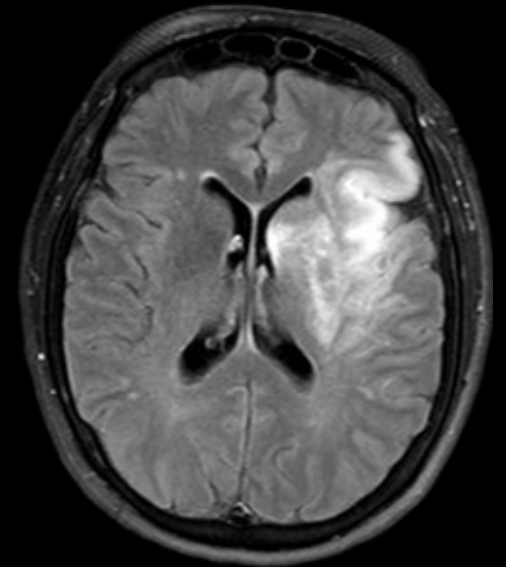
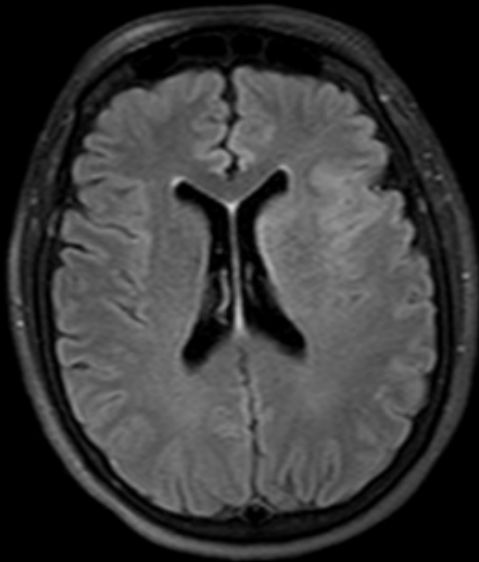


Extending the Treatment Window in Acute Stroke



Shlee S. Song, MD

Associate Professor, Department of Neurology

Associate Director, Comprehensive Stroke Center

Program Director, Vascular Neurology Fellowship Program

Cedars-Sinai Medical Center

October 27, 2016



Introduction

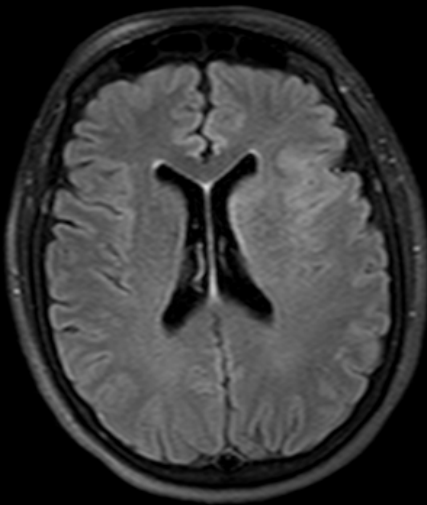
- Time as a marker for evolution of ischemia
- 25% patients wake-up with their stroke symptoms
 - Chaturvedi S, et al. *Stroke* (1999)
- MRI as a "tissue clock"
- Defining this time window may help identify more patients who are eligible for thrombolytic therapy.

FLAIR as a Tissue Clock

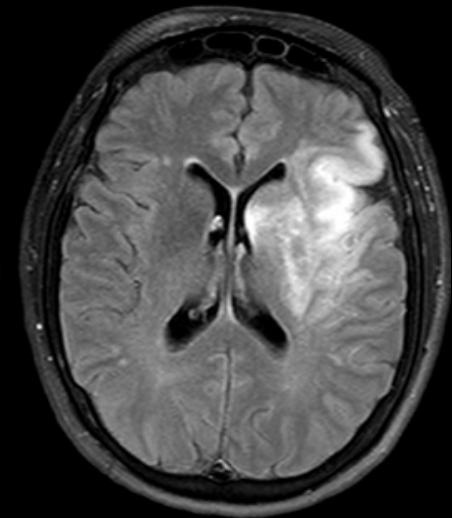
- DWI positive- FLAIR negative scans identify patients within the 3-hour time window
 - » Thomalla G, et al. *Annals of Neurology* (2009)
- Lesion to normal signal intensity ratios on FLAIR co-registered to DWI images
 - Quantify changes that occur with time
 - » Petkova M, et al. *Radiology* (2010)
 - Such measurements may be impractical within the time constraints of thrombolytic treatment

Purpose

- **Aim** : Investigate the timing of changes on MRI in patients with well-defined stroke onset.
- Design a clinical trial using imaging parameters to treat stroke patients with unknown onset time.



FLAIR < 6 hours



FLAIR > 12 hours

Methods

Subjects

- April 2005- December 2010
- Lesion Evolution in Stroke and Ischemia On Neuroimaging (LESION) Project registry*

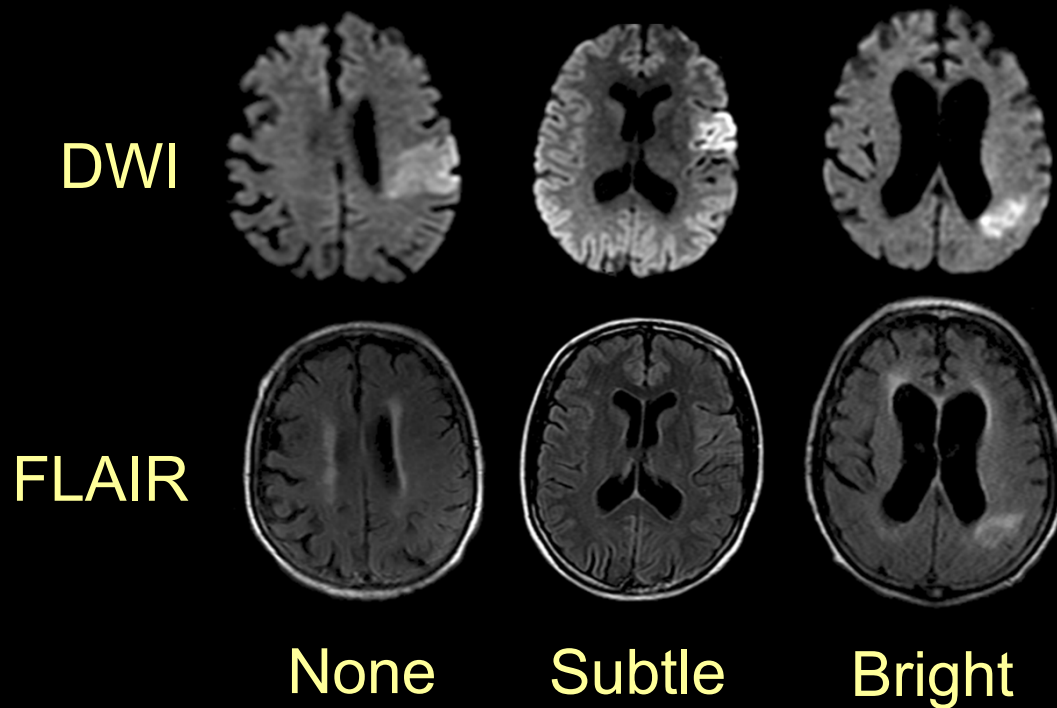
*Prospective series of stroke patients screened with MRI within 24 hours from witnessed stroke onset, DWI-confirmed acute ischemic stroke, and admission NIH Stroke Scale (NIHSS) >3 or received an acute intervention.

MRI

- 1.5T or 3T MRI
- DWI to evaluate acute ischemic stroke lesion
- FLAIR to evaluate acute lesion hyperintensity and signal intensity ratios

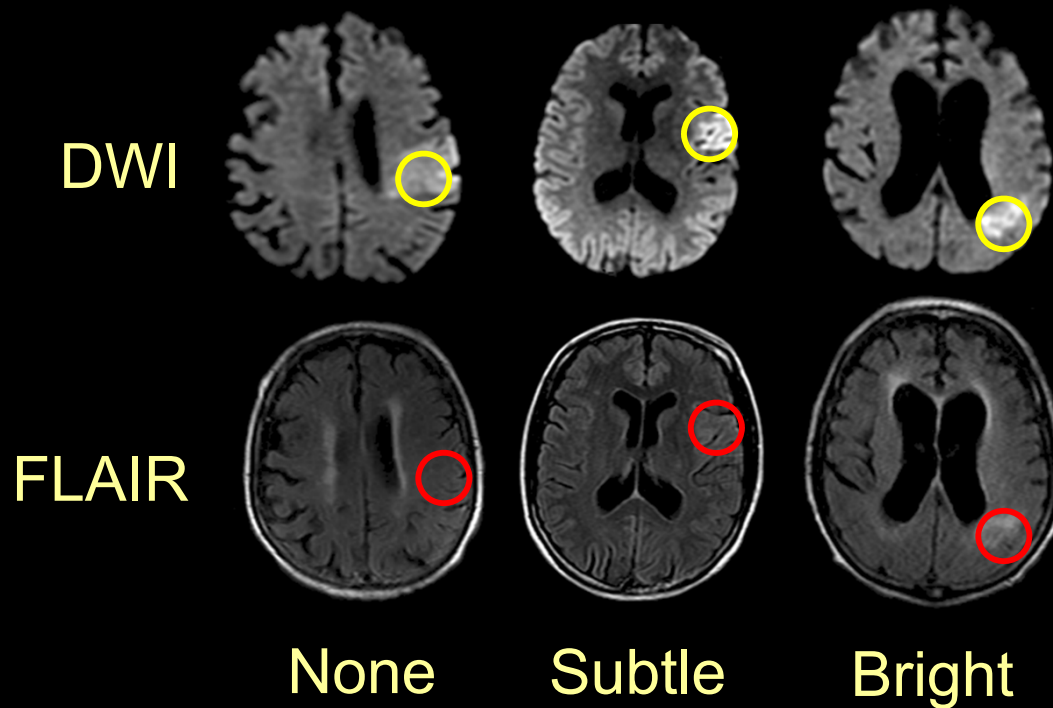
Methods

- 3 readers blinded to time from LSN to MRI scan
- Qualitative Scoring
 - FLAIR Hyperintensity Rating



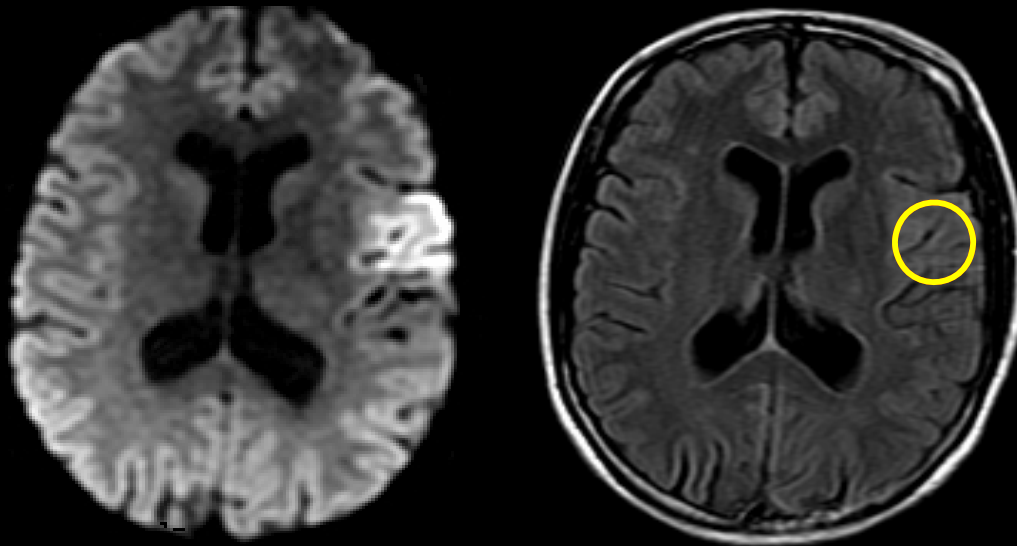
Methods

- 3 readers blinded to time from LSN to MRI scan
- Qualitative Scoring
 - FLAIR Hyperintensity Rating



Methods

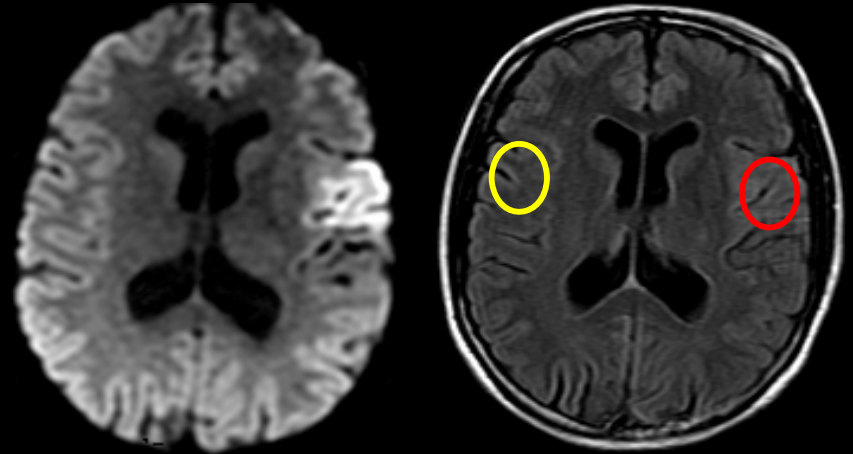
- 3 readers blinded to time from LSN to MRI scan
- Quantitative Measures:
Signal Intensity (SI) Ratio = $\frac{\text{Lesion}}{\text{Normal}}$



Methods

- 3 readers blinded to time LSN to MRI scan
- Quantitative Measures

$$\text{Signal Intensity Ratio} = \frac{\text{Lesion}}{\text{Normal}}$$



Signal Intensity Ratio: 1.15

○ Lesion: 239

○ Normal: 208

Results

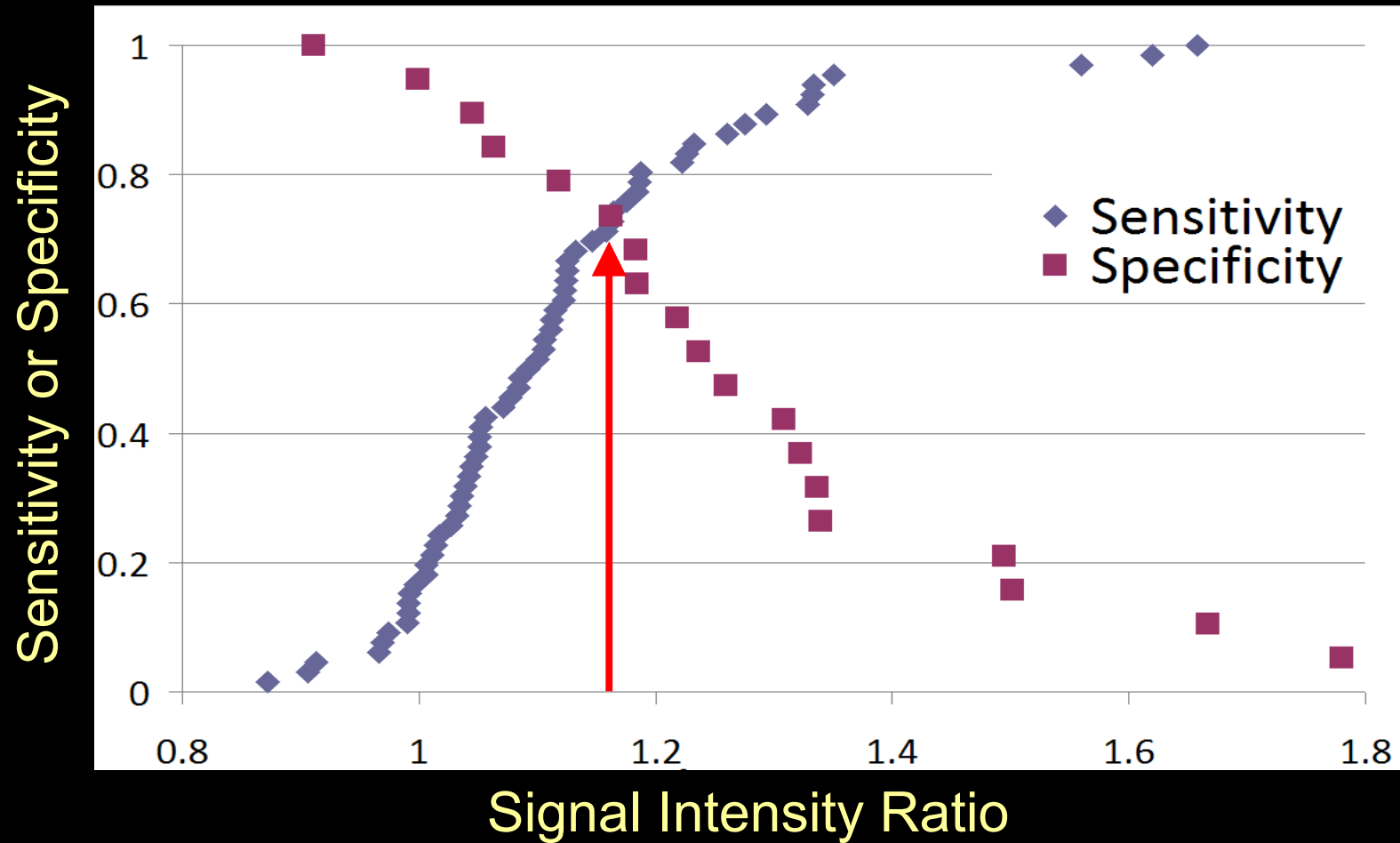
- Lesion conspicuity increased with time on FLAIR ($p=0.006$)
- Qualitative assessment: FLAIR-negative vs FLAIR-positive
 - good interrater agreement ($k=0.7091$, 95% CI 0.61-0.81)
 - Subtle hyperintensity was less reliably categorized ($k=0.59$, 95% CI 0.47-0.71)
- Reader measured SIR <1.15 can identify patients within the treatable time window of 4.5 hours (positive predictive value= 0.90).
- The average time for FLAIR MRI to remain negative was 3.2h (SD=3.7h, range 0.75-22.22; 95%CI 2.0-4.3)
- The SIR was greater for right hemisphere lesions ($p=0.04$) for a given reported time from stroke symptom onset.

Results

- Co-registered DWI-FLAIR measures vs Reader selected SIRs for FLAIR scans ($p=0.82$)
- Accuracy using Reader measured SIR threshold of 1.15 was comparable to that of co-registered DWI-FLAIR-SIR at same threshold
sensitivity=0.78, specificity=0.78
vs
sensitivity=0.85, specificity=0.67

Results: Signal Intensity Ratios

Signal Intensity Ratio for Predicting Time <6h



Summary

- SIR on FLAIR provides a quantitative tool to identify early ischemic strokes.
- In developing SIR thresholds, right hemisphere lesions may confound the accurate estimate of stroke onset
- Image co-registration for thrombolytic trial enrollment not needed
- A SIR < 1.15 on FLAIR yields a practical estimate of stroke onset within 4.5 hours.

A Pragmatic Approach Using Magnetic Resonance Imaging to Treat Ischemic Strokes of Unknown Onset Time in a Thrombolytic Trial

Shlee S. Song, MD; Lawrence L. Latour, PhD; Carsten H. Ritter, MD; Ona Wu, PhD;
Mourad Tighiouart, PhD; Daymara A. Hernandez, BA; Katherine D. Ku, BS;
Marie Luby, PhD; Steven Warach, MD, PhD

Background and Purpose—Toward the goal of designing a clinical trial using imaging parameters to treat stroke patients with unknown onset time, we investigated the timing of changes on MRI in patients with well-defined stroke onset.

Methods—Hypothesis-generating (n=85) and confirmatory (n=111) samples were scored by blinded readers for fluid-attenuated inversion recovery (FLAIR) hyperintensity in diffusion-positive regions. Reader-measured signal intensity ratio (SIR) of the lesion to contralateral tissue was compared with SIR measured by coregistration.

Results—Lesion conspicuity increased with time on FLAIR ($P=0.006$). Qualitative assessment of FLAIR-negative vs FLAIR hyperintensity ($k=0.7091$; 95% CI, 0.61–0.81) showed good interrater agreement. Subtle hyperintensity was less reliably categorized ($k=0.59$; 95% CI, 0.47–0.71). Reader-measured SIR <1.15 can identify patients within the treatable time window of 4.5 hours (positive predictive value=0.90). The SIR was greater for right hemisphere lesions ($P=0.04$) for a given reported time from stroke symptom onset.

Conclusion—The SIR on FLAIR provides a quantitative tool to identify early ischemic strokes. In developing SIR thresholds, right hemisphere lesions may confound the accurate estimate of stroke onset time. Image coregistration for thrombolytic trial enrollment is not necessary. A SIR <1.15 on FLAIR yields a practical estimate of stroke onset within 4.5 hours. (*Stroke*. 2012;43:2331-2335.)

Key Words: diffusion-weighted imaging ■ fluid-attenuated inversion recovery ■ stroke ■ thrombolysis

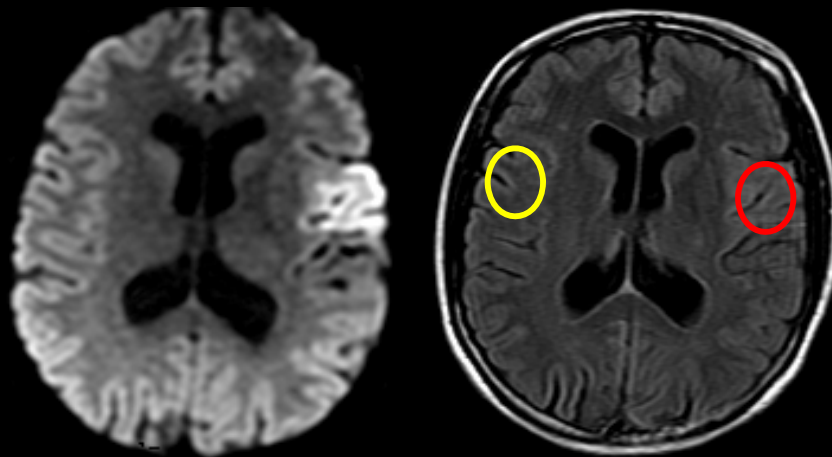
As a matter of convention, time of stroke onset for thrombolytic eligibility is estimated as the time that a patient was last known to be normal. Although this conservative estimate assures that treatment is started within the established time window, it excludes potentially treatable stroke if the time of onset is uncertain, such as patients with symptoms first noted on awakening or those with unwitnessed onset who are unable to provide an accurate history. This factor likely contributes to low treatment percentage rates of intravenous tissue plasminogen

imaging changes on acute MRI in patients with well-defined stroke onset time. A recent study comparing CT changes in wake-up strokes with those in strokes of known onset time concluded that the time of true onset in wake-up strokes was soon before awakening,³ suggesting the potential use of thrombolytic treatment in this patient population. Another center's experience with off-label compassionate use of thrombolysis in wake-up stroke patients who underwent pretreatment CT scans reports higher rates of good clinical

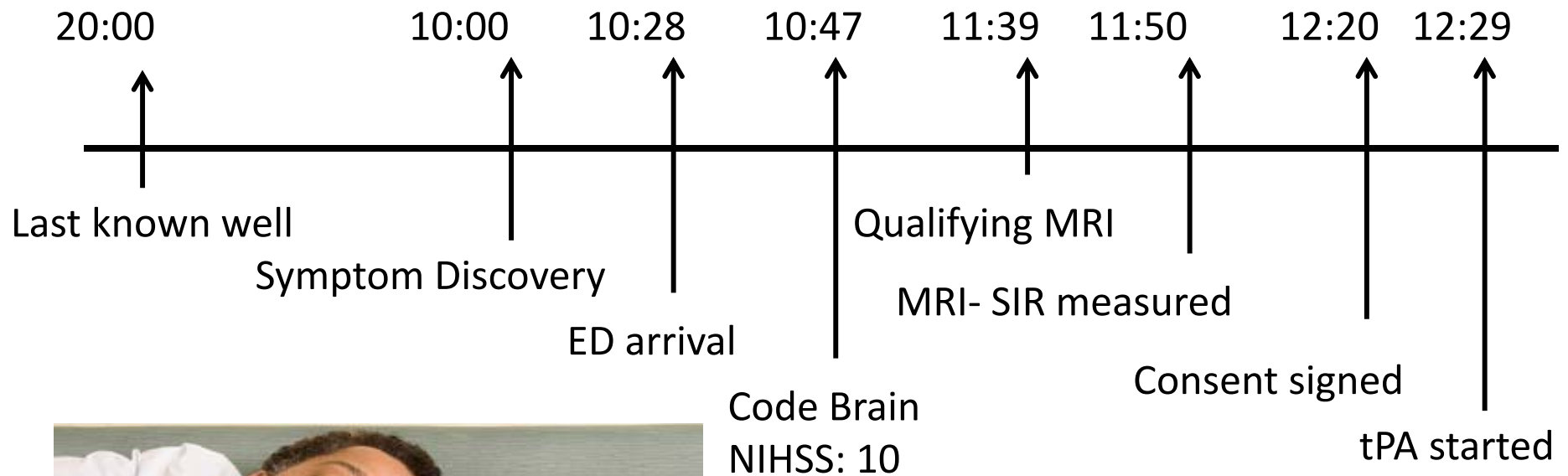
A Pragmatic Approach Using MRI to Treat Ischemic Strokes of Unknown Onset Time in a Thrombolytic Trial

***MR WITNESS Clinical Trial Registration Information:**

<http://clinicaltrials.gov/ct2/show/NCT01282242>

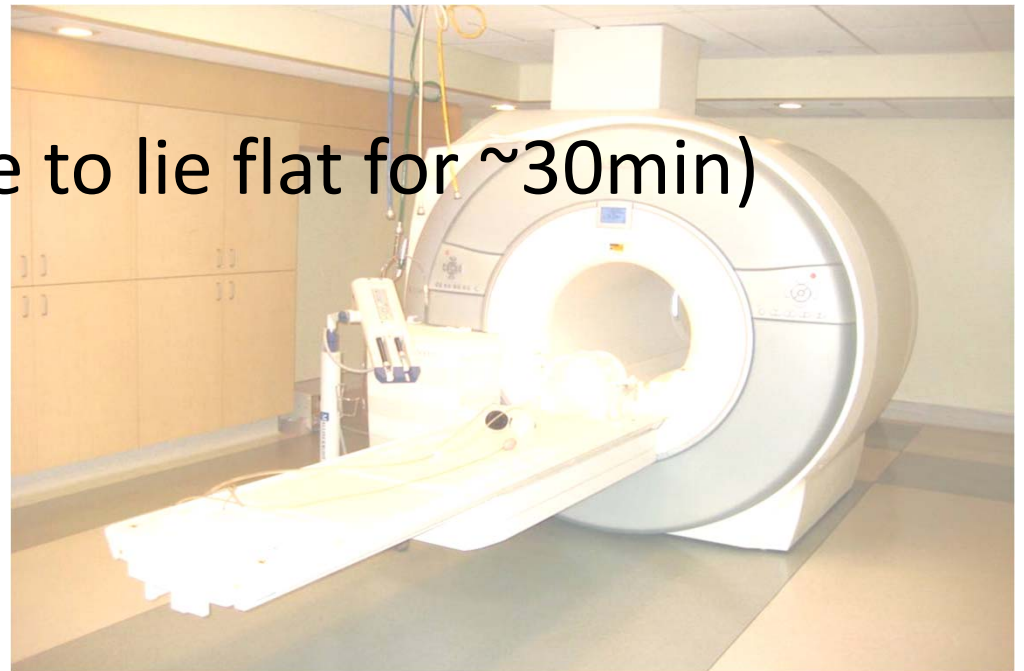


MR WITNESS patient- 58M Lt HP



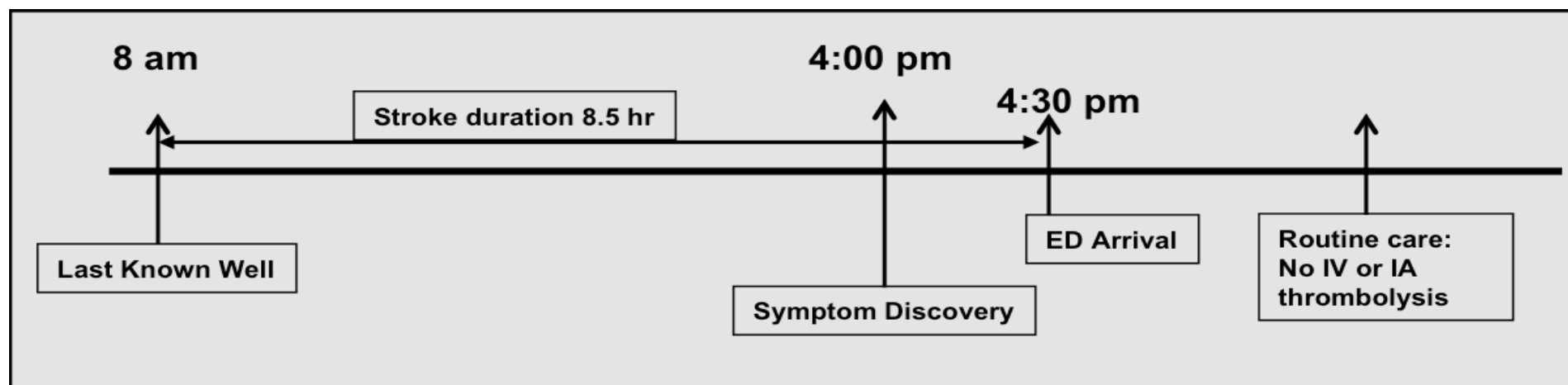
MR WITNESS- Screening in ED

- Age 18-85 (inclusive)
- Last known well within 24 hours
- Eligible to receive IV-tPA within 4.5 hours of symptom discovery
- MRI (no pacemaker, able to lie flat for ~30min)

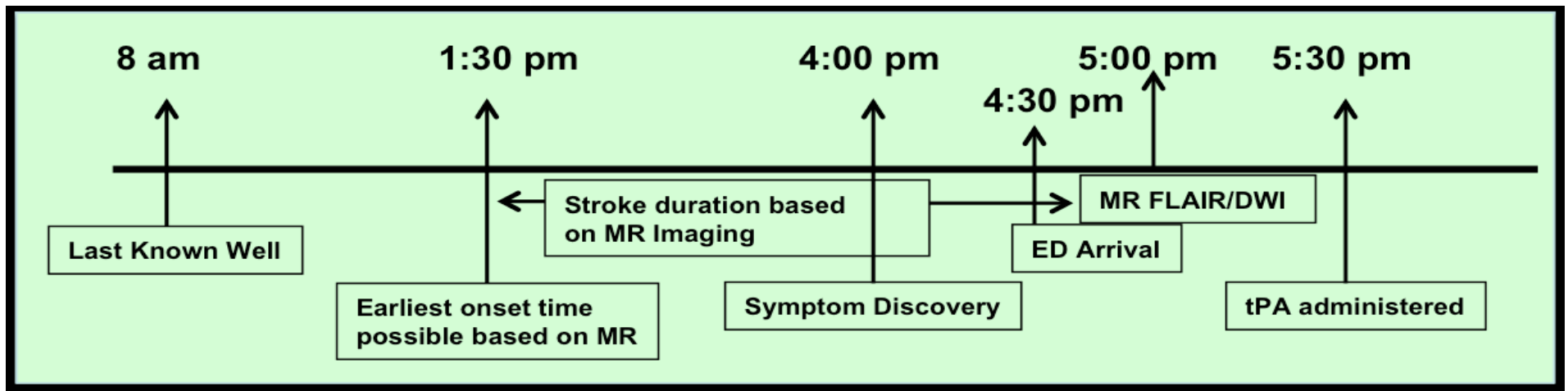


Example 1

Patient outside time window



MR WITNESS patient





Home

- Home
- About WAKE-UP
- The Group
- The Project
- WAKE-UP in the media
- WAKE-UP in your country
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Tweets by @WAKEUPstroke

WAKE-UP @WAKEUPstroke
Great discussions at the #dgnkongress. Thanks for visiting #WAKEUPstroke! Let's keep enrolling!



23 Sep

WAKE-UP @WAKEUPstroke
#WAKEUPstroke and the Young Neurologists are present at the #dgnkongress in Mannheim! Come around and visit us! #stroke #FP7

The WAKE-UP project

WAKE-UP is a European multicentre investigator-initiated randomized placebo-controlled clinical trial of MRI based thrombolysis in acute stroke patients with unknown time of symptom onset, e.g. due to recognition of stroke symptoms on awakening.

Stroke is a devastating disease leading to death and disability in large numbers of patients with massive social and economic impact. Intravenous thrombolysis with Alteplase is available as effective and safe treatment of acute stroke within 4.5 hours of symptom onset. However, in about 20% of acute stroke patients time of symptom onset is unknown e.g. because symptoms are recognized when waking-up from sleep in the morning. This large group of patients is currently excluded from treatment with Alteplase only due to the missing information on the time of symptom onset. In preparatory work the WAKE-UP consortium has developed an innovative approach of using brain MRI as surrogate marker of stroke lesion age which may be used to identify stroke patients likely to benefit from thrombolysis.

The objective of WAKE-UP is to test efficacy and safety of MRI-based intravenous thrombolysis with Alteplase in patients waking up with stroke symptoms or patients with unknown symptom onset. By this, WAKE-UP aims at providing a new safe and effective treatment option for acute stroke patients waking up with stroke symptoms.

The project is centrally coordinated by the Universitätsklinikum Hamburg-Eppendorf (Prof. Christian Gerloff; deputy coordinator: Dr. Götz Thomalla).

NEWS

The fourth year of the trial (30.09.2016)

On September 22, 2016 the WAKE-UP trial has been active for four years. By the end of the fourth year of the trial, 59 sites were active, and 1.199 patients have been enrolled of whom 432 have been randomised. During the fourth year of the trial the safety interim analysis was performed after 300 patients have completed the trial and reached the outcome evaluation after 90-100

search GO

WAKE-UP in your country



National coordinators

Read → [here](#) what the national coordinators of WAKE-UP think about our trial!!

New WAKE-UP videos

The new WAKE-UP videos are online.

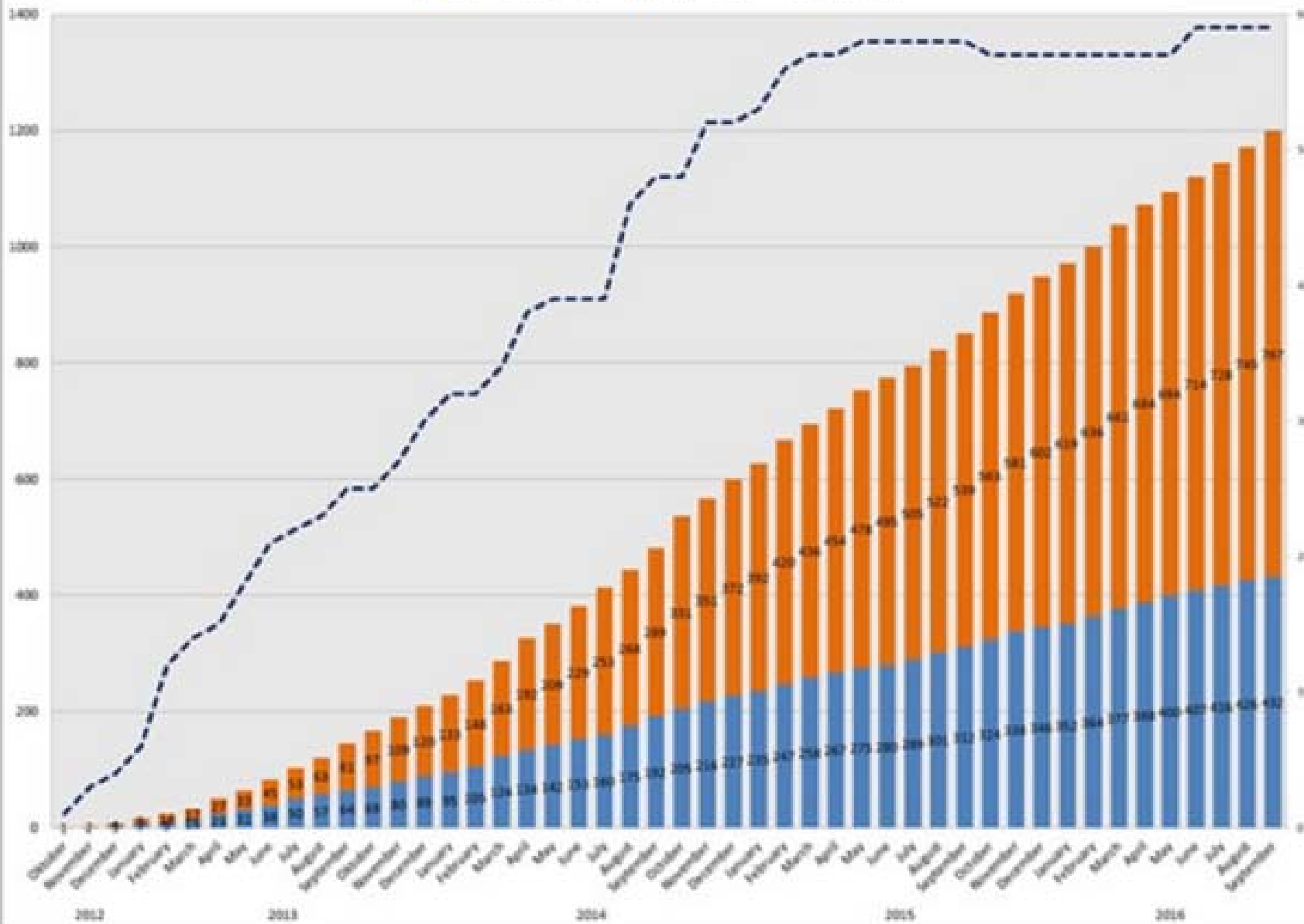


EUROPA - Research

<http://www.wakeup-stroke.eu/>

WAKE-UP patient enrollment

■ Randomized Patients
 ■ Screen Failures
 - - - Active Sites



NEXT STEPS...

IMAGING-WINDOW THROMBOLYSIS IN EMERGENT STROKE SYNDROMES

Lee H. Schwamm, MD (MGH) on behalf of

Ona Wu, PhD (MGH)

Steve Warach, MD PhD (Seton/UT Austin)

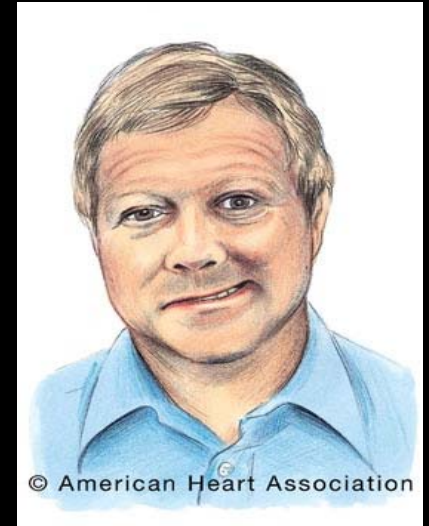
Larry Latour, PhD (NINDS)

Shlee Song, MD (Cedar Sinai)

Expanding thrombolytic indications

Are there patients who present beyond the proven time window who may benefit from thrombolysis?

- ✓ Identify target population
- ✓ Demonstrate tPA safety in this population
- ➔ 3. Demonstrate tPA efficacy in this population



DAWN Trial



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DWI/PWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention "DAWN Trial" [Recruiting](#)

[Overview](#) [Description](#) [Eligibility](#) [References](#) [PHASE N/A](#) [RESULTS N/A](#) [Login to Bookmark](#)

Summary of Purpose

To study the safety and efficacy of endovascular treatment in MR or CT perfusion-selected patients suffering acute ischemic stroke due to a proximal large vessel anterior circulation occlusion (e.g. ICA and/or MCA-M1 segment) who present "beyond the typical therapeutic window" defined as "last time seen well" greater than 8 hours. As such, this time frame applies to both witnessed and unwitnessed (including "wake-up") events.

[Read More](#) →

Trial Milestones

The following dates are available for this trial. Trial information last updated on 9 March 2009.

UNAVAILABLE	UNAVAILABLE	UNAVAILABLE	UNAVAILABLE	UNAVAILABLE	UNAVAILABLE
Start Date	First Received	1st Completion	Completion	Verification	Results

Recruitment

Gender: Both
Minimum Age: 18
Maximum Age: 85
Max Time from Onset: 8 Hours

Principal Investigator

Raul G. Nogueira, MD/ Tudor Jovin, MD
Massachusetts General Hospital/
University of Pittsburgh Medical Center

DEFUSE 3 Trial

NIH STROKENET: ACUTE INTERVENTIONAL STROKE TRIALS

ENDOVASCULAR THERAPY FOLLOWING IMAGING EVALUATION FOR ISCHEMIC STROKE 3 (DEFUSE 3)

Trial Summary:

DEFUSE 3 is a prospective randomized Phase III multicenter controlled trial of patients with acute ischemic anterior circulation strokes due to large artery occlusion treated between 6-16 hours of stroke onset with endovascular thrombectomy therapy vs. control. The primary endpoint, the modified Rankin Score, will be assessed at 3 months. The patients' participation in the study concludes at that time (3 months from stroke onset). The study will randomize up to 476 patients over 4 years. **The purpose of DEFUSE 3 is to assess the safety and efficacy of thrombectomy in carefully selected patients in an extended time window.** Only the devices listed in this protocol will be used. Selection of the specific device (or devices) is determined by the individual endovascular therapist.



Trial Design Summary:

DEFUSE 3 is a prospective randomized Phase III multicenter controlled trial of patients with acute ischemic anterior circulation strokes due to large artery occlusion treated between 6-16 hours of stroke onset. Patients who meet the inclusion criteria will undergo either CT Perfusion/CTA or MR DWI/PWI/MRA studies prior to randomization. Patients who have evidence of an ICA or MCA M1 occlusion and a Target Mismatch Profile will be randomized in a 1:1 ratio to treatment with one or more DEFUSE 3 approved thrombectomy devices (only the devices listed in this protocol are approved for use in DEFUSE 3) plus standard medical therapy versus standard medical therapy alone. Patients who are enrolled, but not randomized, will receive standard therapy according to local guidelines. Baseline data, and information about early stroke therapies, will be captured for this group of patients.

Randomization of a maximum of 476 patients is planned. A novel adaptive design (see below) will identify, at interim analyses, the group with the best prospect for showing benefit from endovascular treatment, based on baseline core lesion volumes and the times since stroke onset. Interim analyses will be conducted at 200 and 340 patients, at which time the study may stop for efficacy/futility, or the inclusion criteria may be adjusted in the case of futility.

Study Sponsor and Chair: Gregory Albers, MD Stanford University

Awarded Investigators:

Protocol Director: Gregory Albers, MD - Stanford University

Protocol Director: Michael Marks, MD - Stanford University

Protocol Director: Maarten Lansberg, MD, PhD - Stanford University

Collaborators:

The National Institute of Neurological Disorders and Stroke (NINDS) U01 NS092076

NIH StrokeNet National Coordinating Center at the University of Cincinnati

NIH StrokeNet National Data Management Center at Medical University of South Carolina

FDA, IDE: # G150028

POSITIVE Trial

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Example: "Heart attack" AND

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POSITIVE Stroke Clinical Trial

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified September 2015 by Medical University of South Carolina

Sponsor:

Medical University of South Carolina

Collaborator:

Vanderbilt University

Information provided by (Responsible Party):

Medical University of South Carolina

ClinicalTrials.gov Identifier:

NCT01852201

First received: April 23, 2013

Last updated: October 1, 2015

Last verified: September 2015

[History of Changes](#)

[Full Text View](#)

[Tabular View](#)

[No Study Results Posted](#)

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[? How to Read a Study Record](#)

▶ Purpose

Primary Endpoint:

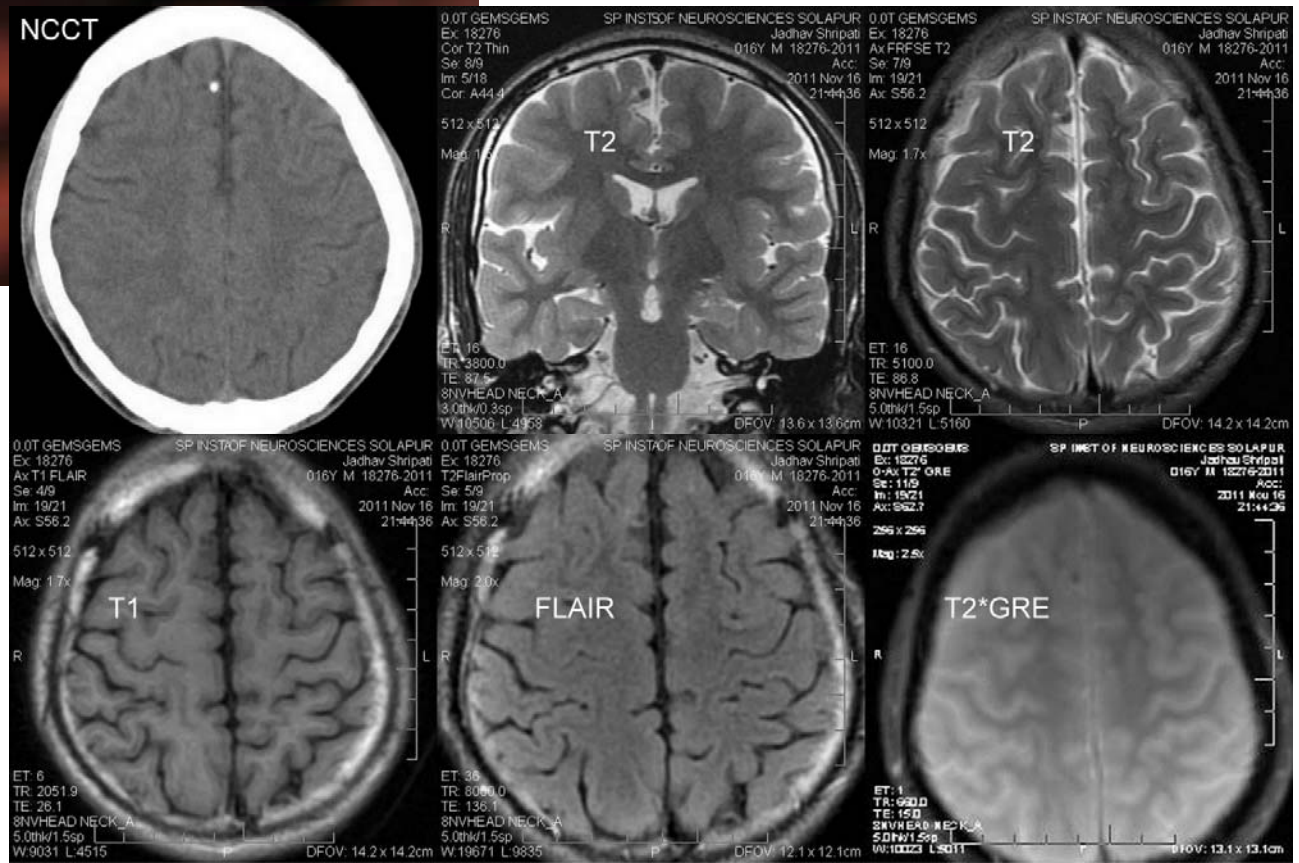
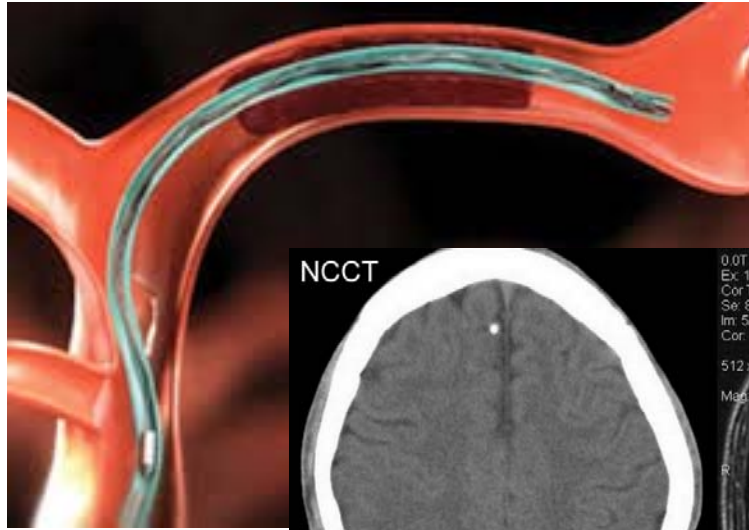
The primary objective is to show that AIS patients, ineligible for or refractory to treatment with IV-tPA, with appropriate image selection, treated with mechanical thrombectomy within 6-12 hours of symptom onset have less stroke good functional outcomes as compared to those treated with best MT with respect to endpoint defined as:

- 90-day global disability assessed via the modified Rankin score (mRS), analyzed using raw mRS scores. Statistical details can be found in section 7.2.

Secondary Endpoints:

- 90-day global disability in the 6-12 hr cohort assessed via the overall distribution of mRS
- Proportion of patients with good functional recovery for the 6-12 hr cohort as defined by mRS 0-2 at 90 days
- Mortality at 30 and 90 days
- Intracranial hemorrhage with neurological deterioration (NIHSS worsening >4) within 24 hours of randomization

Future Direction



IWITNESS Trial Steering Committee

- **Principal Investigator(s)/Co-Investigators:**

- Lee Schwamm (MGH) Overall PI
- Ona Wu (MGH): Imaging PI
- Yuko Palesch (MUSC) Lead Statistician
- Caitlyn Ellerbe (MUSC) Statistician



- **MR GROUP**

- Steve Warach (UT Austin): MR PI
- Larry Latour (NINDS)
- Shlee Song (Cedar Sinai)



- **CT GROUP**

- Andrew Barreto (UT): CT PI
- Victor Urrutia (JHM)



IWITNESS Primary aim

- Determine the safety and efficacy of IV tPA in subjects who meet the usual clinical and imaging criteria for IV tPA except that they arrive after the guideline recommended time window.
- We will test this hypothesis in subjects who are
 - last known well within 24 hours of hospital arrival,
 - have a pattern on brain tissue imaging by CT or MR consistent with hyperacute stroke,
 - can be treated within 4.5 hours of symptom discovery



IWITNESS Secondary Aims

To determine if

- MR and CT are similar in their ability to identify patients likely to respond to the IV tPA treatment
- Strokes upon awakening vs. those with unwitnessed onset later in the day are similar in their response to IV tPA treatment



Preliminary Data

- MR WITNESS
- WAKEUP STROKE
- SAIL ON



MR WITNESS Results: Baseline Characteristics

- 80 subjects were enrolled between 2011-2015 at 10 sites
- 71% symptoms discovered at wake-up, 29% at other times
- 59% white, 54% male, mean age 67
- 14% had pre-stroke mRS >1
- Median NIHSS 7.5 (IQR 4.3-13.8)
- Stroke Subtype: TOAST assigned by site PI
 - Large Artery Athero 15%, Cardioembolic 35%, Lacunar 26%, Cryptogenic 19%, Other 3%, Missing 3%



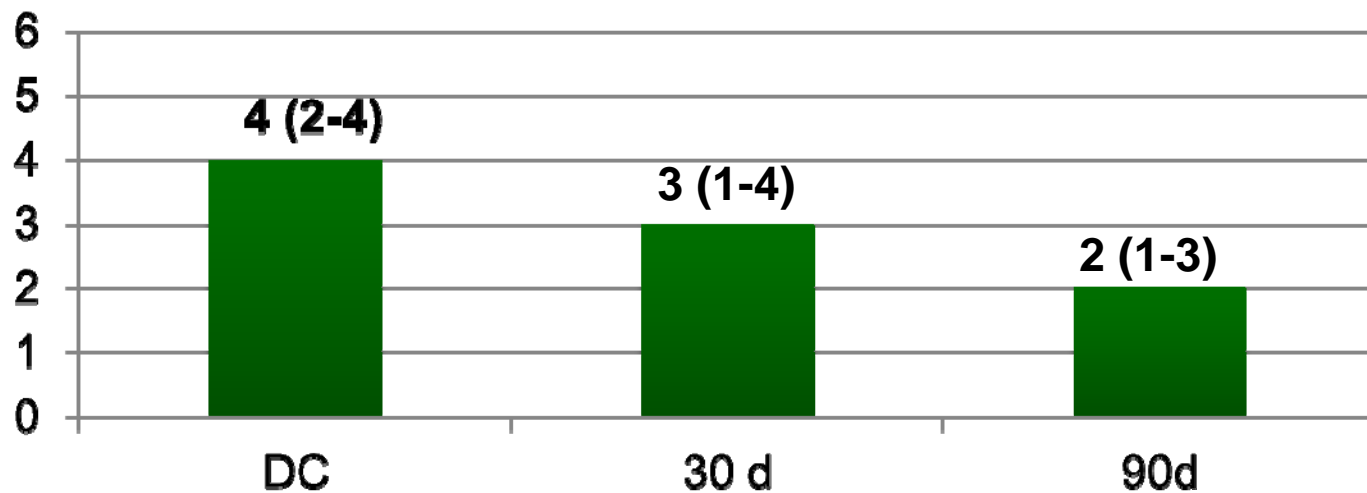
MR WITNESS Results: Primary Outcome

- tPA treatment started at median of 11.3 hr from LSW
- Time from discovery to tPA: 3.85 hr (2.83-4.25)
- Only 1 in 80 patients had sICH for a rate of 1.25%
 - This rate was not different from ECASS3
 - **1.25%** (0.03%-6.80%) vs. 5.30% (3.30%-7.80%) **p=0.15**
 - **The primary outcome of the trial was met**



MR WITNESS Secondary Outcome: Functional Outcomes at 90d

- At study completion at 90 day followup
 - Median Barthel was 95 (75-100)
 - Among the 69 subjects with pre-stroke mRS 0-1, there were 30/69 (43.5%) with mRS 0-1 at 90 d
 - Mortality 8.8%
 - Median mRS (IQR) improved over time (n=80)



WAKE-UP NCT01183533

- Prospective, multicenter, open label, single arm, safety trial
- Standard dose IV tPA administration within 3 hr of awakening with NCCT without hemorrhage, or edema $> 1/3$ MCA territory
- Primary outcome: (sICH) in the first 36 hours $<6.0\%$ by ECASS 3 and NINDS criteria
- Secondary outcomes: modified Rankin Score (mRS) at 90 d
- Age 18-80, NIHSS ≤ 25 , Pre-morbid mRS ≤ 1
- All other standard IV tPA inclusion and exclusion criteria, except time from last seen well

• Andrew D. Barreto, Christopher V. Fanale, Andrei V. Alexandrov, Kara A. Sands, Kevin C. Gaffney, Farhaan S. Vahidy, Digvijaya D. Navalkele, Chad C. Tremont, Robert K. Hamilton, Claude B. Nguyen, Amrou Sarraj, George Lopez, Nicole R. Gonzales, Vivek Misra, Tzu-Ching Wu, Sheryl Martin-Schild, James C. Grotta, Sean I. Savitz

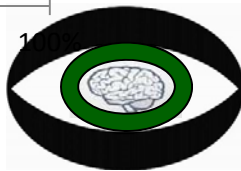
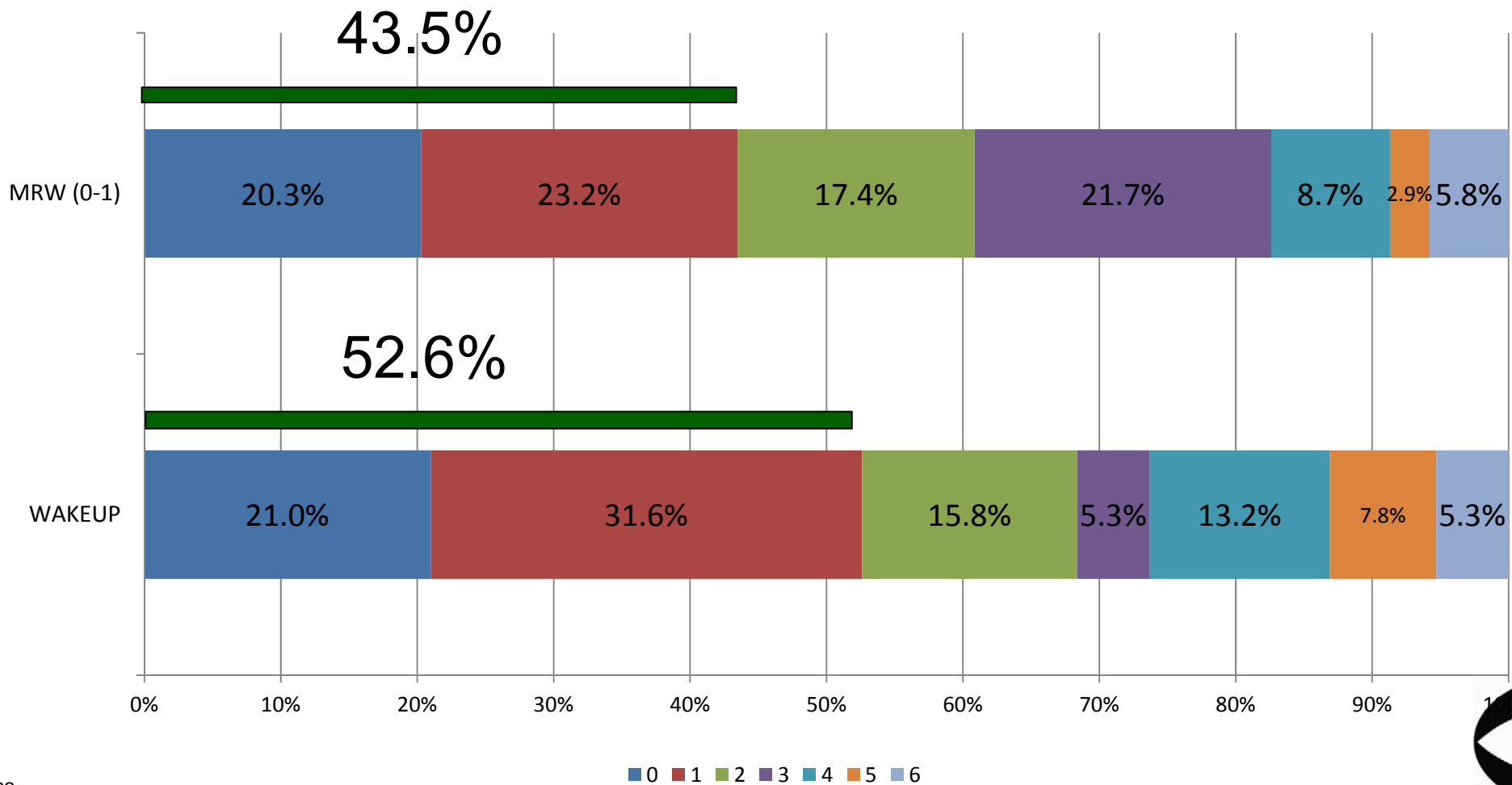


WAKE-UP Results

- 40 subjects were enrolled at 5 sites between 2010–2013
- 100% symptoms discovered at wake-up
- tPA treatment started at mean of 10.3 hr from LSW
- Time from discovery to tPA: mean 2.6 ± 0.6 hr
- mean age 60.8 ± 13.2
- Median NIHSS 6.5 (range 2-24)
- Median ASPECTS 10 (range 4-10)
- No symptomatic ICH, 5.3% mortality
- 52.6% mRS 0-1 at 90 d with 10% mimics (42.5% w/o mimics)



Results: 90 day mRS Distribution MRWITNESS vs. WAKEUP



Safety of Intravenous thromboLytics in stroke ON awakening (SAIL-ON) NCT01643902

- Prospective, two center, open label, single arm, safety trial.
- Standard dose IV tPA administration within 4.5 hours of awakening with NCCT without hemorrhage, or edema > 1/3 MCA territory
- Primary outcome: (sICH) in the first 36 hours <6.0% by ECASS 3 and NINDS criteria
- Secondary outcomes: modified Rankin Score (mRS) at 90 d
- Age 18-80, NIHSS ≥ 4 , Pre-morbid mRS ≤ 1
- All other standard IV tPA inclusion and exclusion criteria, except time from last seen well

Victor C. Urrutia, Roland Faigle, Steven R. Zeiler, Elisabeth B. Marsh, Mona Bahouth, Mario Cerdan Trevino, Jennifer Dearborn, Richard Leigh, Susan Rice, Mustapha Saheed, Peter Hill, Rafael Llinas.

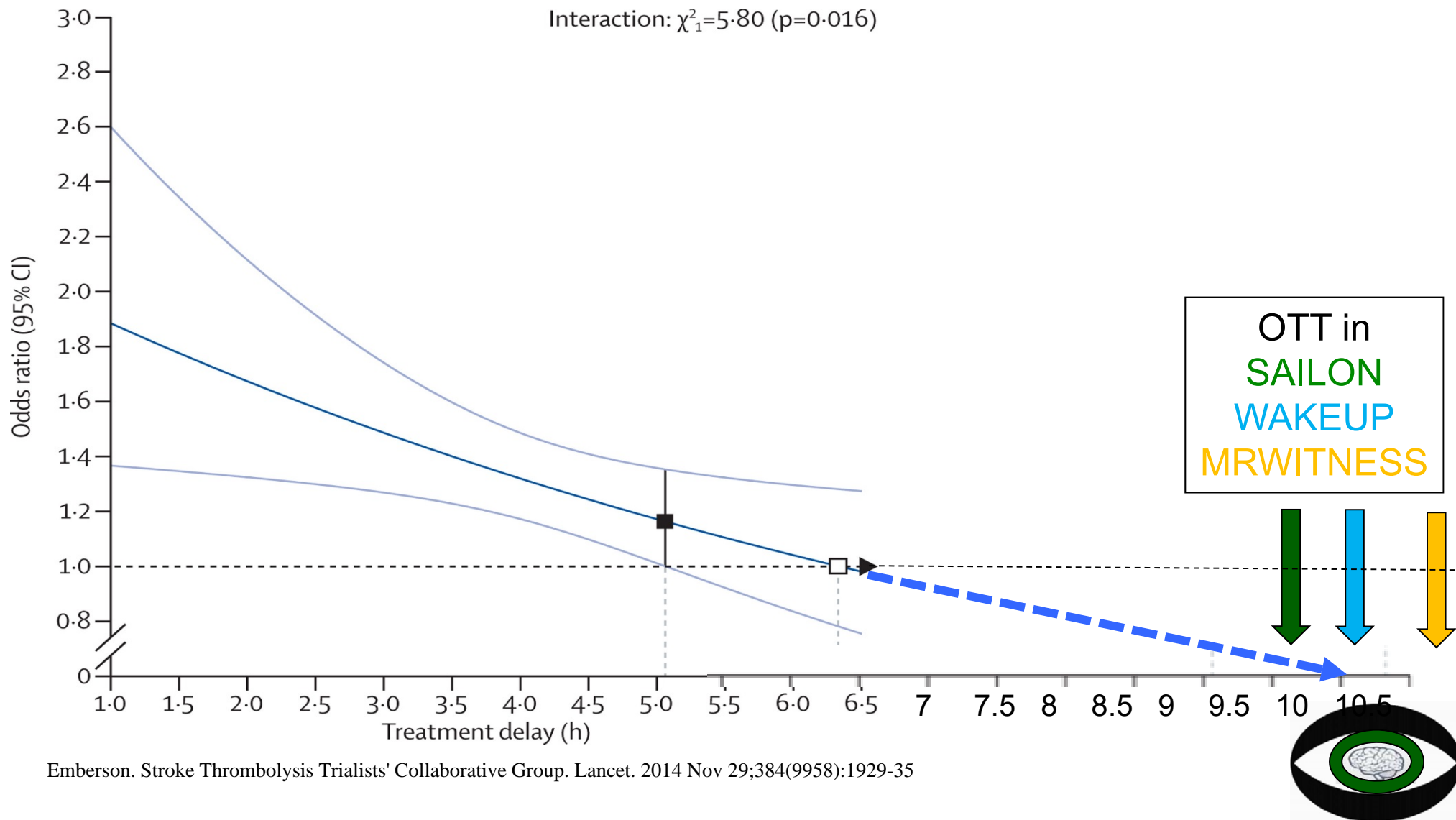


SAIL-ON Results

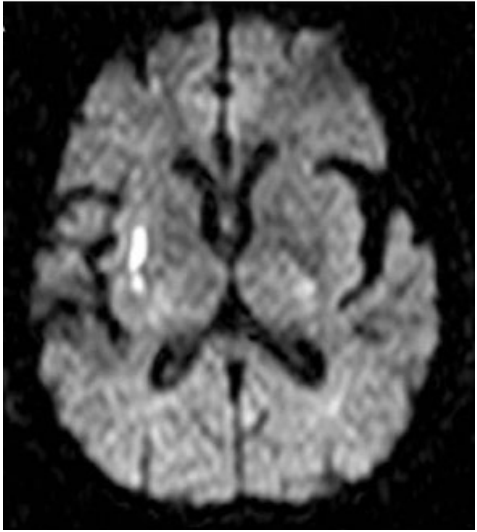
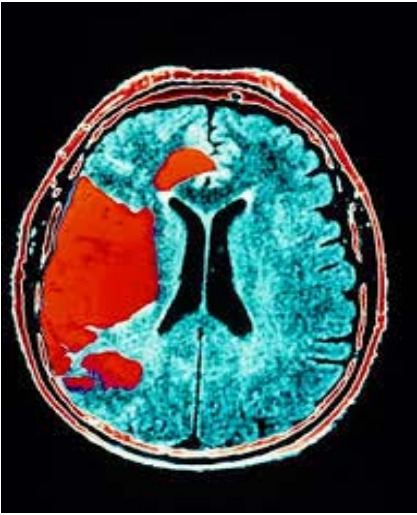
- 20 subjects were enrolled between Jan – Sep 2015
- 100% symptoms discovered at wake-up
- tPA treatment started at median of 9.6 hr from LSW
- Time from discovery to tPA: 3.41hr (1.9-4.5)
- 55% white, 65% male, mean age 65
- Median NIHSS 6 (IQR 4-11)
- No symptomatic ICH
- 70% mRS 0-1 at 90 days (median 1, range 0-5) with 5% mimics



Time Dependent Benefit of tPA on Good Outcome (mRS 0–1) Ends at 5-6.5 hr

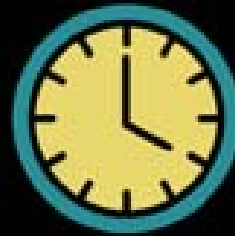


Improved Stroke Outcomes



Thank You

Extending the Treatment Window in Acute Stroke



Shlee S. Song, MD

Associate Professor, Department of Neurology

Associate Director, Comprehensive Stroke Center

Program Director, Vascular Neurology Fellowship Program

Cedars-Sinai Medical Center



CEDARS-SINAI

Department of Neurology