain Ischemia; THAWS, THrombolysis for Acute Wake-up and Unclear-onset Strokes With Alteplase at 0.6 mg/kg Trial.

Table 6. Wake-Up Stroke Recommendations.

Evaluation	• Clinical history, NIHSS, CT head, laboratories per AHA/ASA guidelines[96]
	• Multiparametric CT or MRI (eg, CT or MR perfusion)
Treatment	• No routine therapy can be offered based on available evidence
	• Trial participation is encouraged

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; AHA/ASA, American Heart Association/American Stroke Association; MRI, magnetic resonance imaging.

we as stroke providers may know how best to treat our patients with wake-up stroke (Table 6).

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References

1. Saver JL. Time is brain—quantified. *Stroke J Cereb Circ*. 2006; 37(1):263-266.
2. Meretoja A, Keshtkaran M, Saver JL, et al. Stroke thrombolysis: save a minute, save a day. *Stroke J Cereb Circ*. 2014;45(4): 1053-1058.
3. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333(24):1581-1588.
4. Albers GW, Clark WM, Madden KP, Hamilton SA, Davis SM, Donnan GA. ATLANTIS trial: results for patients treated within 3 hours of stroke onset * editorial comment: results for patients treated within 3 hours of stroke onset. *Stroke*. 2002;33(2): 493-496.
5. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.
6. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004; 363(9411):768-774.
7. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA J Am Med Assoc*. 2013;309(23): 2480-2488.
8. California Acute Stroke Pilot Registry (CASPR) Investigators. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. *Neurology*. 2005;64(4):654-659.
9. Michel P, Odier C, Rutgers M, et al. The Acute STroke Registry and Analysis of Lausanne (ASTRAL): design and baseline analysis of an ischemic stroke registry including acute multimodal imaging. *Stroke J Cereb Circ*. 2010;41(11):2491-2498.
10. Tanimoto A, Mehndiratta P, Koo BB. Characteristics of wake-up stroke. *J Stroke Cerebrovasc Dis*. 2014;23(6):1296-1299.
11. Marler JR, Price TR, Clark GL, et al. Morning increase in onset of ischemic stroke. *Stroke J Cereb Circ*. 1989;20(4):473-476.
12. Ricci S, Celani MG, Vitali R, La Rosa F, Righetti E, Duca E. Diurnal and seasonal variations in the occurrence of stroke: a community-based study. *Neuroepidemiology*. 1992;11(2):59-64.
13. Lago A, Geffner D, Tembl J, Landete L, Valero C, Baquero M. Circadian variation in acute ischemic stroke: a hospital-based study. *Stroke J Cereb Circ*. 1998;29(9):1873-1875.
14. Bornstein NM, Gur AY, Fainshtein P, Korczyn AD. Stroke during sleep: epidemiological and clinical features. *Cerebrovasc Dis Basel Switz*. 1999;9(6):320-322.
15. Chaturvedi S, Adams HP, Woolson RF. Circadian variation in ischemic stroke subtypes. *Stroke J Cereb Circ*. 1999;30(9): 1792-1795.
16. Serena J, Dávalos A, Segura T, Mostacero E, Castillo J. Stroke on awakening: looking for a more rational management. *Cerebrovasc Dis Basel Switz*. 2003;16(2):128-133.
17. Nadeau JO, Fang J, Kapral MK, Silver FL, Hill MD; Registry of the Canadian stroke network. Outcome after stroke upon awakening. *Can J Neurol Sci J Can Sci Neurol*. 2005;32(2):232-236.
18. Boode B, Welzen V, Franke C, van Oostenbrugge R. Estimating the number of stroke patients eligible for thrombolytic treatment if delay could be avoided. *Cerebrovasc Dis Basel Switz*. 2007; 23(4):294-298.
19. Jiménez-Conde J, Ois A, Rodríguez-Campello A, Gomis M, Roquer J. Does sleep protect against ischemic stroke? Less frequent ischemic strokes but more severe ones. *J Neurol*. 2007;254(6):782-788.
20. Silva GS, Lima FO, Camargo ECS, et al. Wake-up stroke: clinical and neuroimaging characteristics. *Cerebrovasc Dis Basel Switz*. 2010;29(4):336-342.
21. Turin TC, Kita Y, Rumana N, et al. Wake-up stroke: incidence, risk factors and outcome of acute stroke during sleep in a

Japanese population. Takashima Stroke Registry. 1988-2003. *Eur Neurol*. 2013;69(6):354-359.
22. Fink JN, Kumar S, Horkan C, et al. The stroke patient who woke up: clinical and radiological features, including diffusion and perfusion MRI. *Stroke J Cereb Circ*. 2002;33(4):988-993.
23. Moradiya Y, Janjua N. Presentation and outcomes of ''wake-up strokes'' in a large randomized stroke trial: analysis of data from the international stroke trial. *J Stroke Cerebrovasc Dis*. 2013; 22(8):e286-e292.
24. Koton S, Tanne D, Bornstein NM; NASIS Investigators. Ischemic stroke on awakening: patients' characteristics, outcomes and potential for reperfusion therapy. *Neuroepidemiology*. 2012;39(3-4):149-153.
25. Todo K, Moriwaki H, Saito K, Tanaka M, Oe H, Naritomi H. Early CT findings in unknown-onset and wake-up strokes. *Cerebrovasc Dis Basel Switz*. 2006;21(5-6):367-371.
26. Huisa BN, Raman R, Ernstrom K, et al. Alberta Stroke Program Early CT Score (ASPECTS) in patients with wake-up stroke. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc*. 2010;19(6): 475-479.
27. Mackey J, Kleindorfer D, Sucharew H, et al. Population-based study of wake-up strokes. *Neurology*. 2011;76(19):1662-1667.
28. Roveri L, La Gioia S, Ghidinelli C, Anzalone N, De Filippis C, Comi G. Wake-up stroke within 3 hours of symptom awareness: imaging and clinical features compared to standard recombinant tissue plasminogen activator treated stroke. *J Stroke Cerebrovasc Dis*. 2013;22(6):703-708.
29. Manawadu D, Bodla S, Keep J, Jarosz J, Kalra L. An observational study of thrombolysis outcomes in wake-up ischemic stroke patients. *Stroke*. 2013;44(2):427-431.
30. Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. *Am J Cardiol*. 1997;79(11): 1512-1516.
31. Elliott WJ. Circadian Variation in the timing of stroke onset: a meta-analysis. *Stroke*. 1998;29(5):992-996.
32. Pizza F, Biallas M, Kallweit U, Wolf M, Bassetti CL. Cerebral hemodynamic changes in stroke during sleep-disordered breathing. *Stroke J Cereb Circ*. 2012;43(7):1951-1953.
33. Ozdemir O, Beletsky V, Hachinski V, Spence JD. Cerebrovascular events on awakening, patent foramen ovale and obstructive sleep apnea syndrome. *J Neurol Sci*. 2008;268(1-2):193-194.
34. Ciccone A, Proserpio P, Roccatagliata DV, et al. Wake-up stroke and TIA due to paradoxical embolism during long obstructive sleep apnoeas: a cross-sectional study. *Thorax*. 2013;68(1): 97-104.
35. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med*. 1993;328(5):303-307.
36. Redon J. The normal circadian pattern of blood pressure: implications for treatment. *Int J Clin Pract Suppl*. 2004;(145):3-8.
37. Musumeci V, Rosa S, Caruso A, Zuppi C, Zappacosta B, Tutinelli F. Abnormal diurnal changes in in-vivo platelet activation in patients with atherosclerotic diseases. *Atherosclerosis*. 1986; 60(3):231-236.
38. Andrews NP, Gralnick HR, Merryman P, Vail M, Quyyumi AA. Mechanisms underlying the morning increase in platelet aggregation: a flow cytometry study. *J Am Coll Cardiol*. 1996; 28(7):1789-1795.
39. Kozinski M, Bielis L, Wisniewska-Szmyt J, et al. Diurnal variation in platelet inhibition by clopidogrel. *Platelets*. 2011;22(8): 579-587.
40. Otto ME. Early morning attenuation of endothelial function in healthy humans. *Circulation*. 2004;109(21):2507-2510.
41. Ehrly AM, Jung G. Circadian rhythm of human blood viscosity. *Biorheology*. 1973;10(4):577-583.
42. Soulban G, Labrecque G. Circadian rhythms of blood clotting time and coagulation factors II, VII, IX and X in rats. *Life Sci*. 1989;45(25):2485-2489.
43. Andreotti F, Davies GJ, Hackett DR, et al. Major circadian fluctuations in fibrinolytic factors and possible relevance to time of onset of myocardial infarction, sudden cardiac death and stroke. *Am J Cardiol*. 1988;62(9):635-257.
44. Bremner WF, Sothern RB, Kanabrocki EL, et al. Relation between circadian patterns in levels of circulating lipoprotein(a), fibrinogen, platelets, and related lipid variables in men. *Am Heart J*. 2000;139(1):164-173.
45. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*. 2003;289(16): 2073-2082.
46. Deguchi Y, Amino M, Adachi K, et al. Circadian distribution of paroxysmal atrial fibrillation in patients with and without structural heart disease in untreated state. *Ann Noninvasive Electrocardiol*. 2009;14(3):280-289.
47. Riccio PM, Klein FR, Pagani Cassara F, et al. Newly diagnosed atrial fibrillation linked to wake-up stroke and TIA: hypothetical implications. *Neurology*. 2013;80(20):1834-1840.
48. Nakano S, Iseda T, Kawano H, Yoneyama T, Ikeda T, Wakisaka S. Correlation of early CT signs in the deep middle cerebral artery territories with angiographically confirmed site of arterial occlusion. *AJNR Am J Neuroradiol*. 2001;22(4):654-659.
49. Moseley ME, Kucharczyk J, Mintorovitch J, et al. Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. *AJNR Am J Neuroradiol*. 1990;11(3):423-429.
50. Venkatesan R, Lin W, Gurleyik K, et al. Absolute measurements of water content using magnetic resonance imaging: preliminary findings in an in vivo focal ischemic rat model. *Magn Reson Med*. 2000;43(1):146-150.
51. Thomalla G, Rossbach P, Rosenkranz M, et al. Negative fluid-attenuated inversion recovery imaging identifies acute ischemic stroke at 3 hours or less. *Ann Neurol*. 2009;65(6):724-732.
52. Huisa BN, Liebeskind DS, Raman R, et al. Diffusion-weighted imaging-fluid attenuated inversion recovery mismatch in nocturnal stroke patients with unknown time of onset. *J Stroke Cerebrovasc Dis*. 2013;22(7):972-977.
53. Aoki J, Kimura K, Iguchi Y, Shibazaki K, Sakai K, Iwanaga T. FLAIR can estimate the onset time in acute ischemic stroke patients. *J Neurol Sci*. 2010;293(1-2):39-44.

54. Ebinger M, Galinovic I, Rozanski M, Brunecker P, Endres M, Fiebach JB. Fluid-attenuated inversion recovery evolution within 12 hours from stroke onset: a reliable tissue clock? *Stroke*. 2010;41(2):250-255.
55. Petkova M, Rodrigo S, Lamy C, et al. MR imaging helps predict time from symptom onset in patients with acute stroke: implications for patients with unknown onset time. *Radiology*. 2010; 257(3):782-92.
56. Emeriau S, Serre I, Toubas O, Pombourcq F, Oppenheim C, Pierot L. Can diffusion-weighted imaging-fluid-attenuated inversion recovery mismatch (positive diffusion-weighted imaging/negative fluid-attenuated inversion recovery) at 3 tesla identify patients with stroke at <4.5 hours? *Stroke*. 2013;44(6): 1647-1651.
57. Thomalla G, Cheng B, Ebinger M, et al. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study. *Lancet Neurol*. 2011;10(11):978-986.
58. Kim BJ, Kim Y-H, Kim Y-J, et al. Color-coded fluid-attenuated inversion recovery images improve inter-rater reliability of fluid-attenuated inversion recovery signal changes within acute diffusion-weighted image lesions. *Stroke*. 2014;45(9):2801-2804.
59. Barreto AD, Martin-Schild S, Hallevi H, et al. Thrombolytic therapy for patients who wake-up with stroke. *Stroke*. 2009; 40(3):827-832.
60. Iosif C, Oppenheim C, Trystram D, Domigo V, Meder J-F. MR Imaging-based decision in thrombolytic therapy for stroke on awakening: report of 2 cases. *Am J Neuroradiol*. 2008;29(7): 1314-1316.
61. Cho A-H, Sohn S-I, Han M-K, et al. Safety and efficacy of MRI-based thrombolysis in unclear-onset stroke. *Cerebrovasc Dis*. 2008;25(6):572-579.
62. Breuer L, Schellinger PD, Huttner HB, et al. Feasibility and safety of magnetic resonance imaging-based thrombolysis in patients with stroke on awakening: initial single-centre experience. *Int J Stroke*. 2010;5(2):68-73.
63. Kim J-T, Park M-S, Nam T-S, et al. Thrombolysis as a factor associated with favorable outcomes in patients with unclear-onset stroke: thrombolysis in unclear-onset stroke. *Eur J Neurol*. 2011;18(7):988-994.
64. Aoki J, Kimura K, Iguchi Y, et al. Intravenous thrombolysis based on diffusion-weighted imaging and fluid-attenuated inversion recovery mismatch in acute stroke patients with unknown onset time. *Cerebrovasc Dis*. 2011;31(5):435-441.
65. Ebinger M, Scheitz JF, Kufner A, Endres M, Fiebach JB, Nolte CH. MRI-based intravenous thrombolysis in stroke patients with unknown time of symptom onset: MRI-based thrombolysis in stroke of unknown onset. *Eur J Neurol*. 2012;19(2): 348-350.
66. Manawadu D, Bodla S, Jarosz J, Keep J, Kalra L. A case-controlled comparison of thrombolysis outcomes between wake-up and known time of onset ischemic stroke patients. *Stroke*. 2013;44(8):2226-2231.
67. Bai Q, Zhao Z, Fu P, et al. Clinical outcomes of fast MRI-based thrombolysis in wake-up strokes compared to superacute ischemic strokes within 12 hours. *Neurol Res*. 2013;35(5): 492-497.
68. Natarajan SK, Snyder KV, Siddiqui AH, Ionita CC, Hopkins LN, Levy EI. Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes. *Stroke*. 2009;40(10):3269-3274.
69. Stampfl S, Ringleb PA, Haehnel S, et al. Recanalization with stent-retriever devices in patients with wake-up stroke. *Am J Neuroradiol*. 2013;34(5):1040-1043.
70. Jung S, Gralla J, Fischer U, et al. Safety of endovascular treatment beyond the 6-h time window in 205 patients. *Eur J Neurol*. 2013;20(6):865-871.
71. Kuruvilla A, Norris GM, Xavier AR. Acute endovascular recanalization therapy in wake-up stroke. *J Neurol Sci*. 2011; 300(1-2):148-150.
72. Natarajan SK, Karmon Y, Snyder KV, et al. Prospective acute ischemic stroke outcomes after endovascular therapy: a real-world experience. *World Neurosurg*. 2010;74(4-5):455-464.
73. Manawadu D, Bodla S, Keep J, Kalra L. Influence of age on thrombolysis outcome in wake-up stroke. *Stroke*. 2013;44(10): 2898-2900.
74. Bracco S, Tassi R, Gennari P, et al. Wake-up (or wake-up for) stroke: a treatable stroke. *Neuroradiol J*. 2013;26(5):573-578.
75. Sung S, Lee T. E-070 acute recanalization with stenting for wake-up stroke. *J Neurointerv Surg*. 2014;6(suppl 1):A71-A71.
76. Kang D-W, Sohn S-I, Hong K-S, et al. Reperfusion Therapy in Unclear-Onset Stroke Based on MRI Evaluation (RESTORE): a prospective multicenter study. *Stroke*. 2012;43(12):3278-3283.
77. Hill MD, Kenney C, Dzialowski I, et al. Tissue Window in Stroke Thrombolysis study (TWIST): a safety study. *Can J Neurol Sci J Can Sci Neurol*. 2013;40(1):17-20.
78. Adams HP, Effron MB, Torner J, et al. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). *Stroke J Cereb Circ*. 2008;39(1):87-99.
79. Adams HP, Leira EC, Torner JC, et al. Treating patients with "wake-up" stroke: the experience of the AbESTT-II trial. *Stroke*. 2008;39(12):3277-3282.
80. Michel P, Ntaios G, Reichhart M, et al. Perfusion-CT guided intravenous thrombolysis in patients with unknown-onset stroke: a randomized, double-blind, placebo-controlled, pilot feasibility trial. *Neuroradiology*. 2012;54(6):579-588.
81. Thomalla G, Fiebach JB, Østergaard L, et al. A multicenter, randomized, double-blind, placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP): protocols. *Int J Stroke*. 2014; 9(6):829-836.
82. Thomalla G, Ebinger M, Fiehler J, Fiebach JB, Endres M, Gerloff C. EU-funded treatment study: WAKE-UP: a randomized, placebo-controlled MRI-based trial of thrombolysis in wake-up stroke [in German]. *Nervenarzt*. 2012;83(10):1241-1251.
83. Koga M, Toyoda K, Kimura K, et al. THrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0·6 mg/kg (THAWS) trial. *Int J Stroke*. 2014;9(8):1117-1124.

84. Ma H, Parsons MW, Christensen S, et al. A multicentre, randomized, double-blinded, placebo-controlled Phase III study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND). *Int J Stroke*. 2012;7(1): 74-80.
85. MR WITNESS: a study of intravenous thrombolysis with alteplase in MRI-selected patients [Internet]; 2014. Web site. http://www.clinicaltrials.gov/show/NCT01282242. Accessed October 9, 2014.
86. Safety of Intravenous Thrombolysis for Wake-up Stroke [Internet]; 2014. Web site. http://clinicaltrials.gov/ct2/show/NCT01183533. Accessed October 9, 2014.
87. Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN) [Internet]; 2014. Web site. http://clinicaltrials.gov/ct2/show/NCT02142283.
88. Safety of Intravenous Thrombolytics in Stroke on Awakening (SAIL-ON) [Internet]; 2014. Web site. http://clinicaltrials.gov/ct2/show/NCT01643902.
89. Wake up Symptomatic Stroke in Acute Brain Ischemia (WASSABI) Trial [Internet]; 2014. Web site. http://clinicaltrials.gov/ct2/show/NCT01455935.
90. Chernyshev OY, Garami Z, Calleja S, et al. Yield and accuracy of urgent combined carotid/transcranial ultrasound testing in acute cerebral ischemia. *Stroke*. 2005;36(1):32-37.
91. Chambers BR, Merory JR, Smidt V. Doppler diagnosis in cases of acute stroke. *Med J Aust*. 1989;150(7):382-384.
92. Camerlingo M, Casto L, Censori B, Ferraro B, Gazzaniga GC, Mamoli A. Transcranial Doppler in acute ischemic stroke of the middle cerebral artery territories. *Acta Neurol Scand*. 1993; 88(2):108-111.
93. Lee DH, Gao FQ, Rankin RN, Pelz DM, Fox AJ. Duplex and color Doppler flow sonography of occlusion and near occlusion of the carotid artery. *AJNR Am J Neuroradiol*. 1996;17(7): 1267-1274.
94. Alexandrov AV, Demchuk AM, Wein TH, Grotta JC. Yield of transcranial Doppler in acute cerebral ischemia. *Stroke J Cereb Circ*. 1999;30(8):1604-1609.
95. Buck D, Shaw LC, Price CI, Ford GA. Reperfusion therapies for wake-up stroke: systematic review. *Stroke*. 2014;45(6):1869-1875.
96. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870-947.