DAWN TRIAL

# DAWN STUDY- MAIN RESULTS

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

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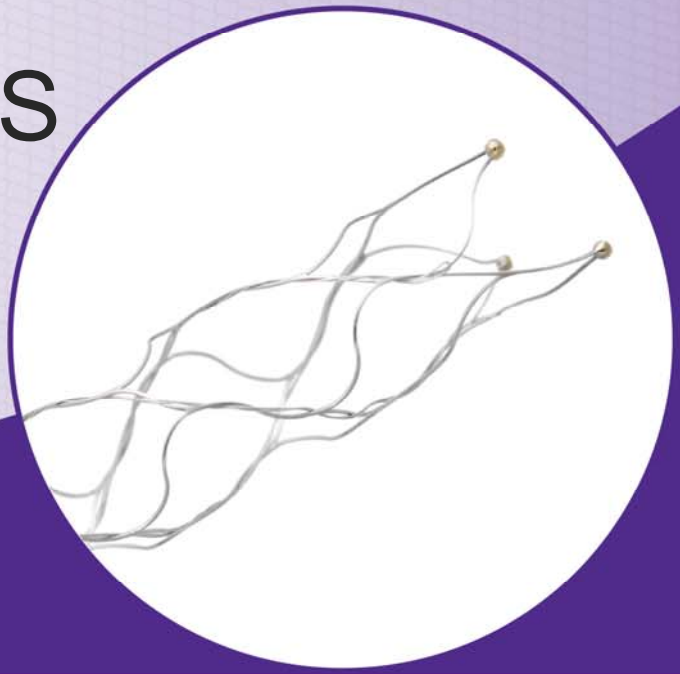
**Director UPMC Center for Neuroendovascular Therapy**
**University of Pittsburgh Medical Center**



# Disclosures

- Drs. Jovin and Nogueira's DAWN-related travel expenses were covered by Stryker Neurovascular for the duration of trial
- Other steering committee members, DSMB members, CEC members, and core lab report consulting fees for their work in this trial.

# Study organization

**Study principal investigators**

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**Steering committee**

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David Liebeskind, MD


stryker


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Steven Hetts, MD

Roger Lewis, MD, PhD

**Clinical Events Committee (CEC)**

Timothy Malisch, MD

Ansaar Rai, MD

Kevin Sheth, MD

**Independent Statisticians**

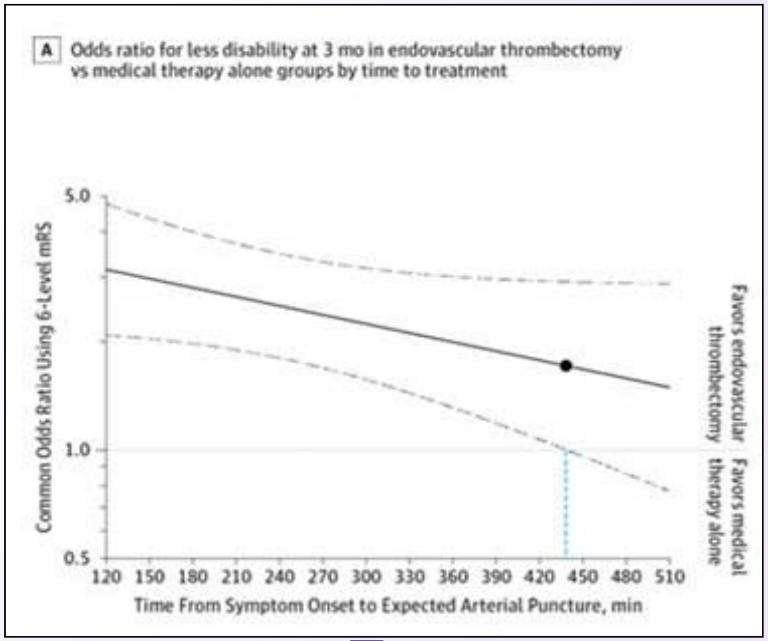
Berry Consultants

Scott Berry PhD

Todd Graves PhD

# Study background

- Current evidence suggests that benefit of thrombectomy rapidly decays over time and may no longer exist beyond 7.3 hours from stroke onset (or TLSW)[1]
- Indeed, the current AHA and ESO guidelines define a rigid therapeutic window of 6 hours as level 1a evidence[2,3]
- This treatment paradigm disregards individual variations in compensatory mechanisms for ischemia led by but not restricted to collateral flow.
- Growing evidence supports a physiologic rather than a purely time based approach where patients with Clinical-Core Mismatch (e.g. significant clinical deficits but still limited infarct size) may benefit from reperfusion regardless of time to treatment.[4]
- Wake-up strokes, strokes with unclear onset time, and witnessed late presenting strokes (> 6 hours) represent a large proportion of LVOS (~40%) yet no proven treatment options exist for this population.




Outcomes = $\frac{\text{Collaterals}}{\text{Time}}$

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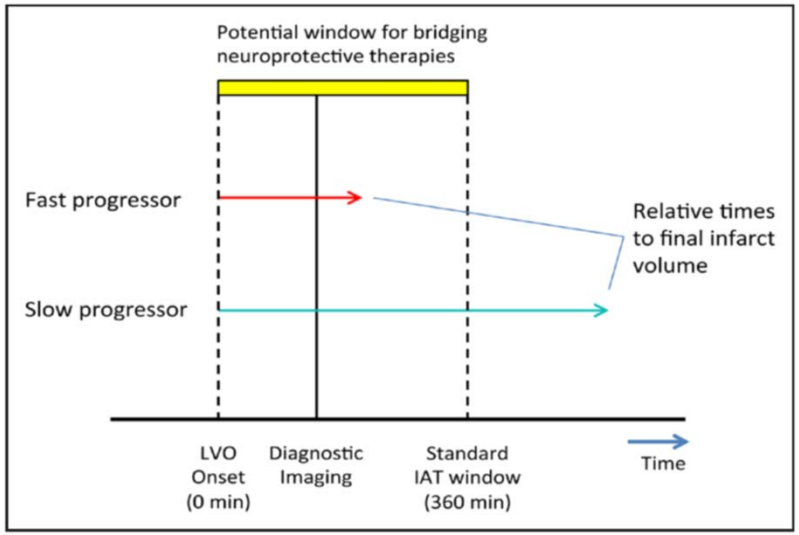
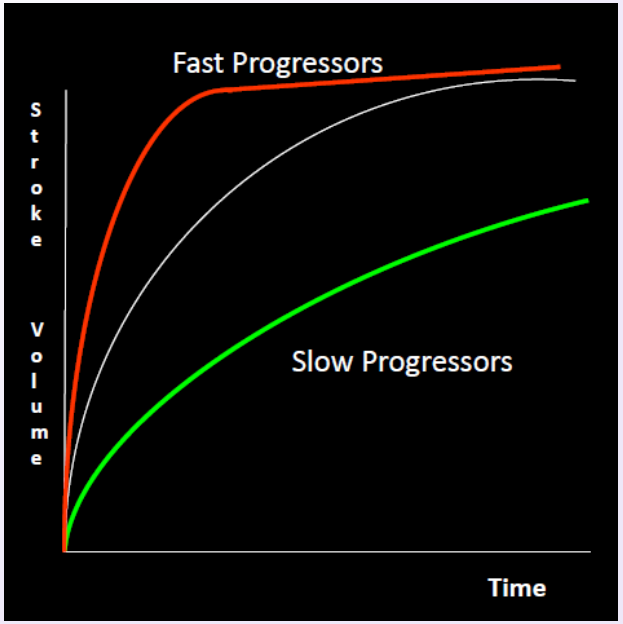
[1] Saver et al, JAMA. 2016 [2] Powers et al, Stroke 2015 [3] Wahlgren Int J Stroke 2016 et.al, [4] Jovin et.al, Stroke 2011

# Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke

## Clinical and Research Implications

Marcelo Rocha, MD, PhD; Tudor G. Jovin, MD

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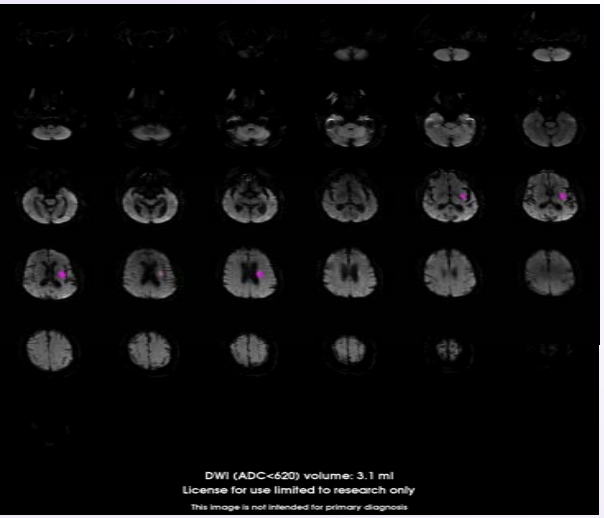
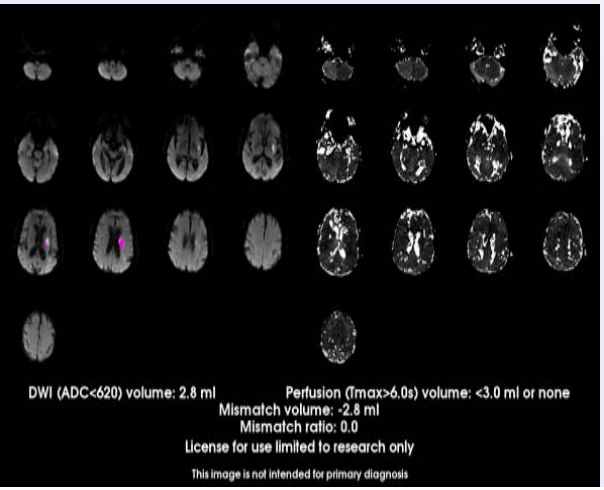
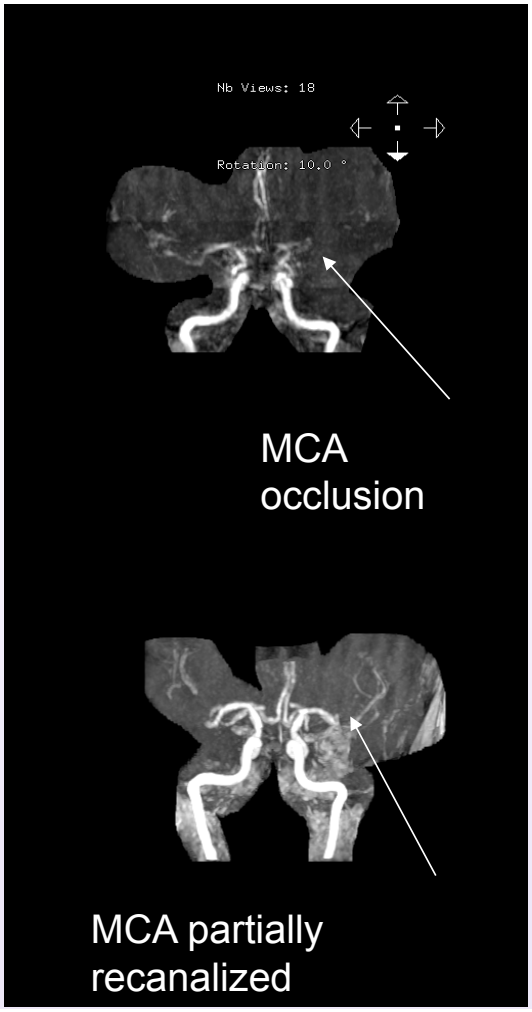
Rocha M, Stroke 2017

# SHOULD WE TREAT PATIENTS WITH LVO AND MISMATCH BEYOND 6 HOURS WITH NO TIME LIMIT ???

# 88 year old woman with L M1 occlusion, TLSW 22 hours, NIHSS 21, no interventio
# mRS at 3 weeks: 3



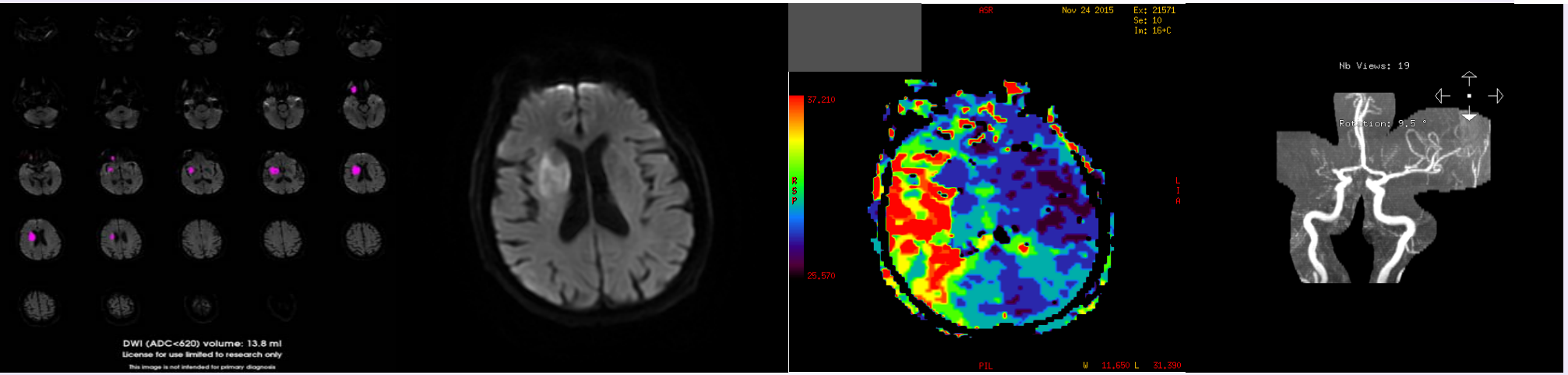




Baseline MRI/MRA – NIHSS 21

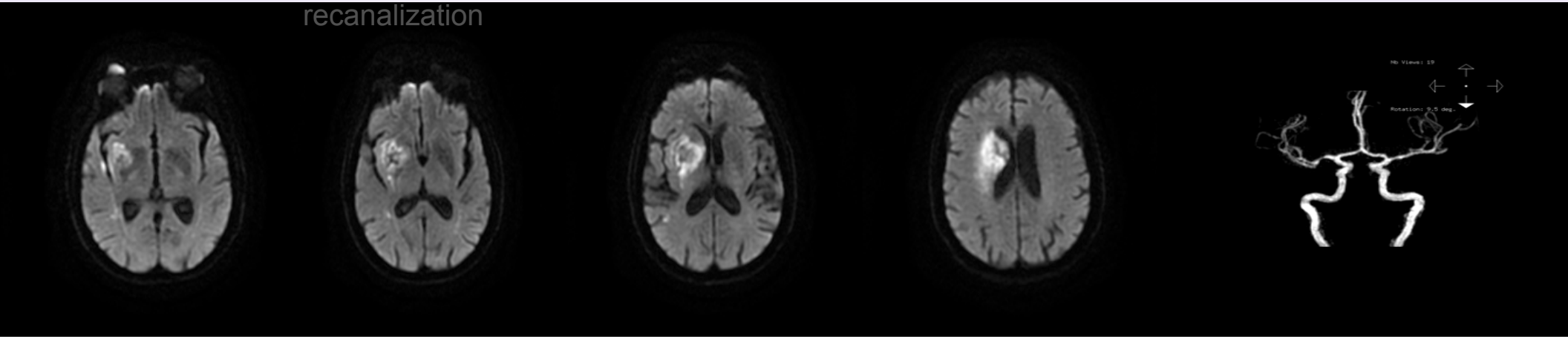
4 day MRI/MRA – NIHSS 11

# 88 year old woman with R M1 occlusion, TLSW 20 hours, NIHSS 17, no intervention mRS at 30 days 1

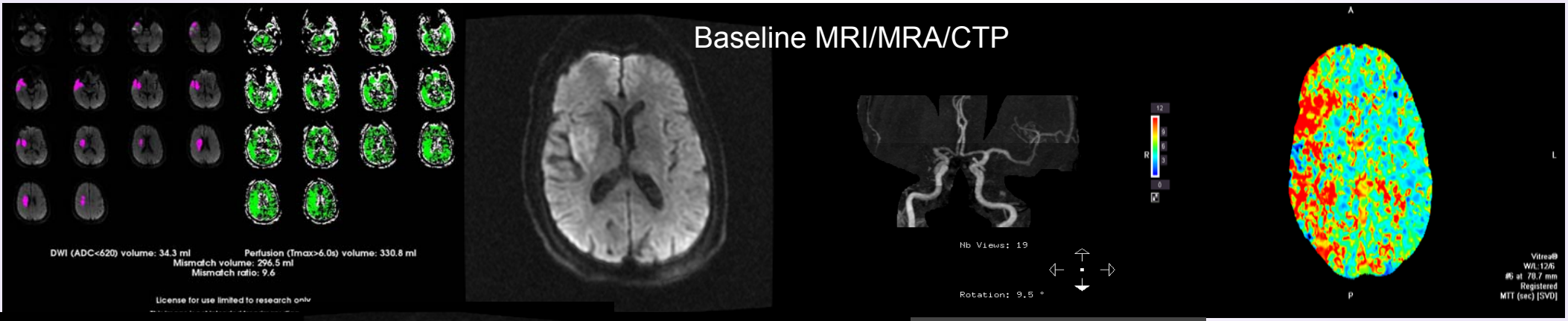
Baseline MRI/MRA

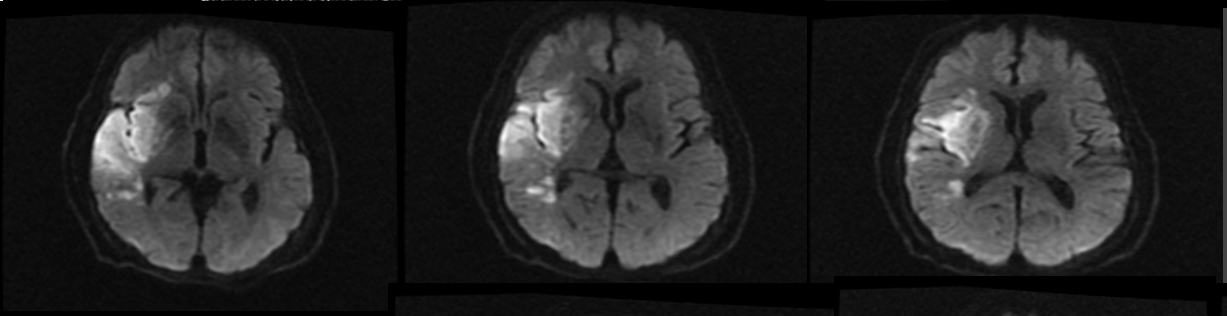



Follow-up MRI/MRA at 24 hours (NIHSS 17) – no infarct growth and partial recanalization

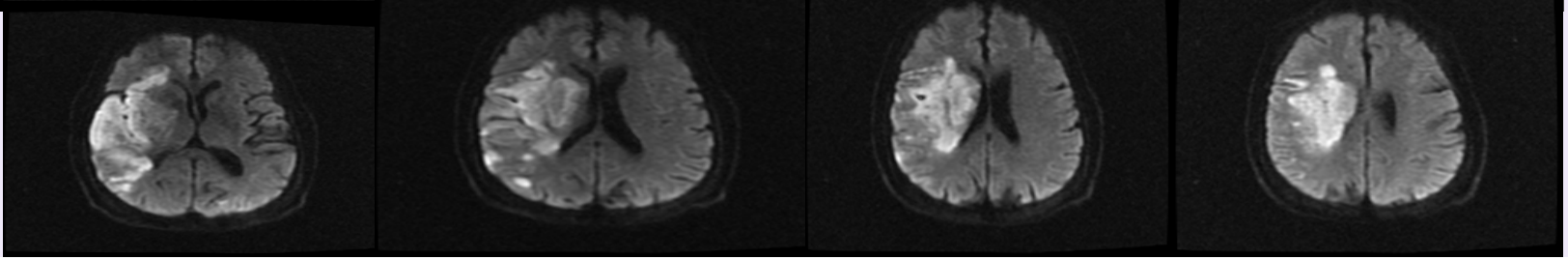


61 year old man with R MCA occlusion, TLSW 14 hours, NIHSS 21, no intervention
3 months mRS 4




MRI/MRA at 24 hours, NIHSS 20



MRI at day 5, NIHSS 18

# Study Objective

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

# Study Design

| | |
|---|---|
| **Study design** | Global, multi-center, adaptive, population enrichment, prospective, randomized, open, blinded endpoint (PROBE), controlled **FDA** IDE trial |
| **Patient population** | • Acute ischemic stroke (AIS) with large vessel occlusion<br>• Able to be randomized between six to 24 hours after time last known well<br>• Clinical imaging mismatch (CIM) defined by age, core, and NIHSS |
| **Target vessel** | Intracranial ICA, M1 segment of the MCA |
| **Randomization** | 1:1 Trevo + medical management vs. medical management alone |
| **Sites** | Up to 50 sites worldwide (30 US and 20 international) |
| **Sample size** | 500 maximum subjects: 250 in the treatment arm and 250 in the control arm. Minimum sample size is 150 subjects. |
| **Follow-up** | 24 hours (-6/+24), day 5-7/discharge, day 30 (± 14), and day 90 (± 14) |

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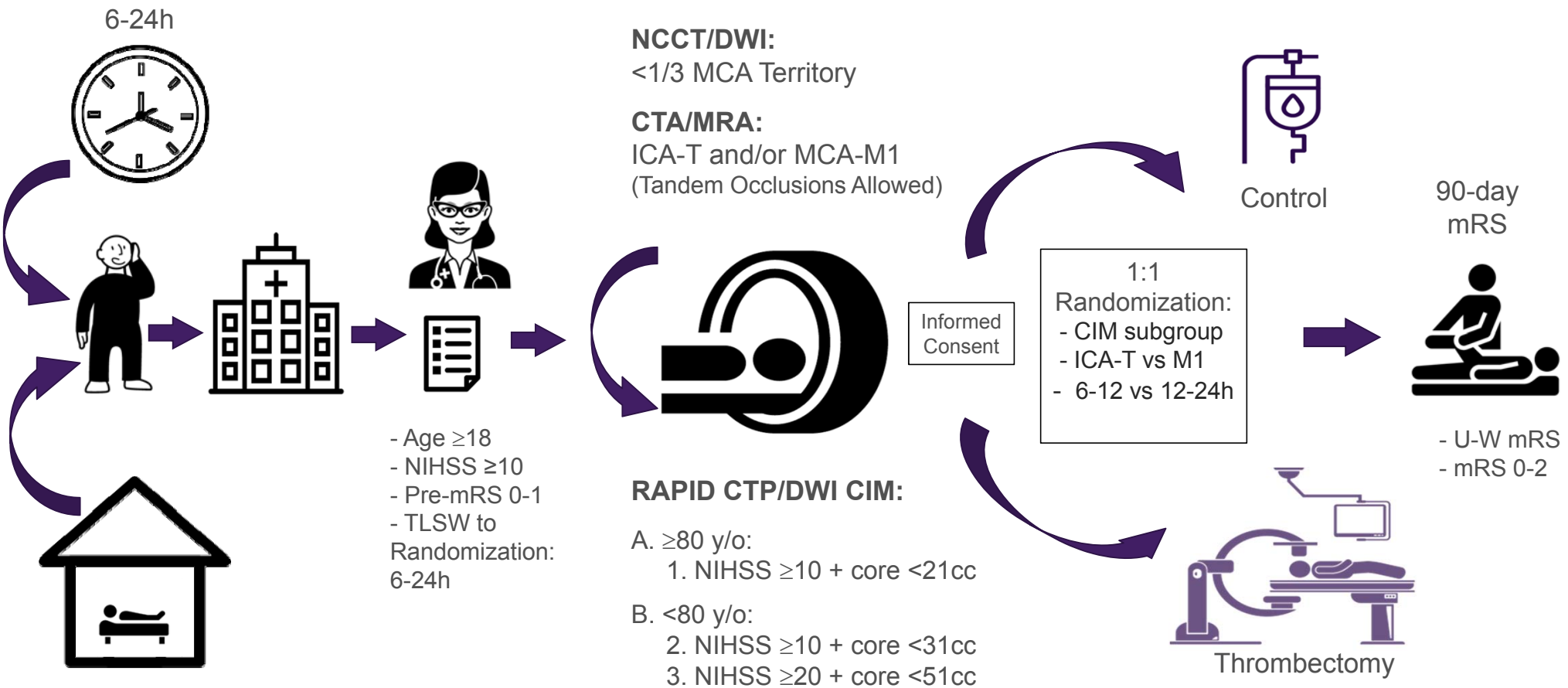
Jovin et al. International Journal of Stroke. 2017

# Study Methods: Workflow




Jovin et al, International Journal of Stroke, 2017

# Study endpoints

| | |
|---|---|
| **Primary endpoint** | **90-day disability assessed by the modified Rankin scale (mRS)**<br>• Assessed via **Utility-Weighted mRS**<br>• Nested **Dichotomous mRS 0-2** |
| **Secondary endpoints** | • "Early response" at day 5-7/discharge, defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1<br>• All cause mortality rates<br>• Median final infarct size at 24 (-6/+24) hours from randomization<br>• Revascularization rates at 24 (-6/+24) hours from randomization<br>• Treatment arm: reperfusion rates post device and post procedure by angiography core lab measurement of modified TICI > 2b |
| **Primary safety endpoint** | **Stroke related mortality at 90 days** |
| **Secondary safety endpoint** | • Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization<br>• Incidence of neurological deterioration from baseline NIHSS score through day 5-7/discharge<br>• Incidence of procedure-related and device-related serious adverse events through 24 (-6/+24) hours post randomization |

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Jovin et al, International Journal of Stroke, 2017

# DAWN Trial utility weighted mRS and enrichment

## Utility weighted mRS

- Better captures health state transitions across the entire spectrum
- Patient-centered outcomes analysis

| mRS | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| **Weight** | **10** | **9.1** | **7.6** | **6.5** | **3.3** | **0** | **0** |

## Enrichment

- Designed to fine tune the patient population based on core infarct size
- Identify subgroups experiencing clinical benefit

**0-50 cc → 0-45 cc → 0-40 cc → 0-35 cc → 0-30 cc**

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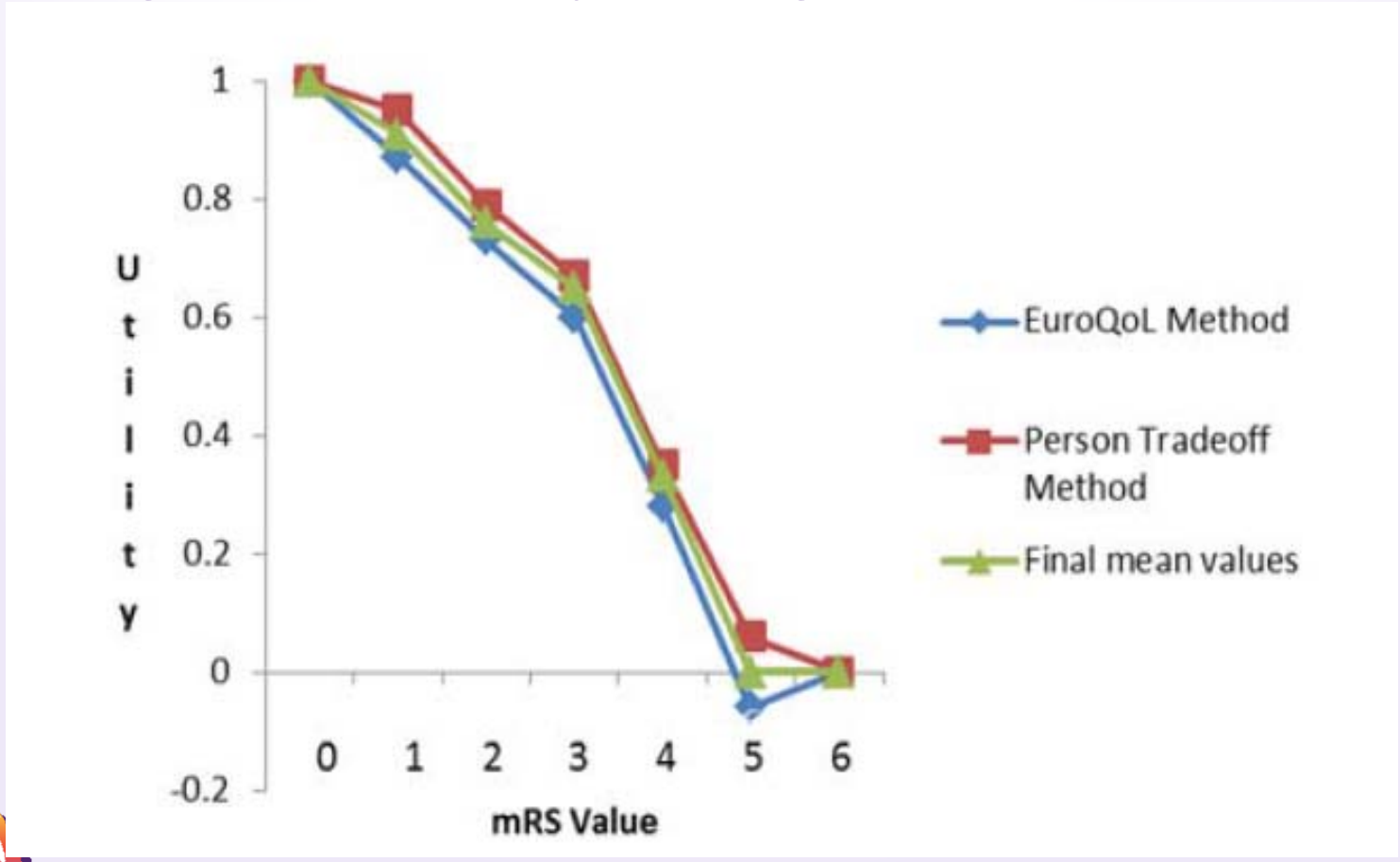
Jovin et al, International Journal of Stroke, 2017

# Origin of the Utility –Weighted mRS




Chasnaianunkul et al., Stroke. 2015;46:2238-2243.

# Key statistical operating characteristics: Bayesian approach

**First futility/enrichment analysis at 150 subjects**
**First efficacy analysis at 200 subjects**
**Interim analysis after every 50 subjects up to 500 max**

- **The threshold for declaring success depends on the degree to which the population has been enriched**
- **If there is no enrichment and the probability of a treatment effect is ≥ 0.986 the intervention is deemed efficacious.**
- **Similar to a "traditional" study design one-sided test at the $\alpha$=0.014 level.**

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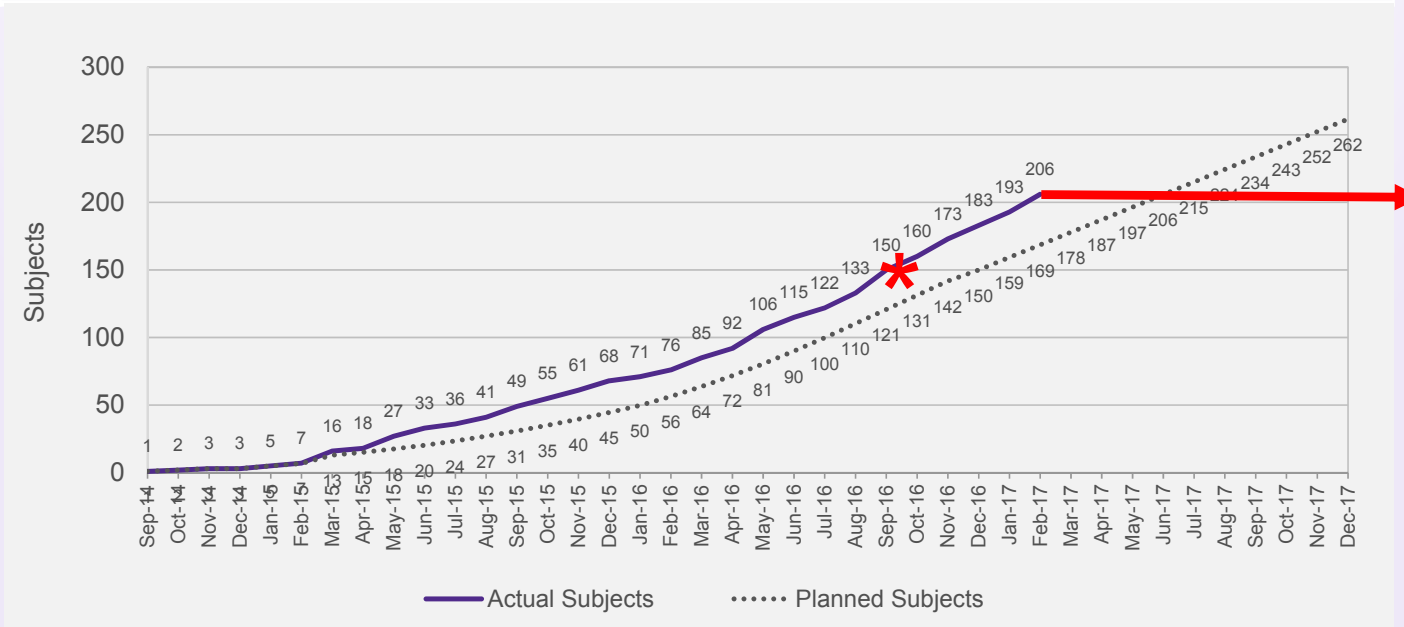
Jovin et al, International Journal of Stroke, 2017

# TRIAL ENROLLMENT RATE AND TERMINATION

| Site Status | | | |
|---|---|---|---|
| Sites Qualified | 36 | Contracts Executed | 31 |
| Sites Initiated | 30 | Sites Activated to Enroll | 30 |
| IRB/EC Approvals | 31 | Subjects Enrolled | 206 |

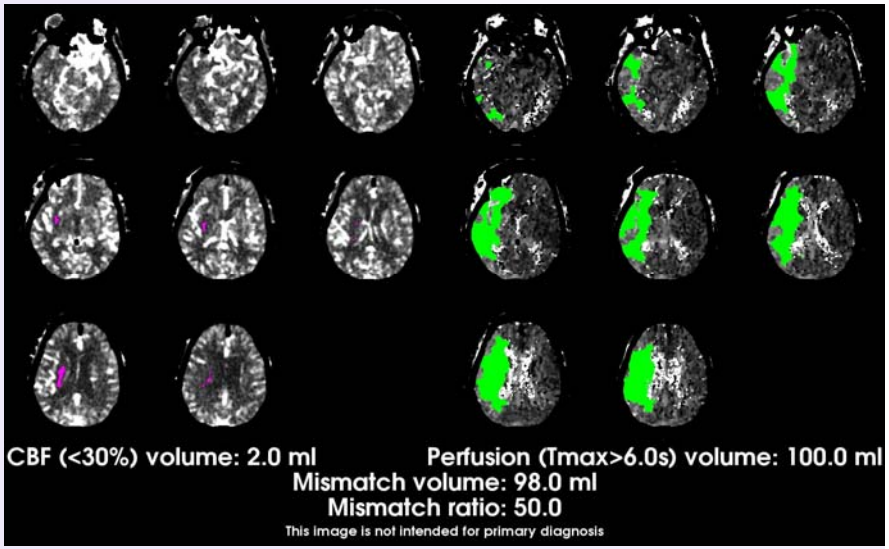
**Actual / Projected Enrollment**




Enrollment stopped at DSMB recommendation.

*Boundary for first enrichment not crossed.

# Results


CBF (<30%) volume: 2.0 ml
Perfusion (Tmax>6.0s) volume: 100.0 ml
Mismatch volume: 98.0 ml
Mismatch ratio: 50.0
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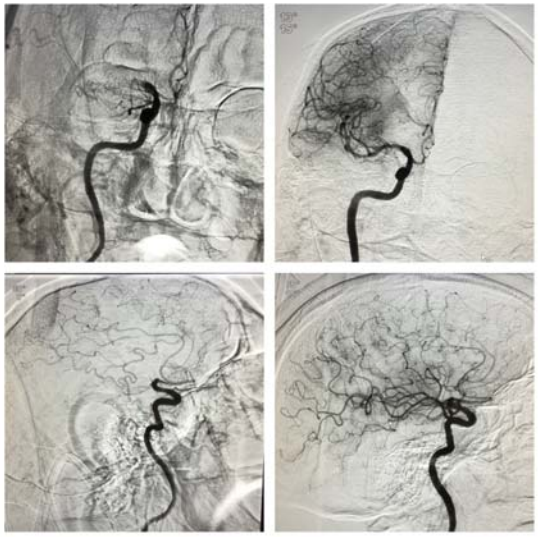
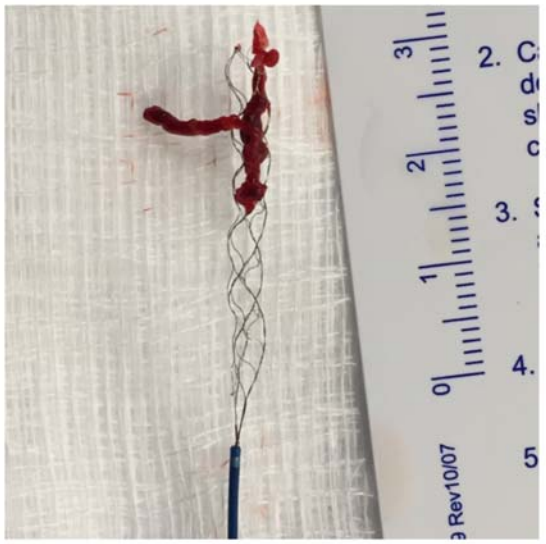
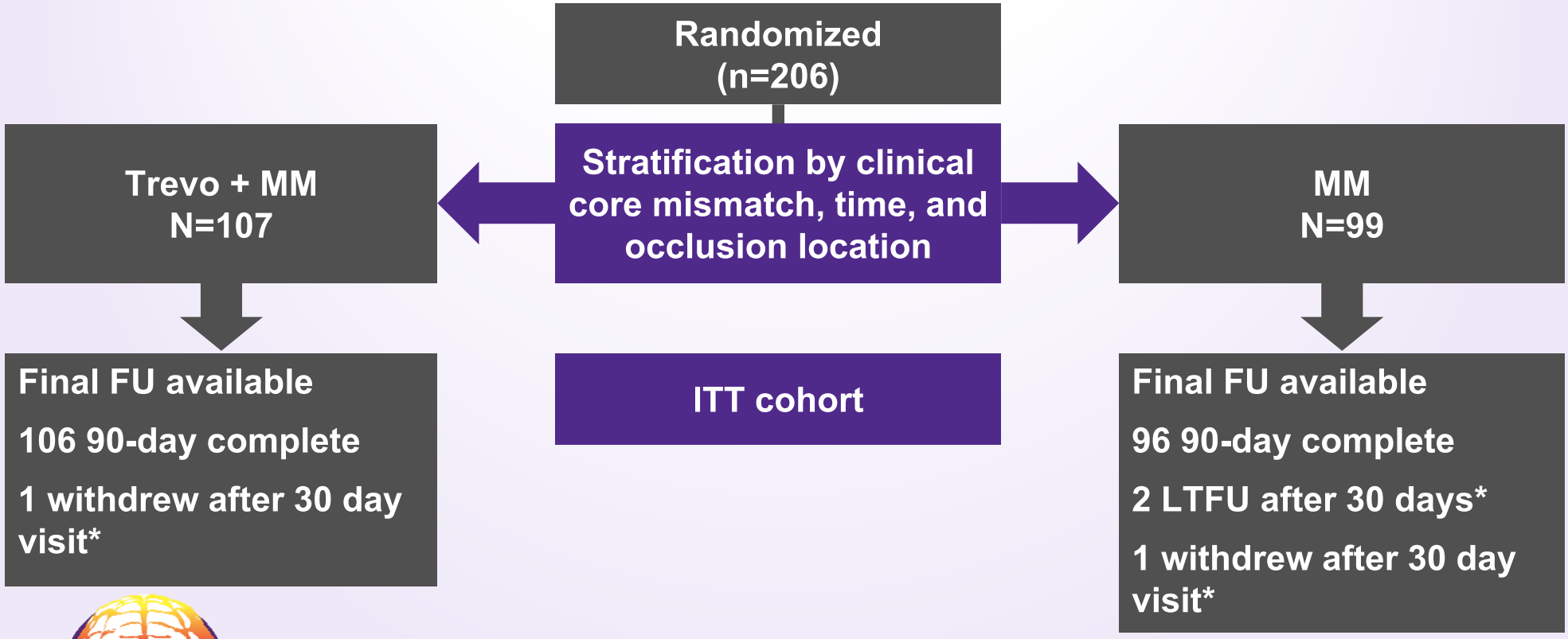




# Randomization and follow-up

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* 30 day mRS carried forward in 4 pts
100% follow-up to 30 days

# Demographics

| | Treatment arm N=107 | Control arm N=99 | P-value |
|---|---|---|---|
| **Age (years) (median, [IQR])** | 72.0 [60.0-79.0] | 73.0 [61.0-82.0] | 0.51 |
| **NIHSS, baseline (median, [IQR])** | 17 [13-21] | 17 [14-21] | 0.64 |
| **Sex, male (%)** | 39.3% | 51.5% | 0.09 |
| **Race** | | | |
| White/Caucasian | 66.0% | 63.6% | 0.77 |
| Black or African American | 21.7% | 15.2% | 0.28 |
| Other* | 12.3% | 21.2% | 0.09 |
| **IV-tPA administered** | 4.7% | 13.1% | 0.05 |

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* Inclusive of Asians and International sites that did not disclose race per local authorities

# Medical history

| | Treatment arm N=107 | Control arm N=99 | P-value |
|---|---|---|---|
| **Hypertension** | 79.0% | 75.8% | 0.62 |
| **Heart failure** | 18.8% | 15.5% | 0.58 |
| **Coronary artery disease** | 31.4% | 24.0% | 0.27 |
| **Atrial fibrillation** | 41.3% | 25.0% | 0.02 |
| **Diabetes mellitus** | 25.2% | 31.6% | 0.35 |
| **Dyslipidemia** | 58.8% | 59.4% | 1.00 |
| **Current smoker (within last year)** | 20.4% | 23.5% | 0.61 |
| **Previous ischemic stroke** | 12.1% | 11.1% | 1.00 |

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# Baseline imaging characteristics

| | Treatment arm N=107 | Control arm N=99 | P-value |
|---|---|---|---|
| Qualifying infarct volume by **site** RAPID (median, [IQR]) | 7.6 [2.0-18.0] | 8.9 [3.0-18.1] | 0.99 |
| Qualifying RAPID volume obtained by CTP– no. (%) | 67 (62.6) | 64 (64.6) | |
| Qualifying RAPID volume obtained by DWI MRI– no. (%) | 40 (37.4) | 35 (35.4) | |
| Patients with baseline MRI (%)* | 43.0% | 37.8% | 0.48 |
| Patients with baseline CT/CTA/CTP(%)* | 76.6% | 76.5% | 1.0 |

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* Patients may have both CTP and MRI

# Baseline occlusion locations – core lab adjudicated

| Intracranial occlusion location– no. (%) (Core Lab assessment) | Treatment arm N=107 | Control arm N=99 |
|---|---|---|
| Intracranial ICA | 22 (20.6) | 19 (19.2) |
| M1 middle cerebral artery segment | 79 (73.8) | 74 (74.7) |
| M2 middle cerebral artery segment | 3 (2.8) | 3(3.0%) |
| Cervical carotid stenosis– no. (%) | | |
| 0-50% | 80 (74.8) | 72 (72.7) |
| 51-99% | 12 (11.2) | 14 (14.1) |
| 100% (occlusion) | 15 (14.0) | 13 (13.1) |

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# Patient presentation

| | Treatment arm N=107 | Control arm N=99 | P- value |
|---|---|---|---|
| **Time since time last seen well to randomization (hrs)** | | | |
| Mean ± SD<br>Median (Q1, Q3)<br>Range (min, max) | 13.4 ± 4.1<br>12.2 (10.2, 16.0)<br>(6.1, 23.5) | 13.0 ± 4.5<br>13.2 (9.4, 15.8)<br>(6.4, 23.9) | 0.53 |
| **Stroke sub-population** | | | |
| Wake up stroke | 64.5% | 47.5% | **0.01** |
| Witnessed stroke | 10.3% | 14.1% | 0.52 |
| Un-witnessed stroke | 25.2% | 38.4% | 0.05 |

# Procedural characteristics and outcomes

| | Treatment arm N=107 |
|---|---|
| Procedure duration (minutes) (median IQR) | 56.0 [33.0-90.0] |
| Total number of Trevo device passes (median IQR) | 2.0 [1.0-3.0] |

| Core lab adjudicated TICIs | Treatment arm N=107 |
|---|---|
| Post procedure mTICI ≥ 2B | 84.0% |
| Post procedure oTICI ≥ 2B* | 72.6% |
| Post procedure TICI 3 | 10.4% |

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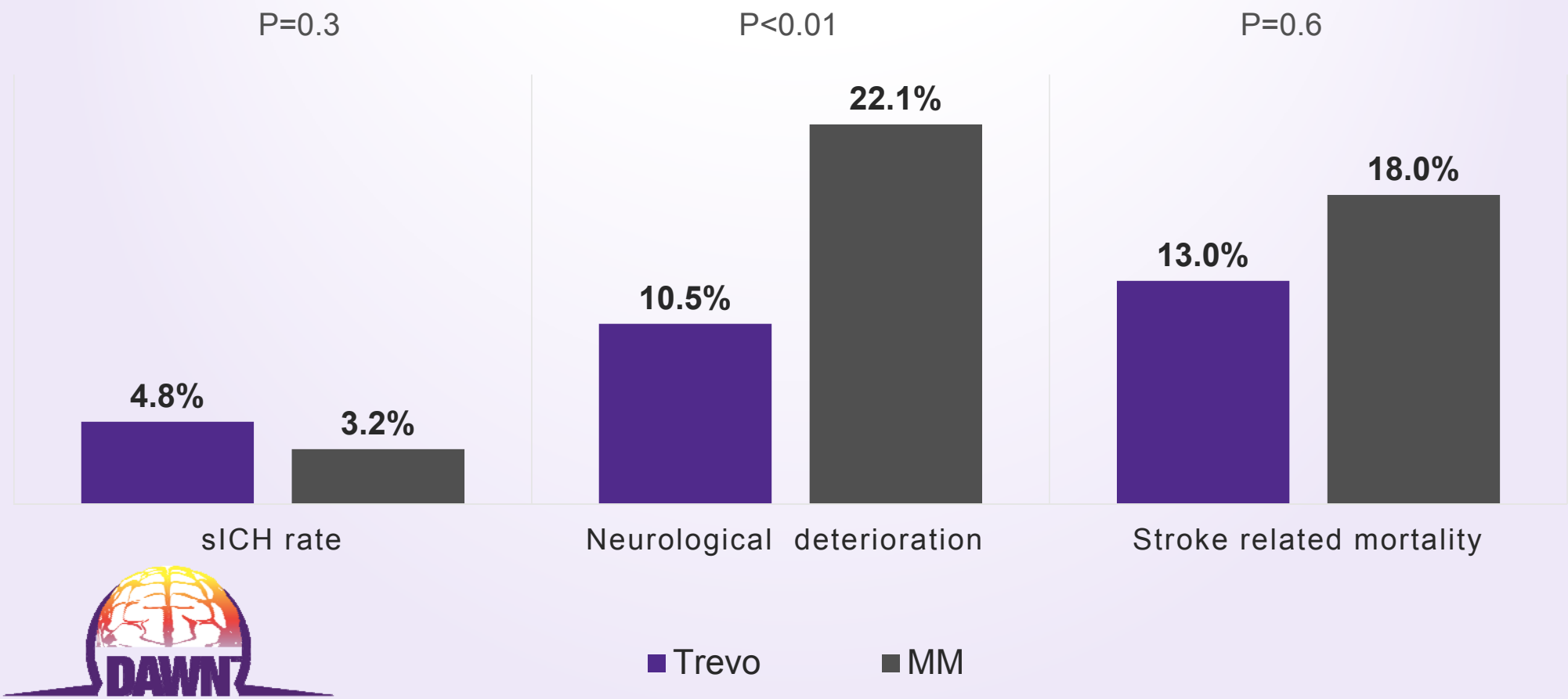
*Protocol advised to stop after oTICI 2b achieved

# CEC adjudicated safety outcomes



# Co-primary endpoints

| | Trevo | MM | Treatment benefit (95% CI) | Bayesian probability of superiority |
|---|---|---|---|---|
| Day 90 weighted mRS | 5.5 ± 3.8 | 3.4 ± 3.1 | 2.1 (1.20, 3.12) | >0.9999* |
| Day 90 mRS (0-2) | 48.6% | 13.1% | 35.5% (23.9%, 47.0%) | >0.9999* |

**NNT for 90-day functional independence = 2.8**

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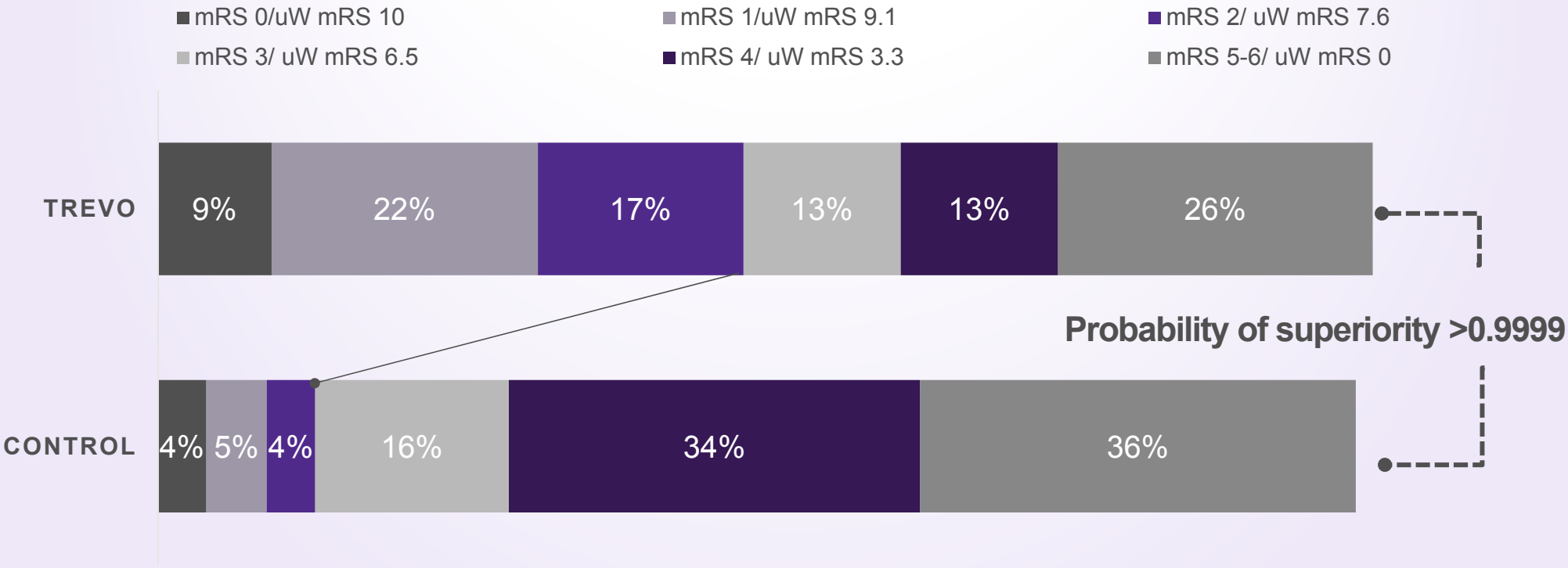
***Similar to p<0.0001**

# Primary outcome




**73% relative risk reduction of dependency in ADL's**

**NNT for any lower disability 2.0**

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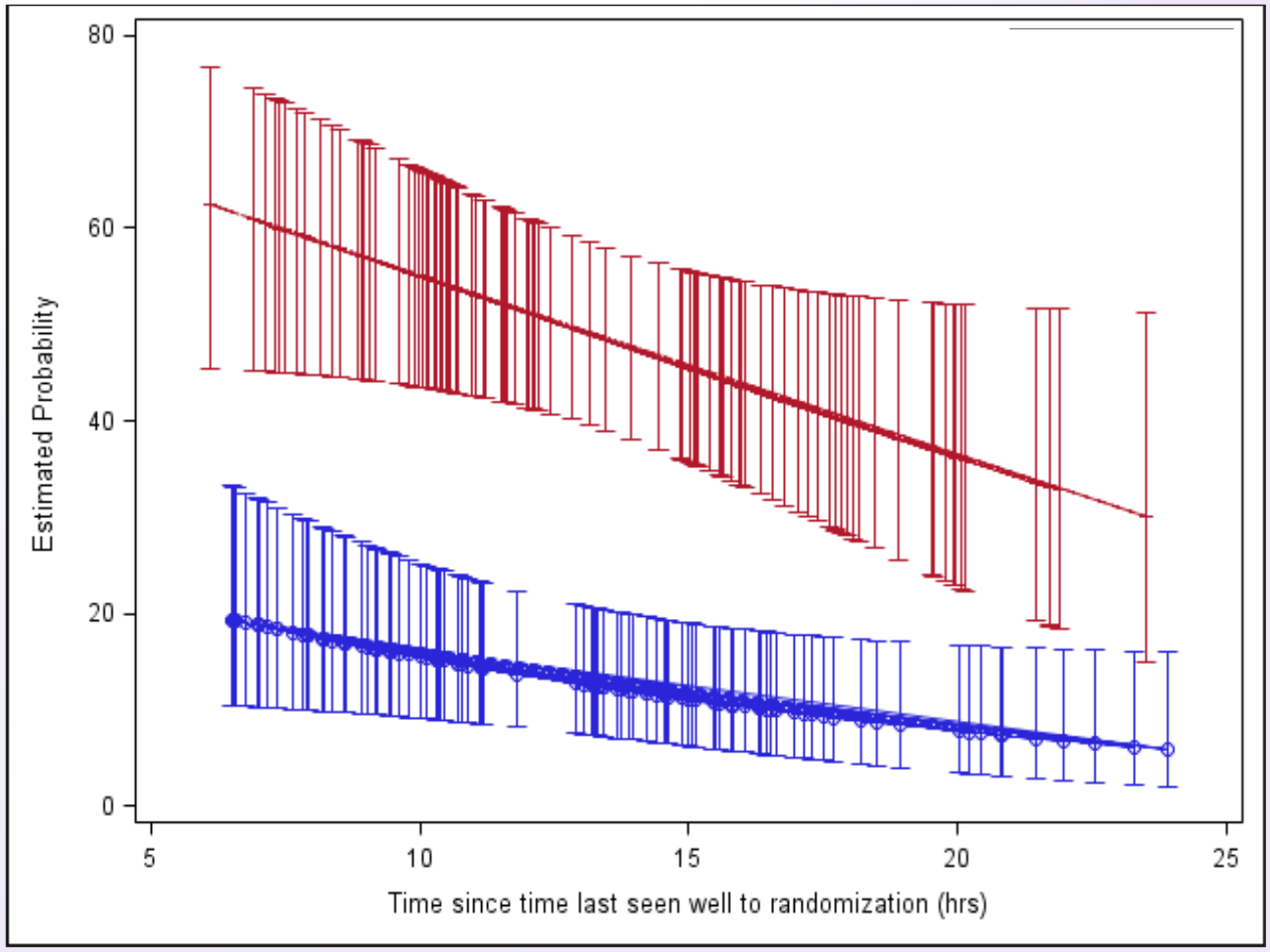
# 90 Day mRS 0-2 by TLSW to Randomization

| | Trevo | MM | P-value |
|---|---|---|---|
| **6-12h** | 55.1% | 20.0% | <0.001 |
| **12-24h** | 43.1% | 7.4% | <0.001 |

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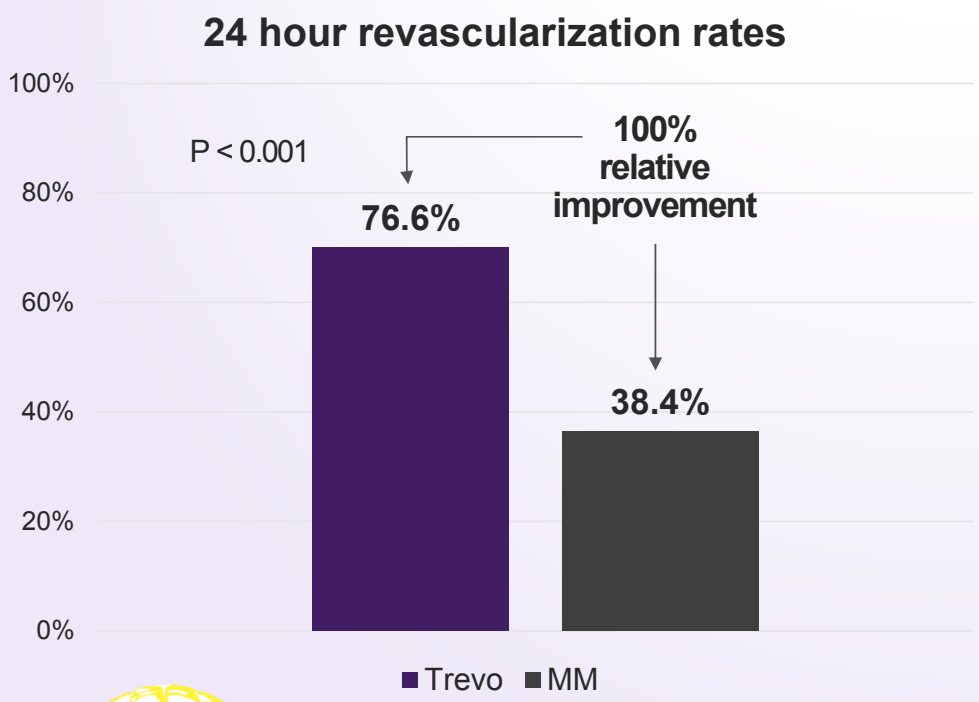
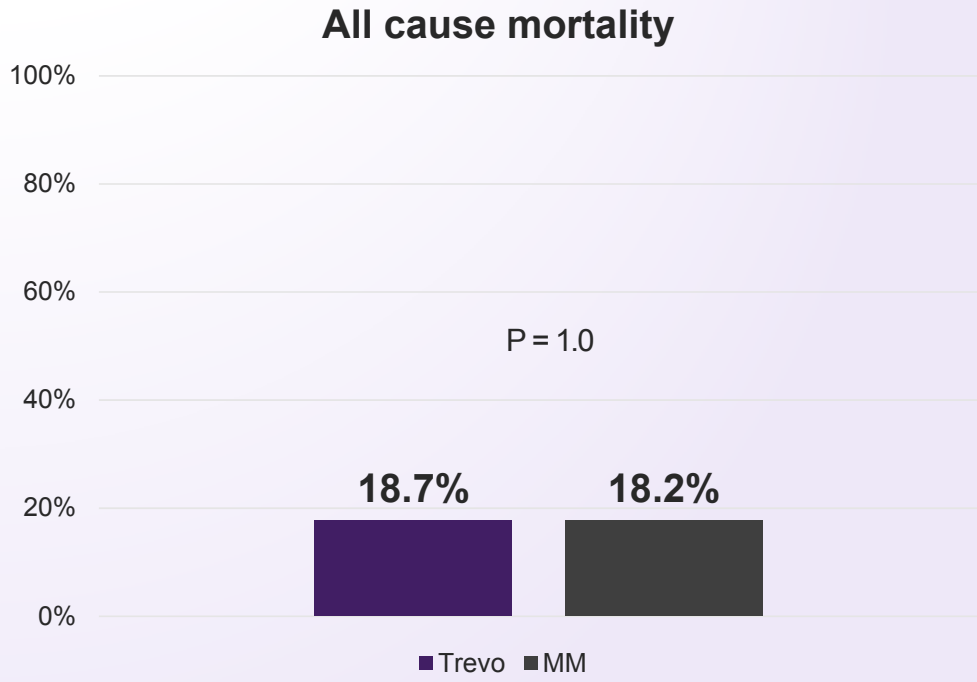
# Secondary effectiveness endpoints

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# Conclusions

- Thrombectomy with Trevo in DAWN-eligible patients is associated with improvement in clinical outcomes across the entire range of utility weighted mRS and with higher rates of functional independence (mRS 0-2) compared to standard medical therapy (48.6% vs 13.1%, probability of superiority >0.999, NNT = 2.8)

- For every 100 patients treated with endovascular therapy, 49 will have a less disabled outcome as a result of treatment, including 36 who will be functionally independent

- The treatment effect size in DAWN is the highest out of any stroke trials to date and suggests that the presence of Clinical-Core Mismatch is a critical predictor of treatment effect independent of time to presentation

- Treatment effect persisted throughout 24 hours from TLKW; however, earlier treated patients do better

- Thrombectomy with the Trevo device in patients presenting beyond 6 hours of TLSW had comparable safety profile to thrombectomy performed within 6 hours

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Research

International Journal of Stroke WSO

International Journal of Stroke
0(0) 1–12

DOI: 10.1177/1747493017710341
journals.sagepub.com/home/wso
SAGE

# Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods

Tudor G Jovin[1], Jeffrey L Saver[2], Marc Ribo[3], Vitor Pereira[4], Anthony Furlan[5], Alain Bonafe[6], Blaise Baxter[7], Rishi Gupta[8], Demetrius Lopes[9], Olav Jansen[10], Wade Smith[11], Daryl Gress[12], Steven Hetts[13], Roger J Lewis[14], Ryan Shields[15], Scott M Berry[16], Todd L Graves[16], Tim Malisch[17], Ansaar Rai[18], Kevin N Sheth[19], David S Liebeskind[2] and Raul G Nogueira[20]

DAWN may have profound implications for treatment of stroke due to LVO, because it would validate the physiological (rather than chronological) approach to patient selection for endovascular therapy. It will also allow many more patients with LVO stroke to be treated with mechanical embolectomy, especially in countries outside of the US, Australia, Canada, and Western Europe, where due to inadequate development for stroke pre-hospital systems of care, a large proportion of patients with LVO stroke present to endovascular centers outside 6 h from TLSW.

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# Enrolling Centers

## North America

1. Abington Memorial, PA
2. Baptist Jacksonville, FL
3. Buffalo, NY
4. Capital Health Trenton, NJ
5. Christiana Delaware, DE
6. CPMC San Francisco, CA
7. Erlanger ,Chattanooga, TN
8. Florida Hospital, FL
9. Grady Atlanta, GA
10. JFK, Edison, NJ
11. Kaiser LA
12. Kennestone, Marietta GA
13. KUMC Kansas City, KA
14. Lexington Memorial, KY
15. Riverside, OH
16. Rush, IL
17. St. Joseph Mercy MI
18. Texas Stroke Institute TX
19. Toronto Western, ON
20. UCLA, CA
21. UH Cleveland, OH
22. University of Miami, FL
23. UPMC, PA
24. Valley Baptist, TX

## Europe

26. Bellvitge Barcelona
27. Germans Trias Barcelona
28. Gui de Chauliac Montpellier
29. Hopital Purpan Toulouse
30. Hospital Clinic Barcelona
31. Vall d'Hebron Barcelona

## Australia

32. Royal Melbourne Hospital

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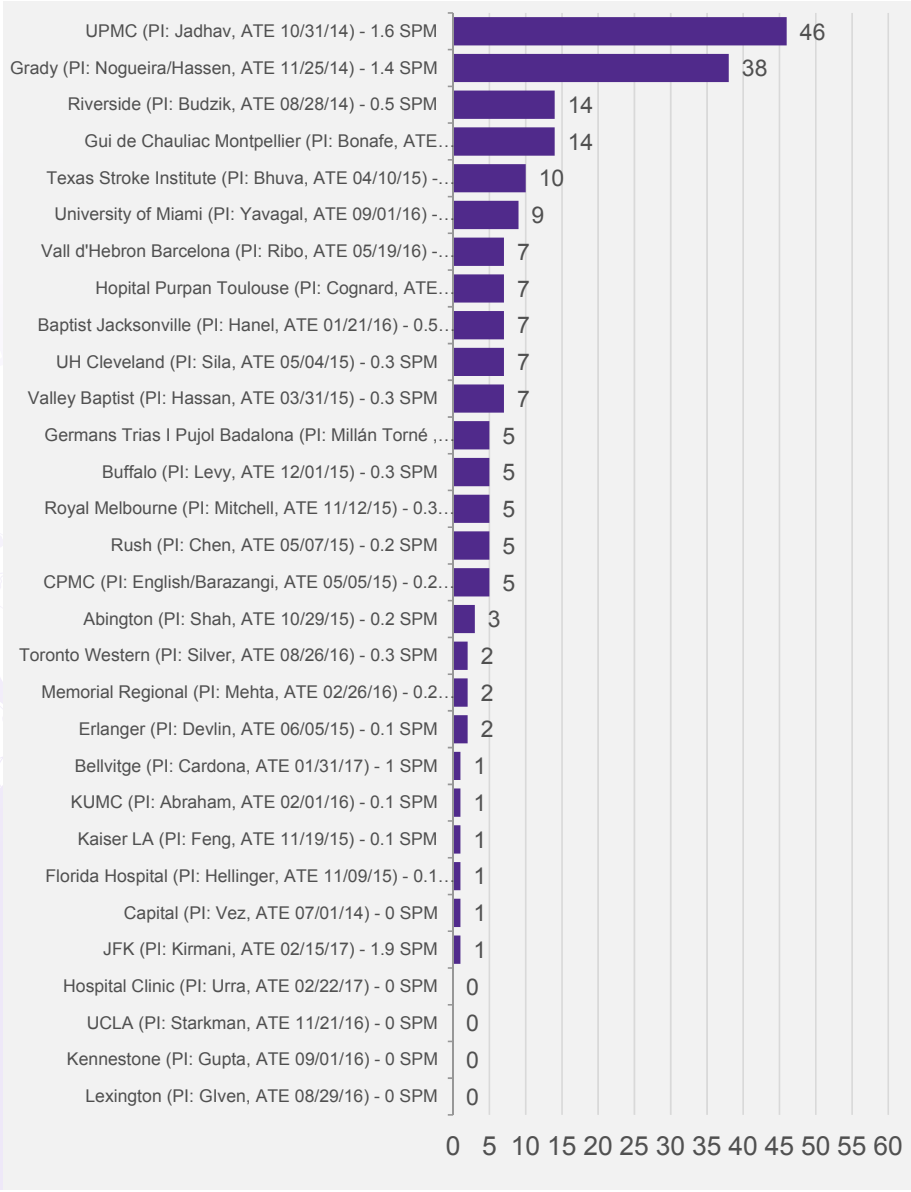


# Real-World Applicability of Endovascular Therapy in ICA and/or MCA-M1 Occlusions Treated in the 6-24-hour Window:

## Subgroup Analysis of the Prospective Trevo Registry

**Raul G Nogueira**, David Liebeskind, Ron Budzik, Rishi Gupta, Antonin Krajina, Joey English, Ameer Malek, Amrou Sarraj, Ana Paula Narata, Muhammad Taqi, Timothy Miller, Thomas Grobelny, Blaise Baxter, Bruno Mario Bartolini, Laurent Estrade, Tudor Jovin, Erol Veznedaroglu

On behalf of the Trevo Retriever Registry Investigators

Trevo® Retriever Registry

# Methods

- **Consecutive Trevo Registry patients fulfilling the basic DAWN trial criteria**
  - Baseline NIHSS ≥ 10
  - Intracranial ICA and/or MCA-M1 occlusion
  - Pre-morbid mRS 0-1

- **Categorized according to their time-from-last-seen-well to arterial puncture as:**
  - Early (≤6 hours)

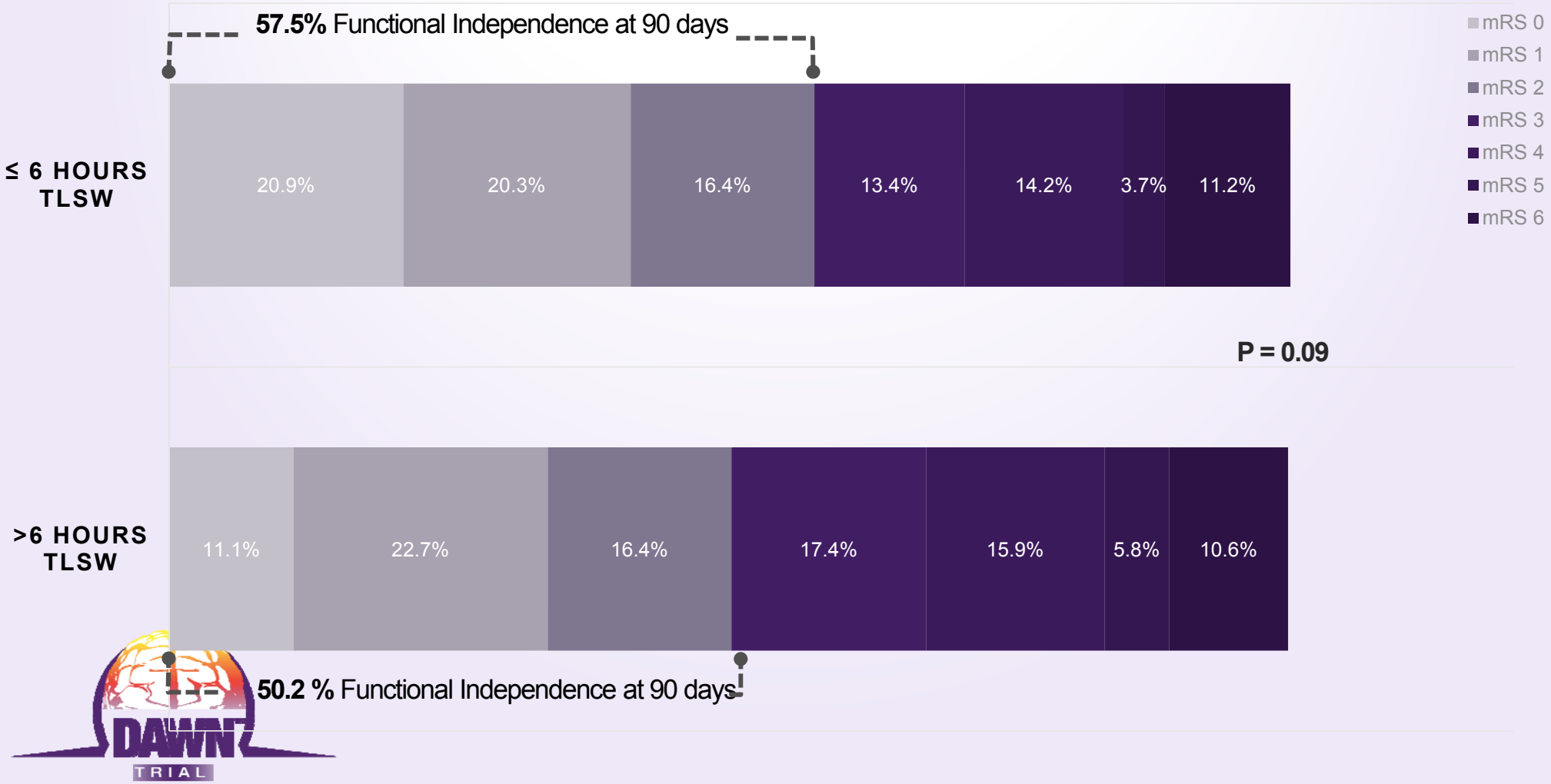
    vs.
  - Late (6-24 hours)

- **Univariate analyses were performed for group comparisons.**

- **Multivariate analysis was performed to identify the predictors of good outcomes (pre-specified)**

DAWN TRIAL

# mRS Distribution



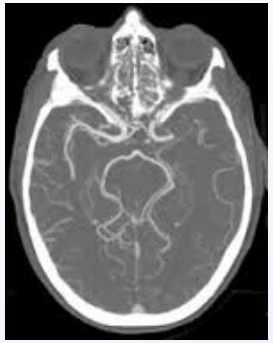
# DEFUSE 3: NIH-funded, prospective, randomized, multi-center, adaptive, blinded endpoint trial

- Paradigm shift
  - From time-based selection to imaging-based selection
- Target population
  - Anterior circulation ischemic stroke; ICA or M1 occlusions (CTA/MRA)
  - Salvageable tissue on CT perfusion or MR diffusion / perfusion
  - Endovascular therapy within 6-16 hours of last known well
- Design
  - 1:1 randomization; standard medical therapy vs. endovascular
  - 45 sites

# Neuroimaging Inclusion Criteria

MRA / CTA reveals

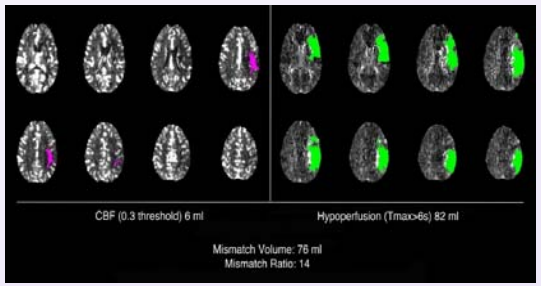
- M1 segment MCA occlusion, or
- ICA occlusion (cervical or intracranial; with or without tandem MCA lesions)



AND

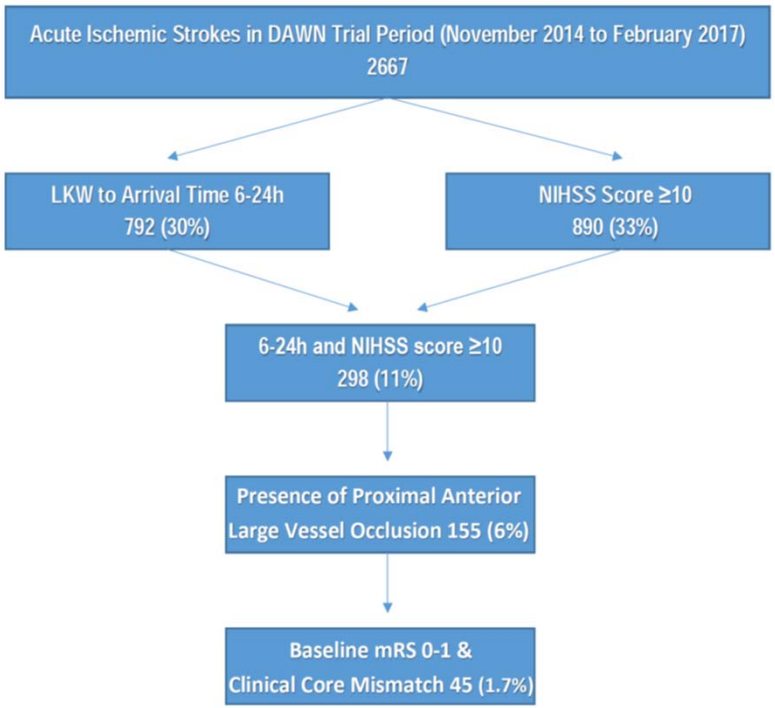
Target Mismatch Profile on CT perfusion or MRI (RAPID)

- Ischemic core volume < 70 mL
- Mismatch ratio > 1.8
- Mismatch volume ≥ 15 mL

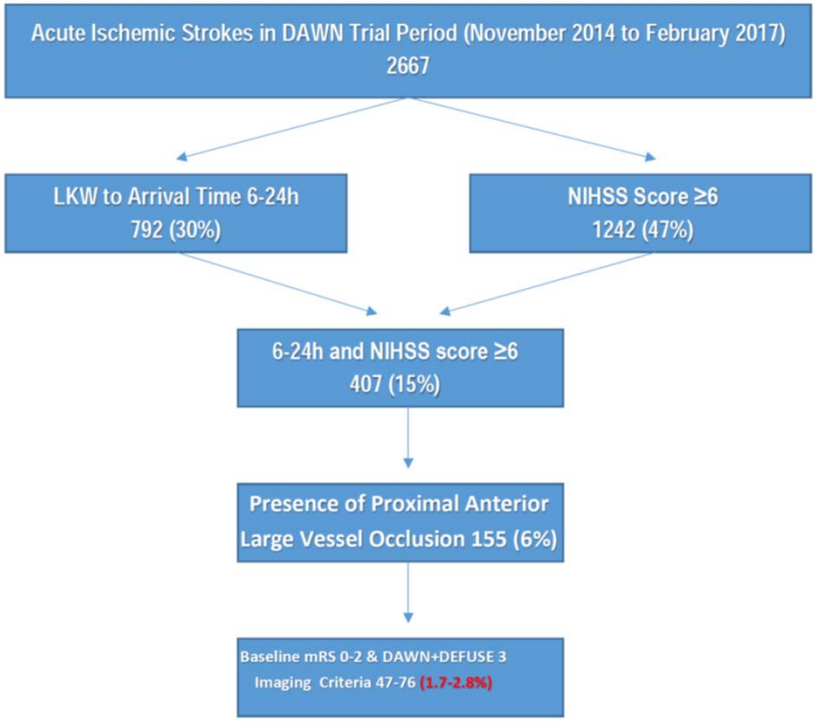


# HOW MANY SYTROKE PATIENTS QUALIFY ??

APPLICATION OF DAWN CRITERIA TO CONSECUTIVE ACUTE ISCHEMIC STROKE PATIENTS DURING DAWN TRIAL PERIOD AT UPMC PRESBYTERIAN HOSPITAL




APPLICATION OF DAWN AND DEFUSE 3 CRITERIA TO CONSECUTIVE ACUTE ISCHEMIC STROKE PATIENTS DURING THE DAWN TRIAL PERIOD AT UPMC PRESBYTERIAN UNIVERSITY HOSPITAL




DAWN TRIAL

# It's a new DAWN!

# Thank you

**to all DAWN investigators, patients and families**