



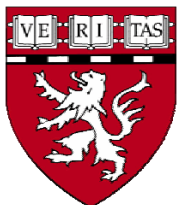
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

I-WITNESS: Imaging-Window Thrombolysis in Emergent Stroke Syndromes

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On behalf of the IWITNESS Investigators

NINDS StrokeNet Steering Committee Webinar Presentation



MASSACHUSETTS
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IWITNESS Trial Steering Committee

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- Ona Wu (MGH): Imaging PI
- **MR GROUP**
- Steve Warach (UT Austin): MR PI
- Larry Latour (NINDS)
- Shlee Song (Cedar Sinai)
- **CT GROUP**
- Andrew Barreto (UT): CT PI
- Sean Savitz (UT)
- Victor Urrutia (JHM)
- **Lead Statistician**
- Yuko Palesch (MUSC)



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



IWITNESS Study Presentation Overview

- Background
- Preliminary Clinical Data Review
- Methods
- Trial Conduct
- Clinical and Imaging Inclusion/Exclusion Criteria
- Estimating Treatment Response Rates
- Primary Outcome
- Secondary Outcomes
- Barriers to Success



Background

- Eligibility for reperfusion in ischemic stroke depends in part on the time since stroke onset, which excludes up to 25% of potential patients.
- Time is easily measured, but is a poor surrogate for infarct evolution which varies widely during the first 12 hours after witnessed strokes.
- We hypothesize that imaging of infarct evolution (i.e., a tissue-based “imaging witness” of stroke onset) is a more reliable clock than the “last known well” time alone, and will better identify patients likely to have favorable outcomes after tPA in delayed time windows.

Mackey J, Kleindorfer D, Sucharew H, et al. *Neurology* 2011;76:1662

Wroe SJ, Sandercock P, Bamford J, et al. *BMJ* 1992;304:155-7

Todo K, Moriwaki H, et al. *Cerebrovascular Dis* 2006;21:367-371

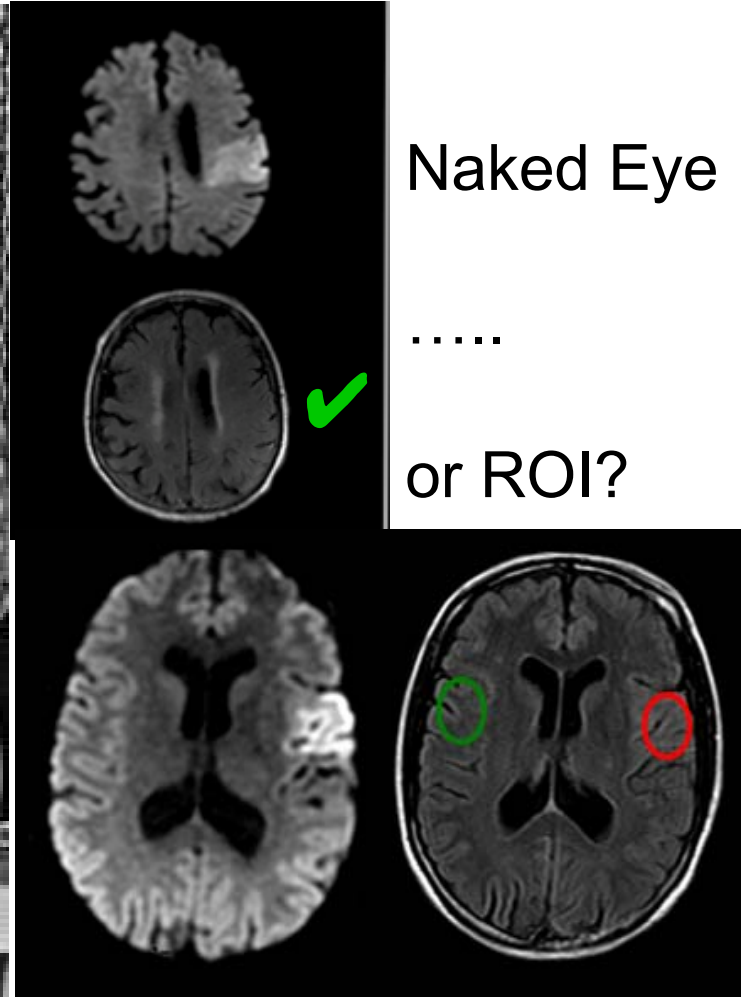
Huisa B, Liebeskind DS, Raman R, et al. *Journal of Cerebrovascular Diseases*. 2012

Manawadu D, Bodla S, Jarosz J, et al. *Stroke*. 2013;44:226-2231

Barreto AD, Martin-Schild S, Hallevi H, et al. *Stroke* 2009;40:827-832



Wake-Up vs. Unwitnessed Stroke: How Can We Tell Timing by Imaging?



Study Rationale for IWITNESS

- It is important to include both methods of imaging because, while MR is more sensitive and specific for infarction and more accurate in characterizing infarct evolution, CT is quicker, less costly and more available
- MR WITNESS, WAKEUP and SAILON studies were single arm phase 2 studies with no concurrent controls
- All 3 showed safety with low rates of sICH and a strong signal of efficacy, setting the stage for a phase 3 RCT



Preliminary Data

- MR WITNESS
- WAKEUP STROKE
- SAIL ON



MR WITNESS: Inclusion Criteria - Clinical and Imaging

INCLUSION CRITERIA – CLINICAL

- Age, **18 to 85** years inclusive
- Clinical diagnosis of acute ischemic stroke with disabling neurological deficit at treatment
- Stroke symptoms present for at least 30 minutes
- Be last known well (without new stroke symptoms) within **24 hours**
- Be able to receive IV **t-PA within 4.5 hr** from symptoms were discovered.

INCLUSION CRITERIA – IMAGING

- MRI diagnostic of acute ischemic stroke and consistent with clinical syndrome
- Brain MRI findings consistent with early stroke onset
- Treatment \leq 1 hr from completion of qualifying MRI studies



MR WITNESS:

Exclusion Criteria - Clinical and Imaging

EXCLUSION CRITERIA – CLINICAL

- Standard t-PA exclusions for patients in 3-4.5 hour window for tPA plus severe stroke (NIHSS >25), pregnancy
- Except that subjects age 80-85 and those with combination of previous stroke and diabetes mellitus were permitted

EXCLUSION CRITERIA – IMAGING

- Severe stroke by imaging (lesion volume > 1/3 MCA by visual inspection or >100 cm³ by ellipsoid formula of ABC/2)
- Non-ischemic etiology on neuroimaging
- Neuroimaging evidence of acute or chronic ICH
- Presence of 10 or more microbleeds on GRE (suggestive of amyloid)
- Any contraindication to MRI or poor quality images



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%



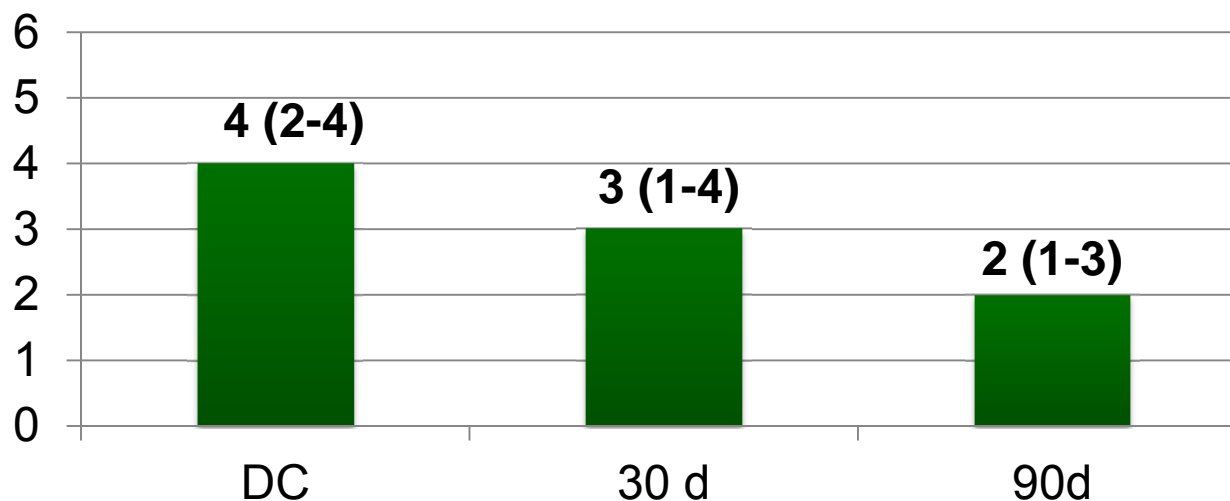
MR WITNESS Results: Primary Outcome

- 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**



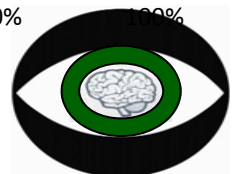
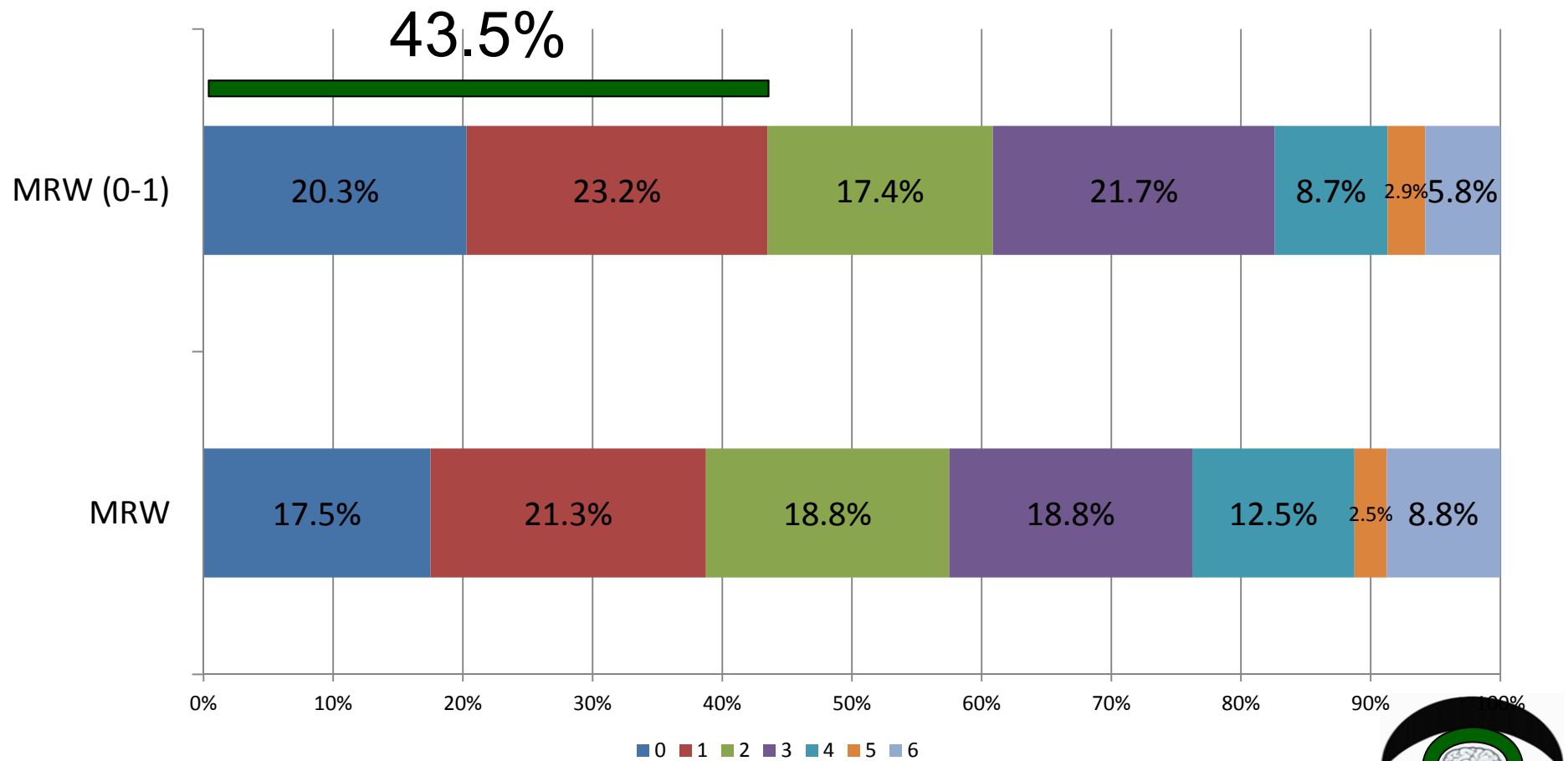
MR WITNESS Secondary Outcome: Functional Outcomes at 90d

- 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)

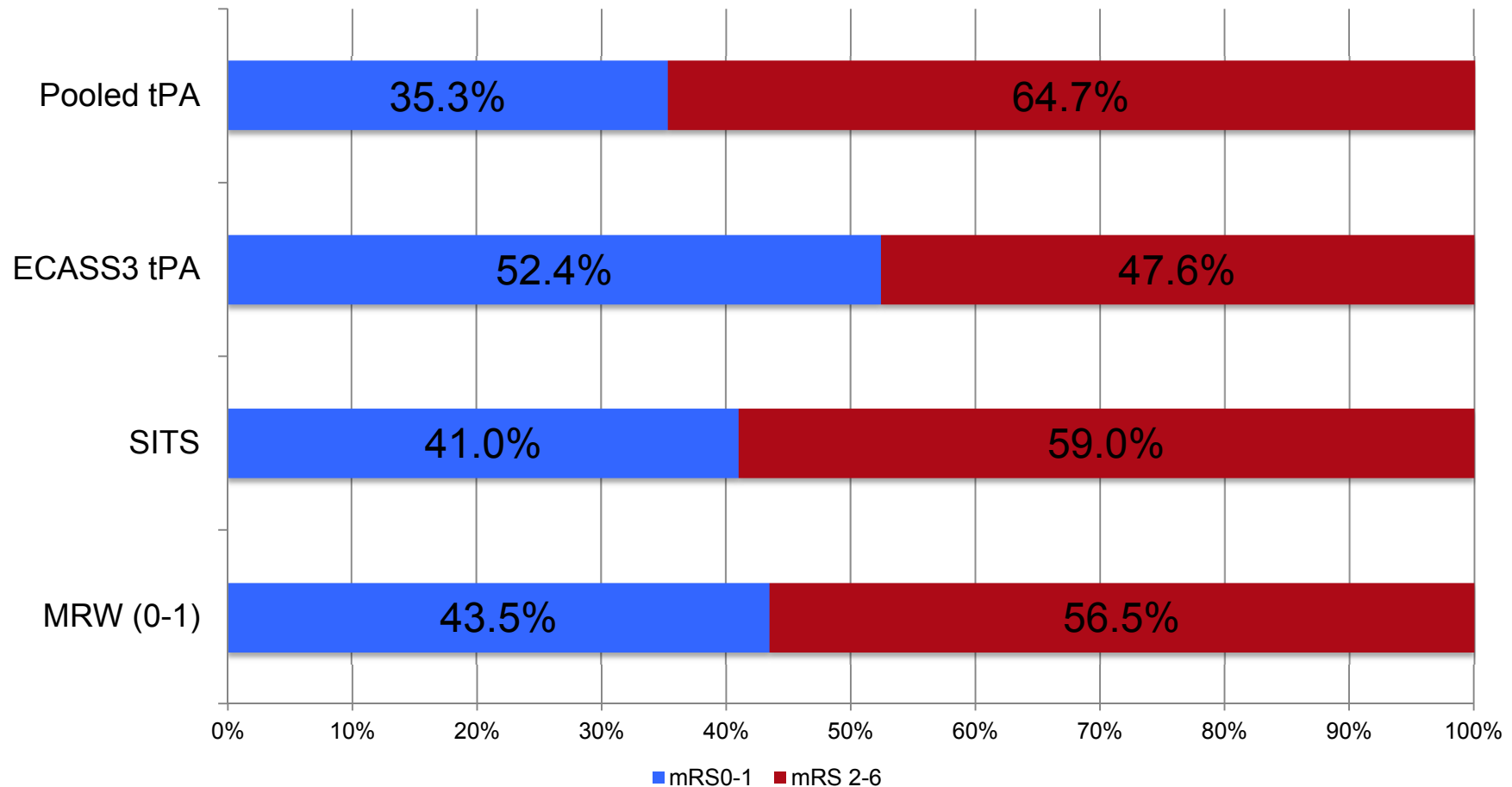


MR WITNESS: 90 day mRS Distribution

Subjects with pre-stroke mRS 0-1 (n=69) vs. all subjects (n=80)



What Is An Appropriate Comparator for Good Outcome (mRS 0-1) at 90 d?



Pooled cohort (Lancet 2014) and SITS (JAMA Neurology 2013)
treated 3-4.5 hr. Both include pts age >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

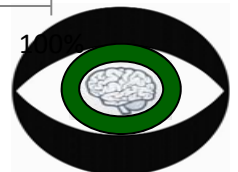
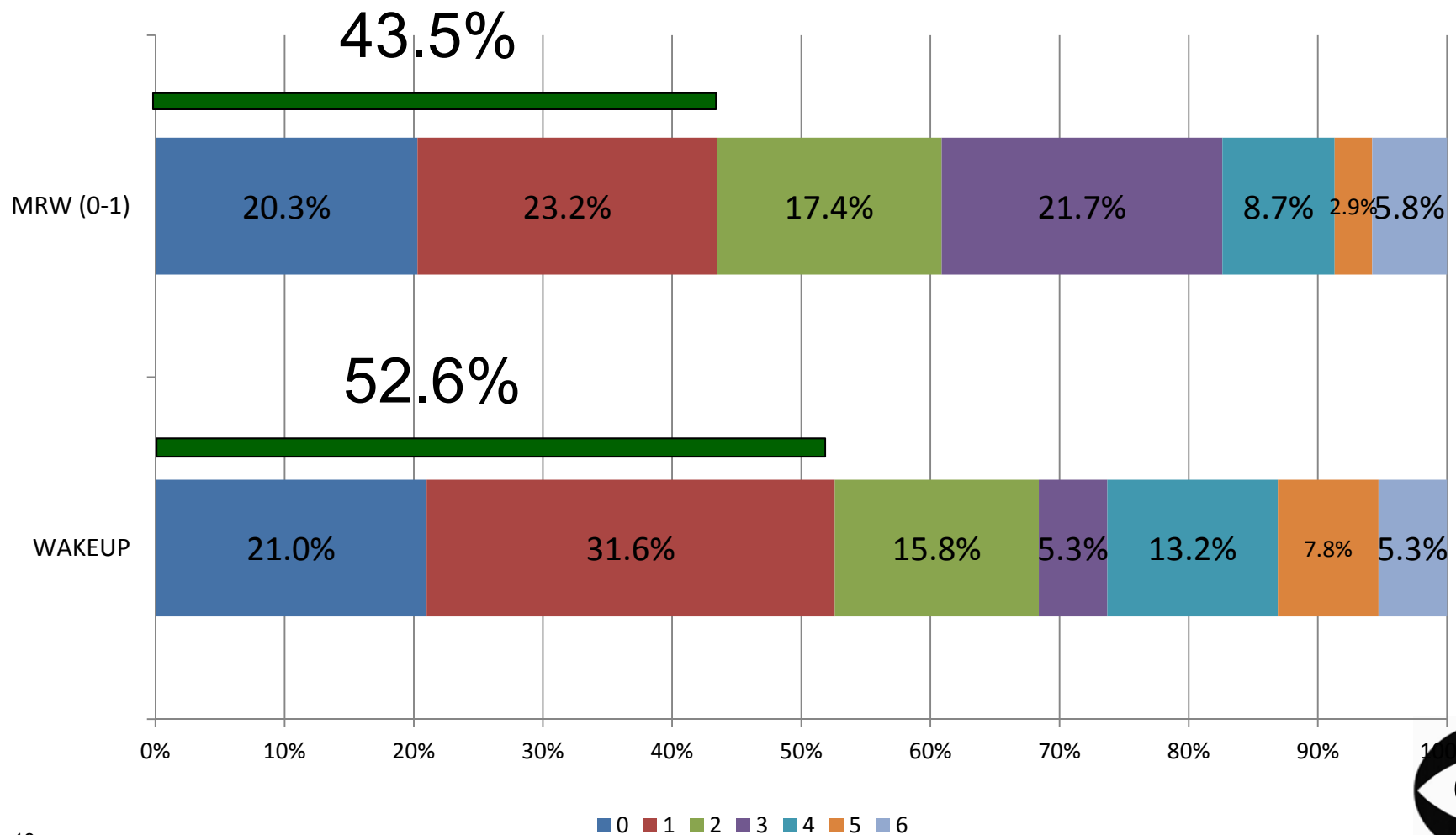


WAKE-UP Results

- 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



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- Barriers to Success



I-WITNESS Methods

- I-WITNESS will be a multi-center, phase 3, double blind RCT testing IV tPA vs. placebo in a 1:1 ratio among 1350 patients with randomization after clinical criteria and imaging in patients who have stroke of unwitnessed onset and who are >4.5 hr but less than 24 h since last seen well
- Sites will be designated as using CT or MR as their qualifying image modality, based on their routine use of imaging type to evaluate acute stroke patients in the first 24 hr after last seen well
- All subjects at the CT-designated sites will enroll based only on the CT criteria, and all subjects at the MR-designated sites will enroll based only on the MR criteria. All subjects (or their legally authorized representative) will be approached for consent if they meet the clinical eligibility criteria and have imaging evidence of an early stroke pattern without hemorrhage
- Sites must be able to perform acute CT or MR imaging, but will not be required to perform vessel or perfusion imaging. Randomized subjects must be able to receive study drug within 60 min (ideally, within 30-45 min) of the qualifying brain imaging.



I-WITNESS Trial Conduct

- All randomized subjects will have a routine CT at 24 hr for safety assessment (i.e., symptomatic intracranial hemorrhage) and admission to a stroke unit or ICU as per standard of care
- Clinical assessments (blinded to treatment assignment) of mRS and PROMIS-10 will occur at enrollment, 24 hr, discharge/day 5, 30 d, and 90 d
- To minimize the risk of harm, subjects with NIHSS >25 will be excluded. To minimize the proportion of stroke mimics, patients with very mild deficits suggestive of non-ischemic causes will be excluded



I-WITNESS Clinical Inclusion Criteria

- Age \geq 18
- Diagnosis of acute stroke w/symptoms present for at least 30 minutes
- Impairment of language, motor function, cognition, and/or gaze, vision or neglect which the investigator judges likely to produce lasting disability at 3 months post stroke
- Last known well (LKW) \leq 24 hours of start of study treatment
- Able to receive study drug within 60 min of qualifying imaging study and within 4.5 hr of symptom discovery
- Able to obtain written informed consent (by the subject or LAR)



I-WITNESS Clinical Exclusion Criteria

- Symptoms improved to a non-disabling level before start of study drug
- **Patients with pure sensory symptoms or acute confusional states strongly suggestive of an alternative symptom etiology or “stroke mimic” (e.g., migraine, encephalopathy)**
- Severe stroke as defined by NIHSS > 25, Pre-stroke mRS >1
- Blood glucose concentration <50 mg/dL
- Life expectancy < 1 year, severe co-morbid illness or comfort measures only
- Women pregnant, lactating or having a positive or indeterminate pregnancy test
- Recent acute ST elevation myocardial infarction (STEMI) involving the left anterior myocardium (within previous 3 months)
- Seizure at onset if residual neurological impairments are felt due to seizure not stroke
- Factors that increase the risk of symptomatic hemorrhage per AHA guidelines
 - (see the concept proposal for full list)



I-WITNESS Imaging Criteria

CT Based Imaging Inclusion Criteria:

- Brain imaging findings by non-contrast CT that are consistent with acute ischemic stroke

CT Based Imaging Exclusion Criteria:

- Multi-lobar infarction (hypodensity $>1/3$ cerebral hemisphere or lesion volume $>70\text{cc}$ by visual inspection or the ellipsoid estimation formula of $ABC/2$)
- Markedly hypodense lesion that is not consistent with early (<3.5 hr) acute infarction
- ASPECTS <7 on non-contrast CT
- Non-ischemic etiology demonstrated by neuroimaging
- Evidence of intracranial hemorrhage



I-WITNESS Imaging Criteria

MR Based Imaging Inclusion Criteria:

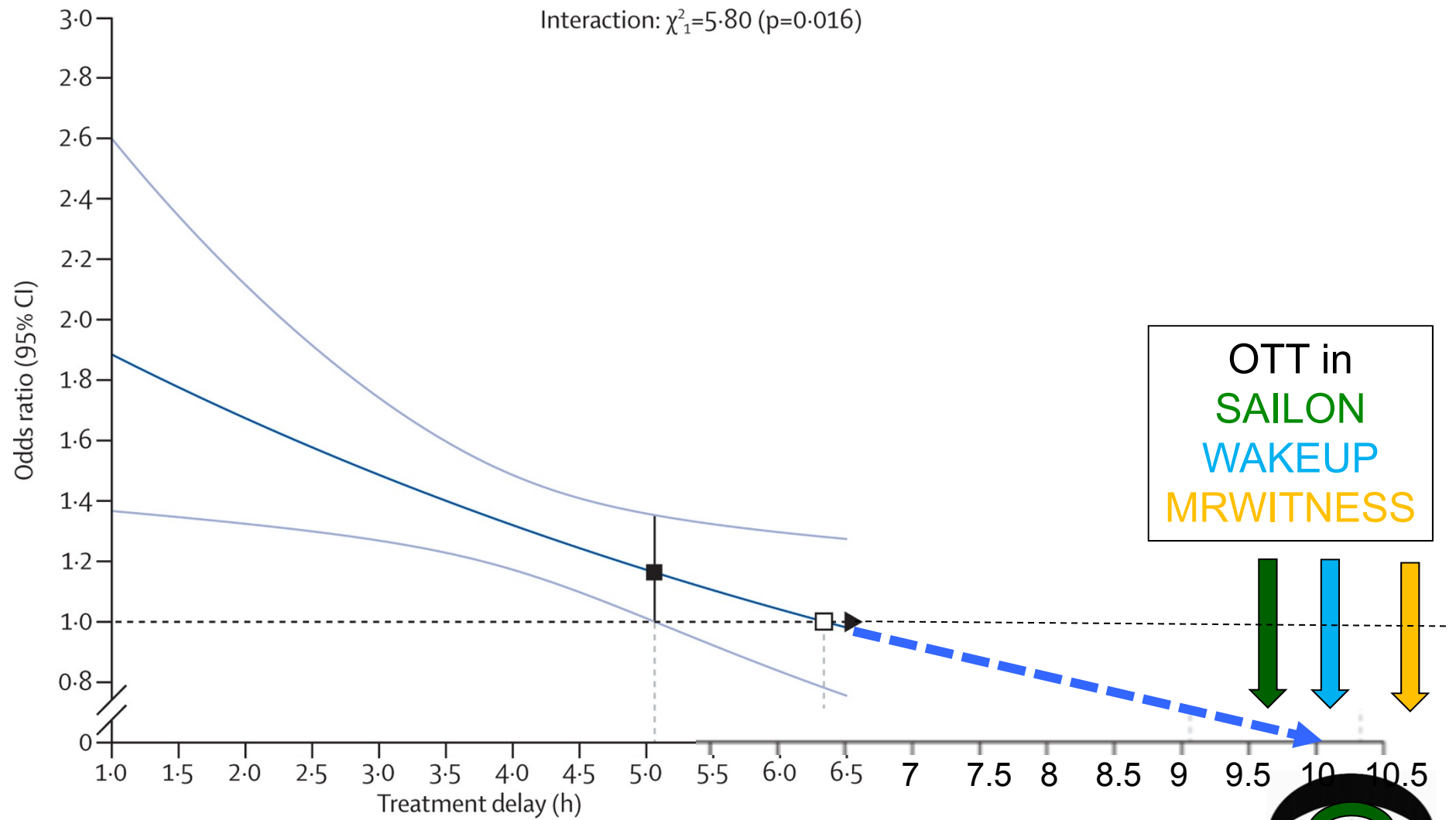
- A DWI hyperintense, ADC hypointense lesion consistent with acute ischemic stroke and a FLAIR image that is of sufficient quality for evaluation
- FLAIR MRI is negative for lesions or if there is a lesion, the FLAIR lesion signal intensity ratio (SIR) is ≤ 1.15 with respect to normal appearing contralateral tissue.

MR Based Imaging Exclusion Criteria:

- Evidence of intracranial hemorrhage, including >10 chronic microbleeds on GRE or superficial siderosis appearing in a pattern suggestive of amyloid angiopathy



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



Estimating The Response Rates in IWITNESS

- There are no available data to predict with certainty the expected response rate in treated vs. control subjects in IWITNESS
- We can estimate a **placebo** response rate range of 30-45% based on the rates observed in the entire pooled tPA trials 3-4.5 hr (30%) and ECASS3 alone (45%).
- A retrospective MGH analysis of consecutive cases (269 patients late arriving* patients who did not get tPA vs. 256 patients tPA \leq 4.5 hr cases) showed lower rates of home despite lower NIHSS (30.5% vs. 39.1%, p 0.04).

*arrived \geq 4.5 but $<$ 24 h from last known well, $<$ 4.5 h from symptom discovery, did not receive on-label IV tPA or thrombectomy, had NIHSS \leq 25, blood glucose 50-400 mg/dL and no current oral anticoagulant treatment



I-WITNESS Primary Outcome: 90 d mRS

- An intention-to-treat efficacy analysis will be conducted on the ordinal mRS using the proportional odds model, with 1 interim analysis for futility at 50% enrollment, and 3 for safety as sICH rates compared with ECASS3 (2.4%, 95%CI 1.0%-4.0%)
- A conservative maximum sample size of 1350 subjects is estimated based on one-sided alpha of 0.025, power of 80%, a response rate of 48% tPA vs. 40% placebo achieving a mRS 0-1 at 90 d with 3% anticipated non-compliance (including lost-to-follow-up, withdrawal, missing 90 d mRS)
- 120 sites (60 CT, 60 MR) at rate of 0.25 cases/month will complete enrollment in ~3.7 yr



I-WITNESS Secondary Analyses

- Safety as measured by the difference in the rates of sICH between IV tPA vs. placebo subjects
- Efficacy as measured by
 - Proportion of subjects with mRS 0-1 or mRS 0-2
 - Multivariable adjusted analysis of the primary efficacy outcome that includes pre-specified covariates known to effect outcome
- Differences in efficacy vs. safety in MRI vs. CT cases, and in wake-up vs. unwitnessed cases
- Correlation between mRS and the PROMIS-10 scores at 90 d analyzed by generalized linear models.



Barriers to Success

- Endovascular: We do not intend to enroll patients for whom acute endovascular treatment is planned, especially beyond 6 hours from onset. There is synergy for screening and virtually no enrollment overlap with DEFUSE3/DAWN
- We do not require large DWI/PWI mismatch for treatment effect so we will seek to enroll subjects who “screen fail” for large mismatch. We are interested in collecting PWI data when available
- Mimics: we will seek to minimize stroke mimics as they are non-informative subjects. We will monitor TOAST etiology and mimic rates closely with prompt feedback to sites



Thank You For Your Attention

- We hope you will be excited to join us in the IWITNESS trial to test the safety and efficacy of IV tPA in patients with stroke of unwitnessed onset selected by imaging criteria

