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Wake Up You're Having A Stroke

Evaluation, Considerations, and Trials for the Unknown Stroke Onset

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IT'S HOW MEDICINE SHOULD BE®

Faculty Disclosure

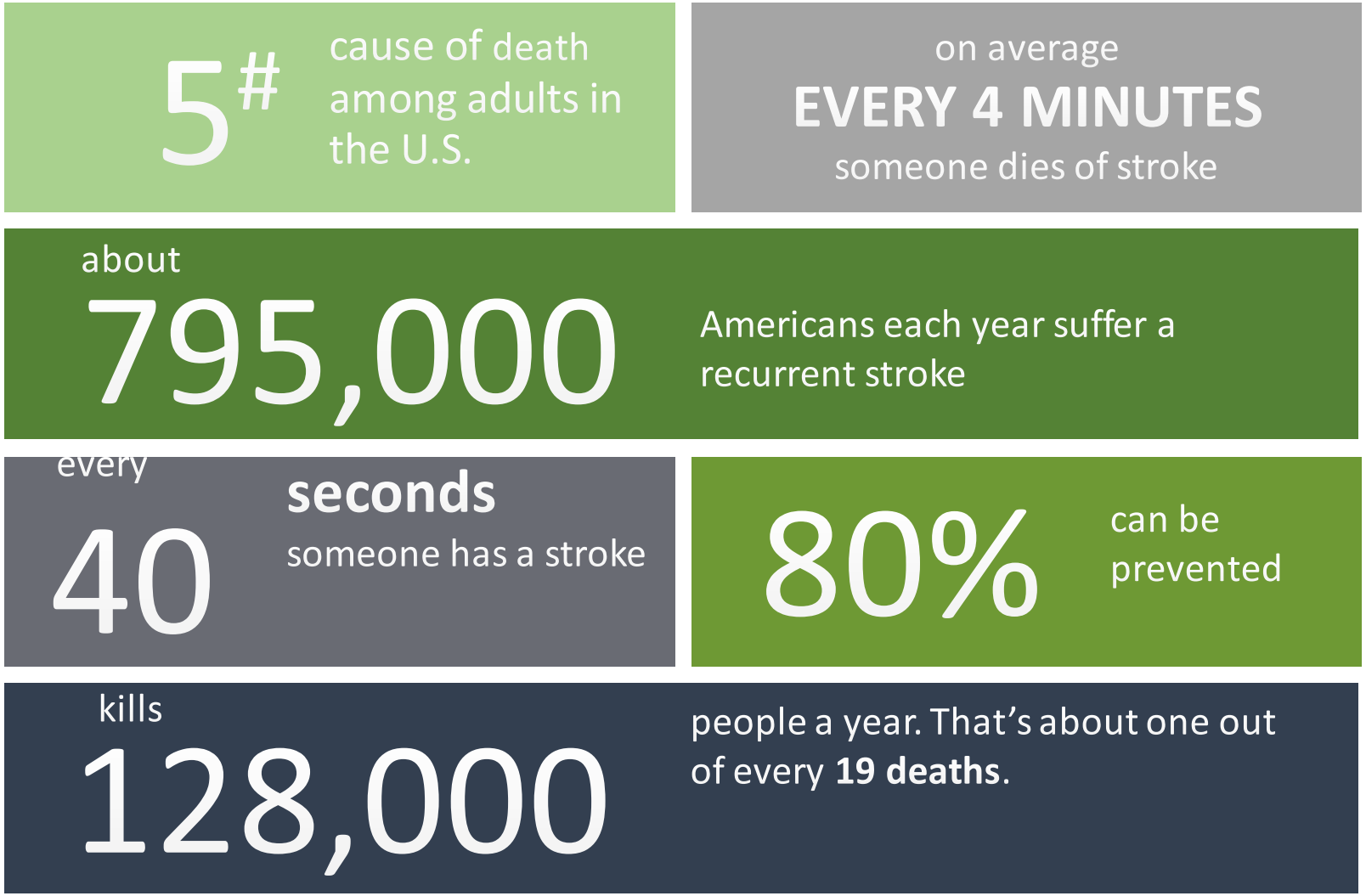
Kiffon M. Keigher

- Conflict of interests: *Cure4Stroke Board Member*
- Employer: *Rush University Medical Center*
- Sponsorship / commercial support: *None*

Objectives

- Evaluate current standard of care treatment for AIS patients
- Describe wake up stroke
- Analyze criteria evaluated for AIS patients with wake up stroke presentation
- Identify at least 2 clinical trials

What You Need to Know About Stroke



Statistics from the American Heart Association/American Stroke Association, World Health Organization and Centers for Disease Control and Prevention. 1/13DS6139

Strokes in Chicago

What Is the Impact Of Stroke on Society

COST OF STROKE

$34 Billion Annually

Statistics from the American Heart Association/American Stroke Association, World Health Organization and Centers for Disease Control and Prevention.

Stroke is the leading cause of disability

Stroke is the leading cause of **PREVENTABLE** disability

Standard of Care

- IV tPA Standard of Care—First Line Therapy
- NINDS: 2 Part Study Design (1991-1994) and (1992-1994)
  - Placebo-controlled trial of intravenous Activase versus placebo in patients with AIS treated within 3 hours of stroke symptom onset.
- Expanded indications up to 4.5 hours since 2009

No other standard of care treatment for over 15 years!

Until 2015…..

Why Does This Matter?

Limitations of IV tPA

-Most patients present outside the 3-4.5 hour window

-IV tPA does not restore blood flow in subgroup of patients (Large Vessel Occlusions-LVO)

Utilization of IV tPA VERY LOW

Nationwide ONLY about 3% of eligible patients receive IV tPA

Early Trials

- SYNTHESIS, IMS-III, MR RESCUE
  - ✓IV thrombolysis for all
  - ✓None showed a benefit of IV tPA over endovascular thrombectomy
  - ✓All used first generation devices (Merci device) and/or IA thrombolysis
  - ✓No benefit for patients treated within 8 hours even if multimodal imaging utilized
  - ✓Achieved recanalization rates of 25%-41%

Endovascular Trials: New Stroke Treatment Options

5 Randomized Controlled Trial's:

-Favorable 90 day Outcomes

-Improved Recanalization rates

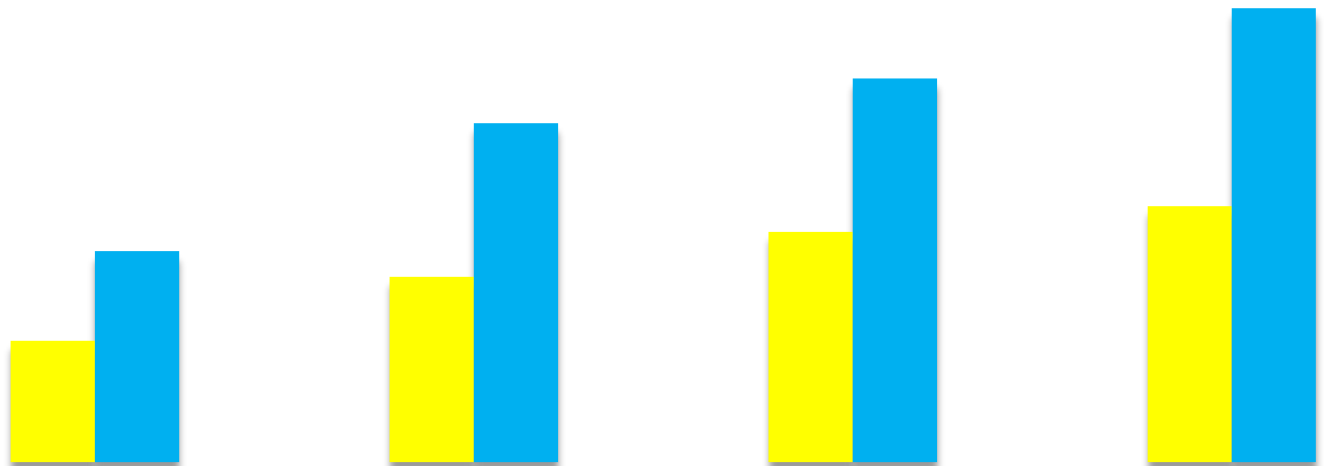
- Less Than 6 Hours to Treatment
- Less Than 8 Hours & up to 12 hours to Treatment

Endovascular Stroke Trials: Key Points

- MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT
  - ✓Almost all patients received IV tPA
  - ✓Used all new generation devices (Trevo and Solitaire stent-retrievers and aspiration systems)
  - ✓Achieved recanalization rates of 59%-88%
    - ✓TICI 2b and TICI 3 scores
  - ✓mRS outcome at 90 days improved
  - ✓No statistical significance in sICH rates

FUNCTIONAL OUTCOMES OVERVIEW

NEW RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY



Endovascular	33%	53%	60%	71%
Control	19%	29%	36%	40%

Taken from MR CLEAN; ESCAPE; EXTEND-IA; SWIFT PRIME, 2015

2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

- MR CLEAN: enrolled up to 6 hours
- ESCAPE: enrolled up to 8-12 hours
- EXTEND: treatment up to 6 hours
- SWIFT PRIME: treatment up to 6 hours
- REVASCAT: enrolled up to 8 hours

Wake Up!
TIME TO GO

The phenomenon of waking up with neurological symptoms consistent with an ischemic stroke with a time of last known well when you went to bed……

THE UNKNOWN TIME

Wake Up Strokes

- Time of stroke symptom onset unknown
- Majority of patients excluded from IV reperfusion therapy AND IA thrombectomy intervention
- No treatment option available

- Wake-Up Strokes approximately 20% of all strokes

Wake-Up Strokes

1 in 5 of all strokes

Older in Age

Higher NIHSS

Wake Up Stroke Phenomenon

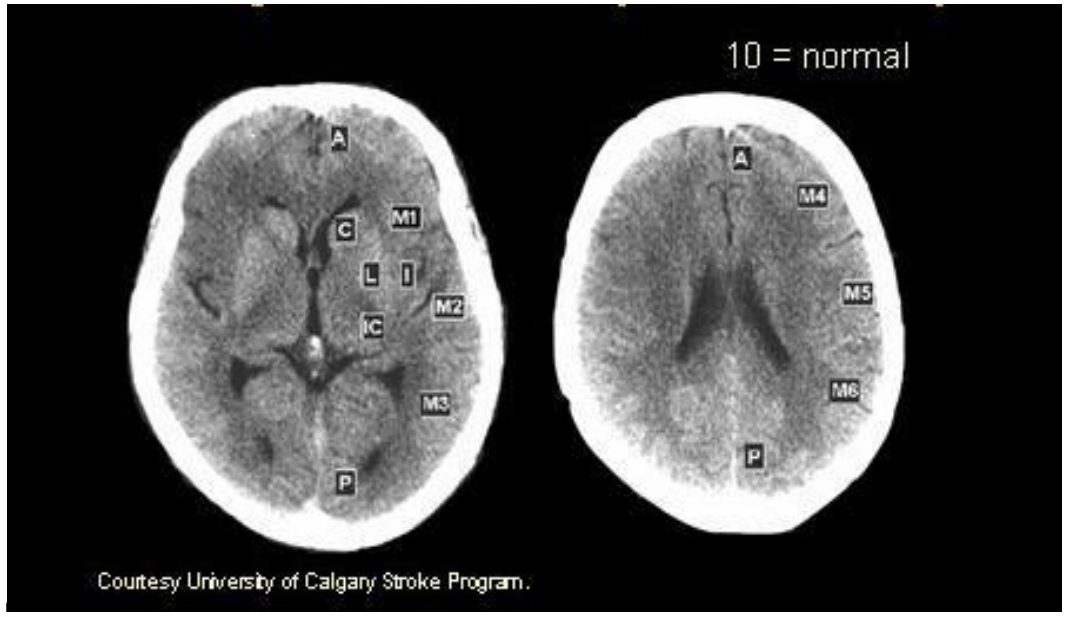
- Hypothesized Pathophysiology
  - ✓Sleep Disorders with or without PFO
  - ✓Overnight changes of autonomic tone with increased morning surges in blood pressure
  - ✓Endothelial dysfunction
  - ✓Elevation of platelet aggregation in morning
  - ✓Fluctuating prothrombotic/fibrinolytic levels

Rubin, MN., Barrett, KM, *Neurohospitalist,* 2015

Selection is Everything for Treatment Options

Time Dependent Criteria

ASPECTS (Alberta Stroke Program Early CT Score)

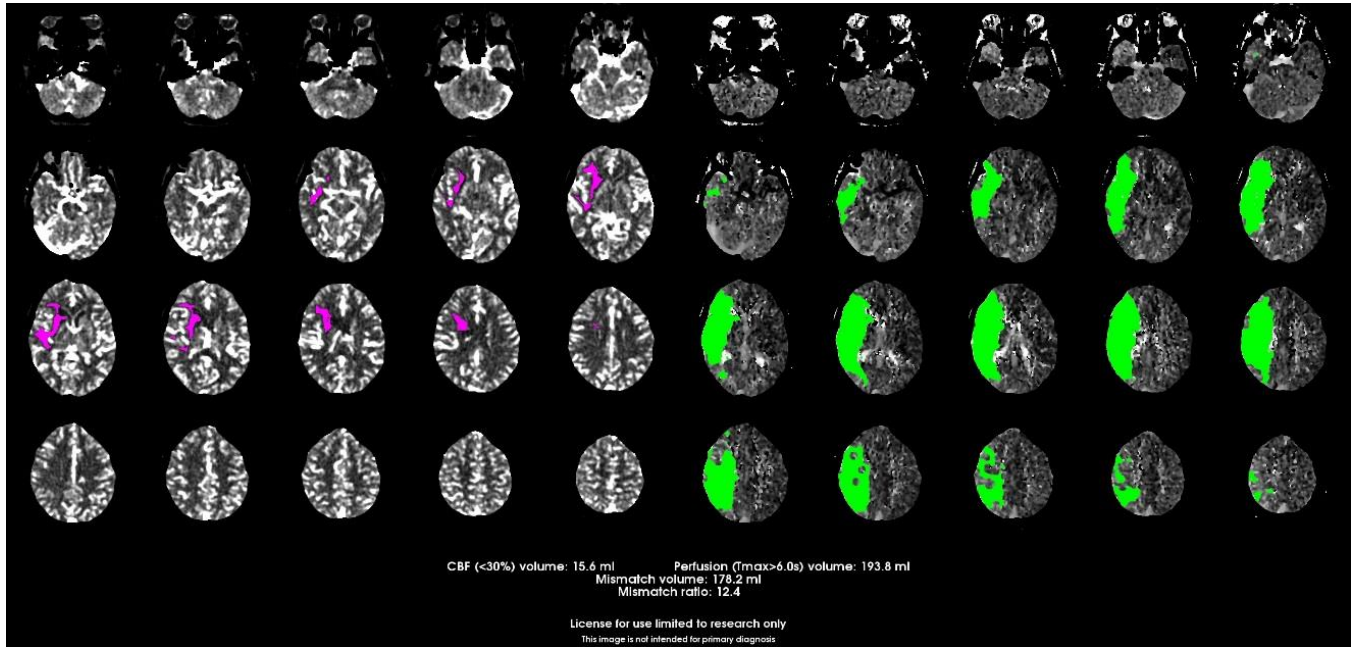


Imaging/Collateral Dependent Criteria

Selection for Eligible IA Thrombectomy

Likely to Benefit

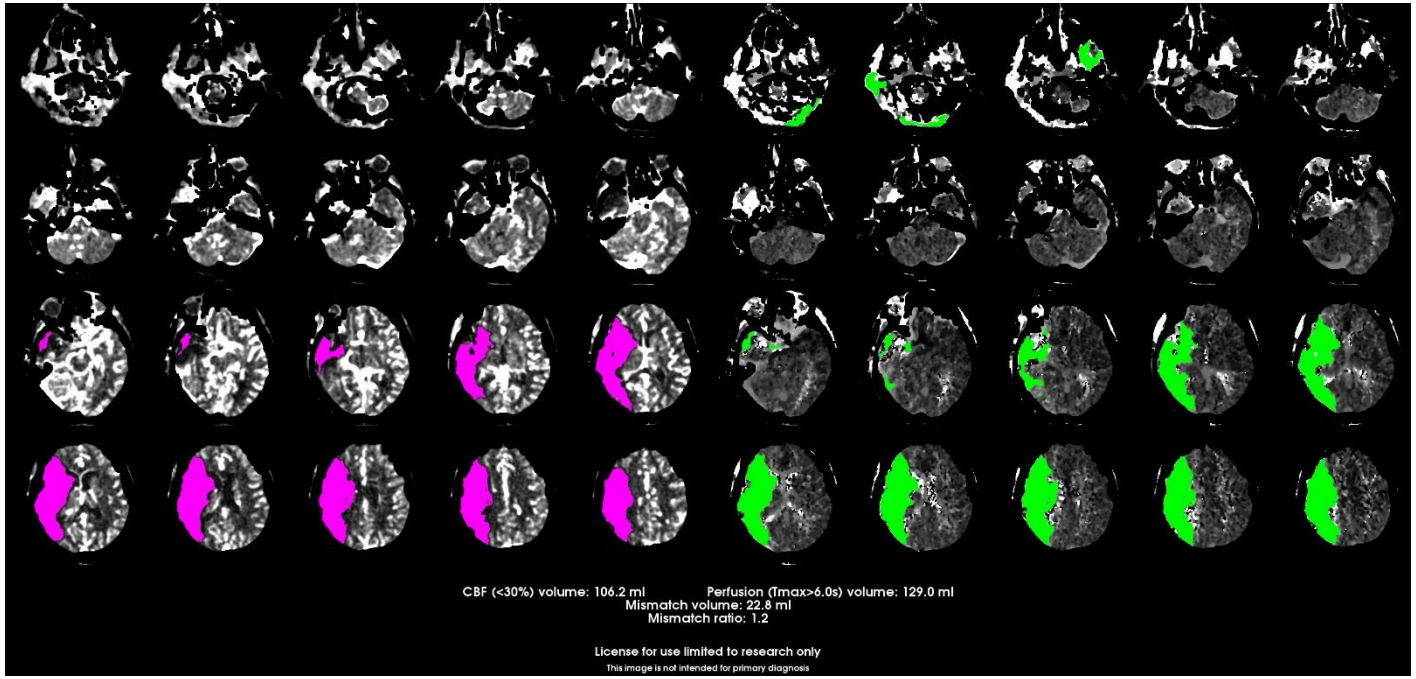
- SMALL CORE
- LARGE PENUMBRA
- MISMATCH



Selection for Eligible IA Thrombectomy

Not Likely To Benefit

- LARGE CORE
- SMALL PENUMBRA
- NO MISMATCH



Considerations: Time and Imaging

- Brain is not a clock
- Studies indicate patients with preserved brain tissue may have favorable outcomes despite time of onset
- Evaluation for this:
  - ✓CT: perfusion studies
  - ✓MRI: rapid imaging sequence looking at clot burden
- ASPECTS Score
  - ✓Scale of 0-10 (10=Perfect brain, 0=Dead brain), Goal Good ASPECTS $\geq$6
  - ✓HIGH ASPECTS = Better Collaterals
  - ✓LOW ASPECTS=POOR Collaterals

Evaluation of Wake Up Stroke

- Recommendations:
  - ✓Clinical History
    - Good HPI, PMH/PSH, pre-stroke Modified Rankin Score (mRS), anticoagulation/antiplatelet therapies
  - ✓NIHSS
  - ✓CT Head
  - ✓Labs (per AHA/ASA guidelines)
  - ✓Multiparametric MRI or CT (MR or CT angiogram and perfusion studies)

Treatment of Wake Up Stroke

- No treatment therapy can be offered at this time based on current evidence
- Enrollment in clinical trial is strongly encouraged for the appropriate patient

Recent and Current Trials

- **WAKE-UP Study (currently enrolling)**
  - 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. Objective of WAKE-UP is to prove efficacy and safety of MRI-based intravenous thrombolysis with Alteplase in patients waking up with stroke symptoms or patients with otherwise unknown symptom onset.
- **DEFUSE 2 (closed)**
  - Multi-center pilot study to determine if cerebral perfusion imaging can help identify which patients, who are ineligible for intravenous tissue plasminogen activator (iv tPA) therapy or have failed iv tPA therapy, are most likely to benefit from an endovascular clot removal procedure up to 12 hours post onset
- **DEFUSE 3 (currently recruiting)**
  - 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
- **MR WITNESS (ongoing, no longer recruiting)**
  - Study to find out if Activase ® can safely be given to people with an acute ischemic stroke when their stroke onset was not witnessed making them ineligible for standard thrombolytic (clot busting) therapy.
  - The purpose of this study is to: 1) see if it is safe to give intravenous (IV) rt-PA to people with unwitnessed stroke but with MRI evidence of early ischemic stroke, 2) see if rt-PA is effective if given to people who are selected for treatment based on MRI evidence of an early stroke, and 3) get information about this new MRI diagnostic methods for guiding stroke treatment.
- **DAWN (currently enrolling)** *Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention*
  - Purpose of the study is to evaluate the hypothesis that Trevo thrombectomy plus medical management leads to superior clinical outcomes at 90 days as compared to medical management alone in appropriately selected subjects experiencing an acute ischemic stroke when treatment is initiated within 6-24 hours after last seen well
- **THAWS, SAIL-ON, WASSABI, ….**

DAWN™ IDE Clinical Trial

DWI or CTP
Assessment with
Clinical Mismatch
in the Triage of
Wake-Up and Late
Presenting Strokes
Undergoing
Neurointervention

Objective

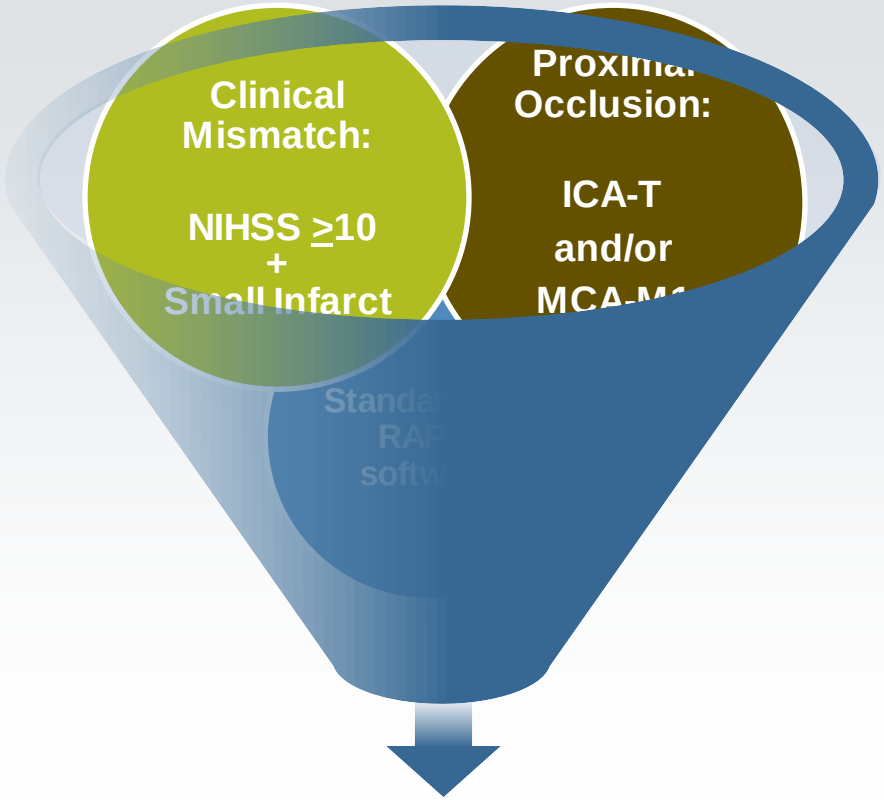
To demonstrate superior *clinical outcomes* at 90 days with Trevo plus medical management compared to medical management alone in *appropriately selected* patients *treated 6–24 hours* after last seen well

Impact

- Provide new options for an unmet need in wake-up and late presenting strokes
- Expand the indication for Trevo Retriever devices

DAWN™ Clinical Trial

Goal: To identify the Target Mismatch Patient in the 6-24h Window (including Wake-Up Strokes)



Randomization
Balanced re: CIM subgroup, time and occlusion location

Stroke Systems of Care: A Teamwork Approach

Increased collaboration focused on improving outcomes

Stroke Team…layers of team players and processes

- Collaborative
- Efficient
- Knowledgeable
- Intuitive
- Resourceful
- Flexible
- Detailed
- Productivity
- Algorithm and Design
- Synergistic
- Combined Effort
- Collective Care
- Knowledge Sharing

How Thick Is the Layer?

- Community Members, EMS Personnel, Emergency Room, ICU, Stroke Teams, Rehabilitation Specialists…
- Hub & Spoke Models of Care
- Drip & Ship
- Telestroke Connected….

Layers and Players Must Communicate and Work With Each Other

Gallup Research Poll in 2013: Employee Engagement in Workflow Contribution

18% ACTIVELY DISENGAGED

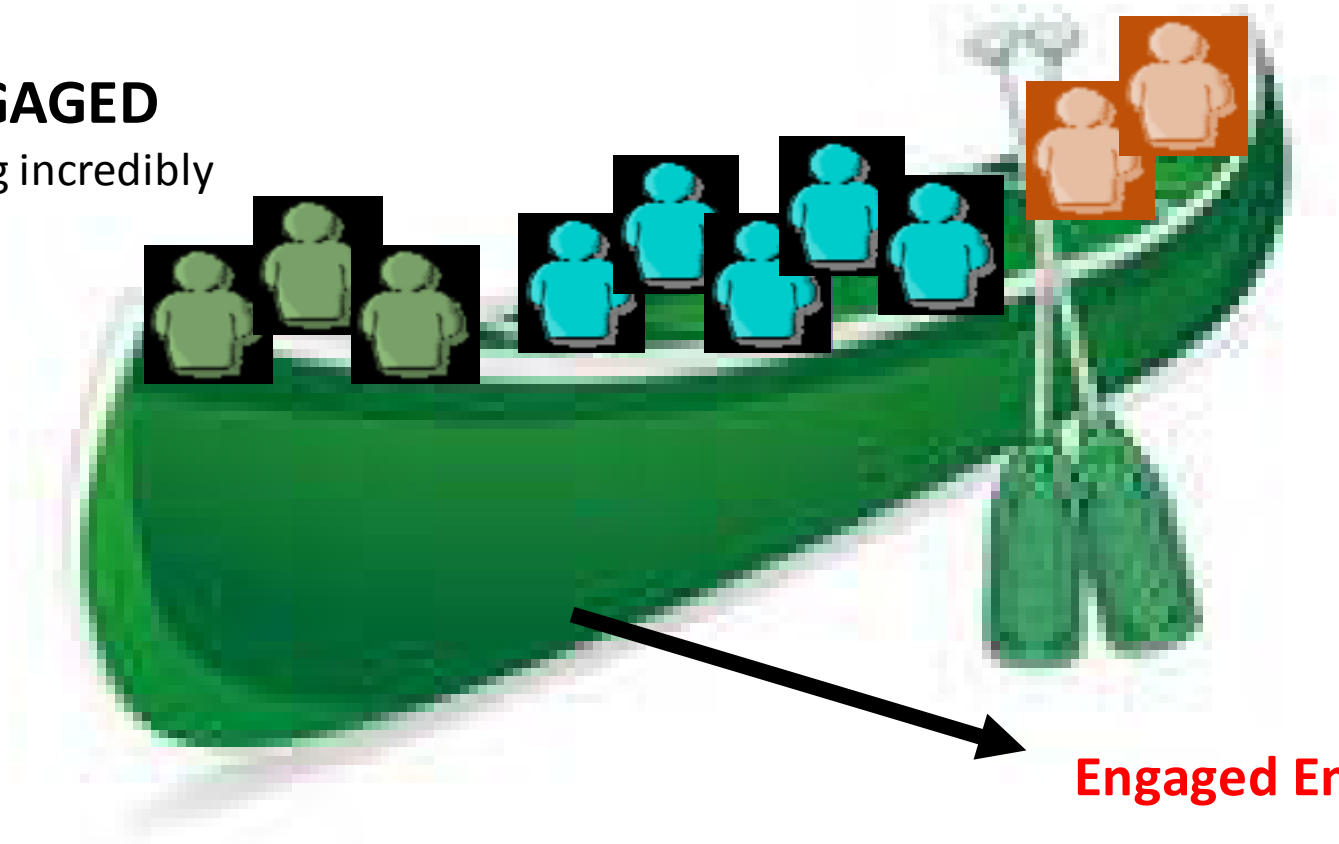
2 of 10 are actively trying to sink the boat

52% DISENGAGED

5 of 10 workers are watching the view

30% ENGAGED

3 of 10 are rowing incredibly hard



Engaged Employees=High Performance

Gallup poll, 2013
Pelletier, M. 2015

Criticality of Teamwork

- Employee Engagement translates to High Performance
- Stroke Patient High Performance Workflow translates to:

  - ✓ Efficient Care
  - ✓ Improved Patient Outcomes (mRS at 90 days)
  - ✓ Decreased Mortality
  - ✓ Decreased Disability
  - ✓ Decreased Society Cost Burden
  - ✓ Increased Number of Patients Returning Home

Final Thoughts

- IV tPA still first line treatment option for acute stroke within 3-4.5 hours
- IA Mechanical Thrombectomy also standard of care for LVO strokes within 6 hours
- Wake Up Strokes outside of the 6 hour window SHOULD be evaluated for POSSIBLE treatment
- Consider Enrollment or Transfer of Patient to Site offering Clinical Trial Enrollment for Wake Up Stroke therapies
- More to come on this topic….

THANK YOU

CURE 4 STROKE