# Stroke Trials
# Sorry to Sensational Overnight
## Results, Analysis, and Implications


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# Disclosure Statement of Financial Interest

**I, Philip Meyers, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.**

# TCT 2014
# Duels and Debates

## Experts Disagree Over Endovascular Therapy for Acute Stroke



**By Kim Dalton**

*Monday, September 15, 2014*

At a Duels and Debates session on Sunday, the proposition that data dictate that an endovascular approach to acute stroke is not indicated in most cases drew spirited defense and rebuttals.

**Evidence unsupportive**

Speaking in favor of the proposition, Philip M. Meyers, MD, of NewYork-Presbyterian Hospital/Columbia University Medical Center, New York, contended that endovascular stroke therapy remains unproven and that evidence to date does not support its use outside of clinical trials. Moreover, CMS payment for endovascular stroke therapy has funded the development of a large network of centers that are underutilized.

He stressed that “time is brain” and thus timely treatment is critical, noting that in the IMS I and II trials, a patient’s chances of good clinical outcome decreased by 10% for every 30 minutes after symptom onset that they went unreperfused.

Interest in endovascular stroke therapy dates back about 30 years, but in 1998, the PROACT II trial put it on the map by showing superior recanalization and improved outcomes with intra-arterial prourokinase plus heparin vs. heparin alone.

# Poor Outcomes 2013

IMS-III
MR RESCUE
SYNTHESIS EXPANSION

# Good Outcomes 2014-2015

MR CLEAN
ESCAPE
SWIFT-PRIME
EXTEND-IA
REVASCAT

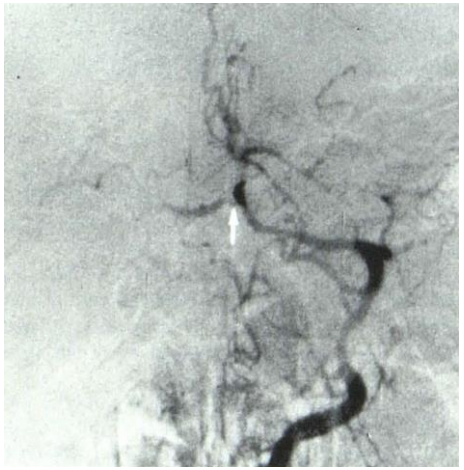
# 3 Main Reasons

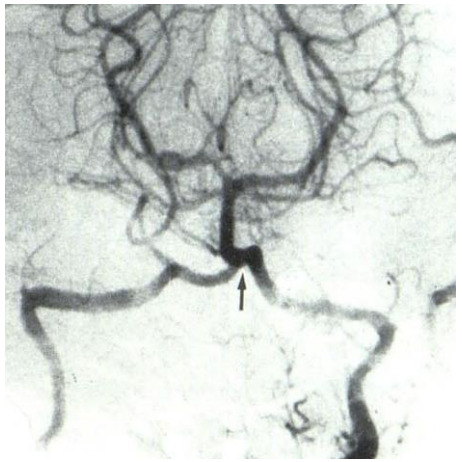
1. Rate of substantial reperfusion
2. Time to reperfusion
3. <u>Selection of patients using imaging</u>
   - Signs suggesting smaller infarcts
   - Vascular Imaging - Large vessel occlusions

# Blast from the Past

## Promise of a better world for stroke victims

- Zeumer, 1982
  - First report of IA fibrinolysis
  - Basilar occlusion reperfused with streptokinase
- PROACT II Trial 1996 – 1998
  - IA rtPA vs. heparin for M1 Occlusion
  - 66% Recanalization
  - 40% modified Rankin 0-2







Zeumer. AJNR 4: 401, 1983
Furlan. JAMA 282:2003, 1999

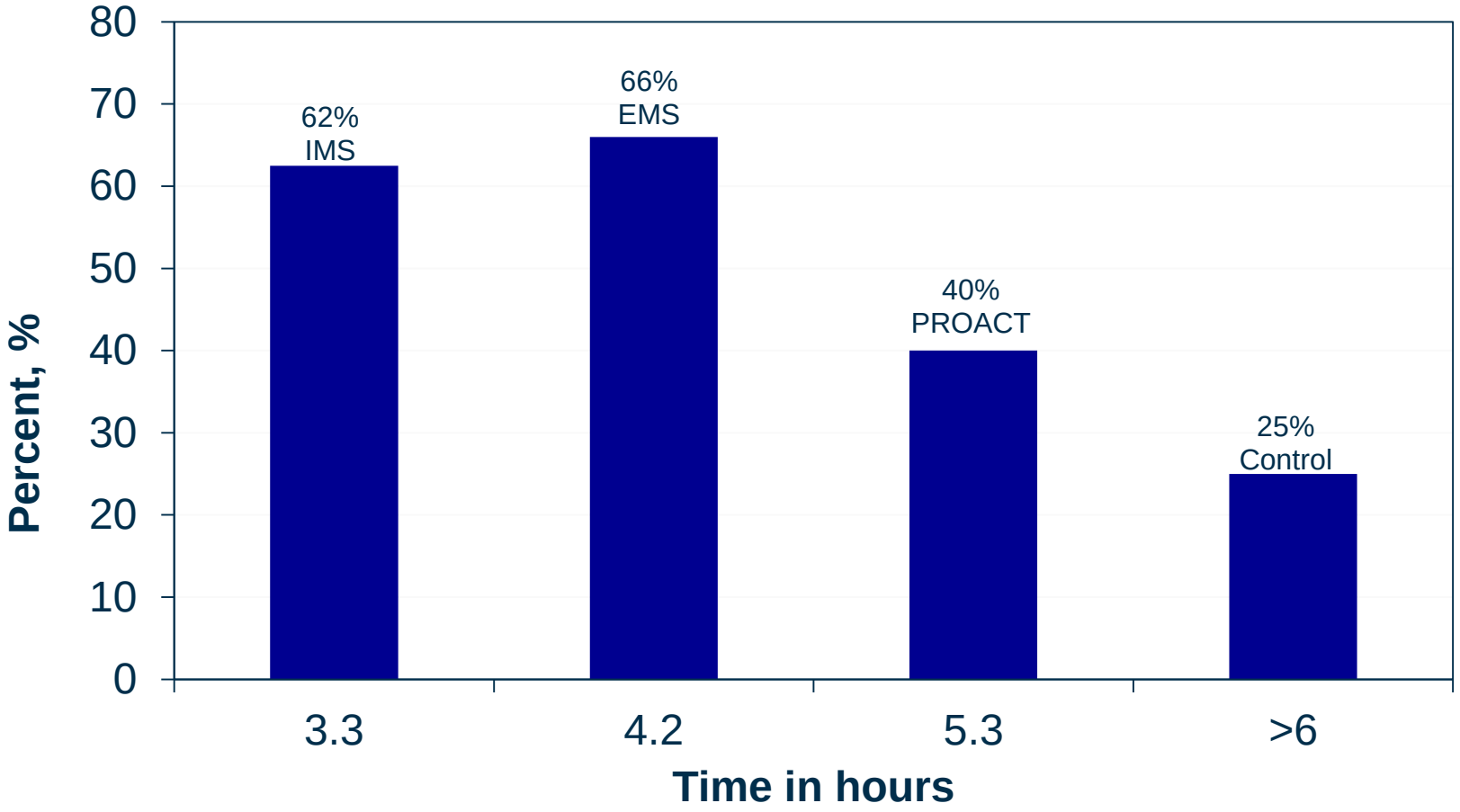
# PROACT II
# Proof of Principle

- **Highly selected population**
  - **12,323 stroke patients screened**
  - **180 eligible patients enrolled**
- **Worst-case scenario:**
  - **Late time to treatment (5.3 hours)**
  - **Limited manipulation, no mechanical maceration of clot**
  - **Severe strokes, NIHSS=17**



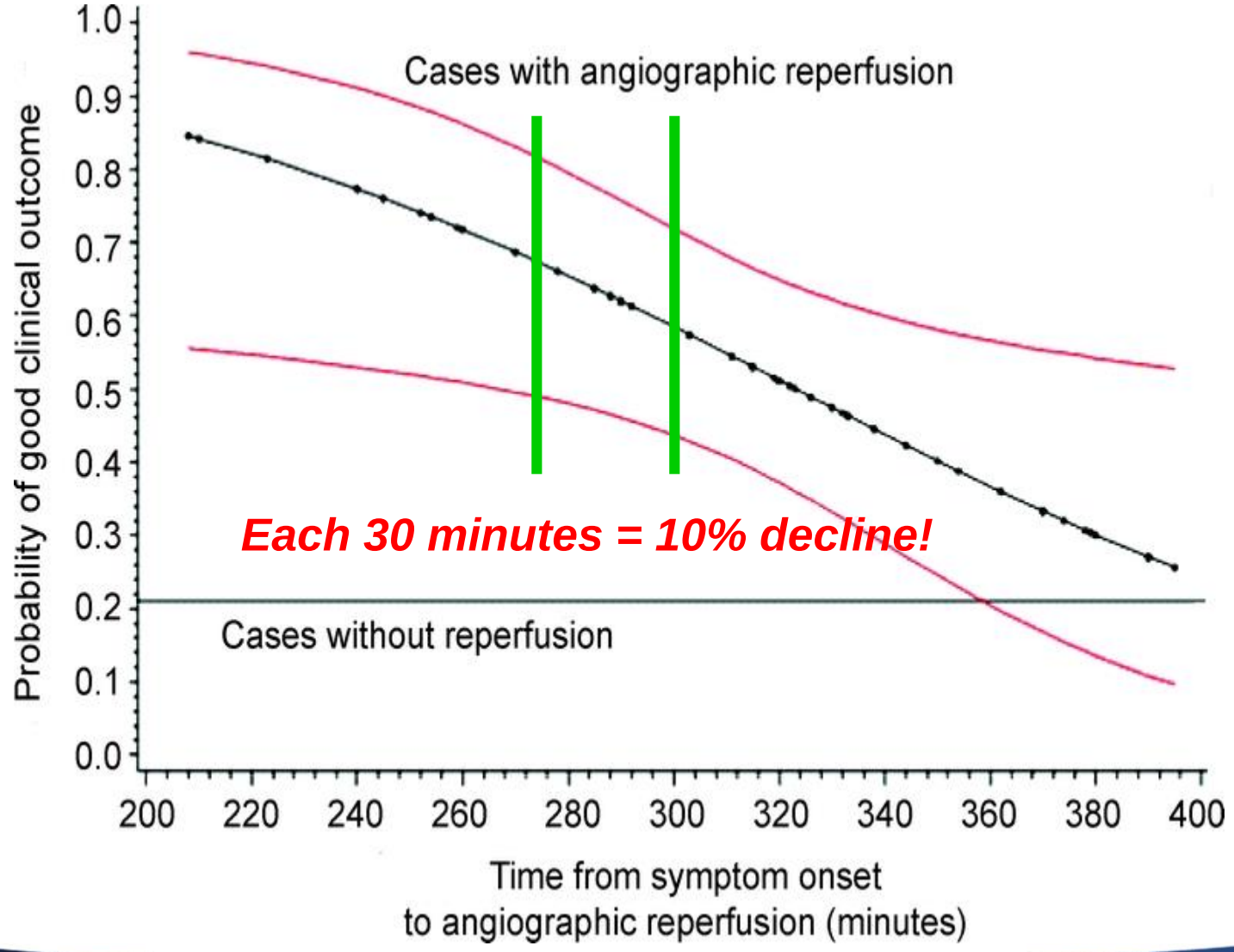
Furlan. JAMA 282:2003, 1999

# Bridging Protocols: Outcome mRS 0-2 vs Time




Lewandowski Stroke 30: 2598, 1999
IMS Investigators. Stroke 35: 904, 2004
Kathri P Stroke 39: 560, 2008

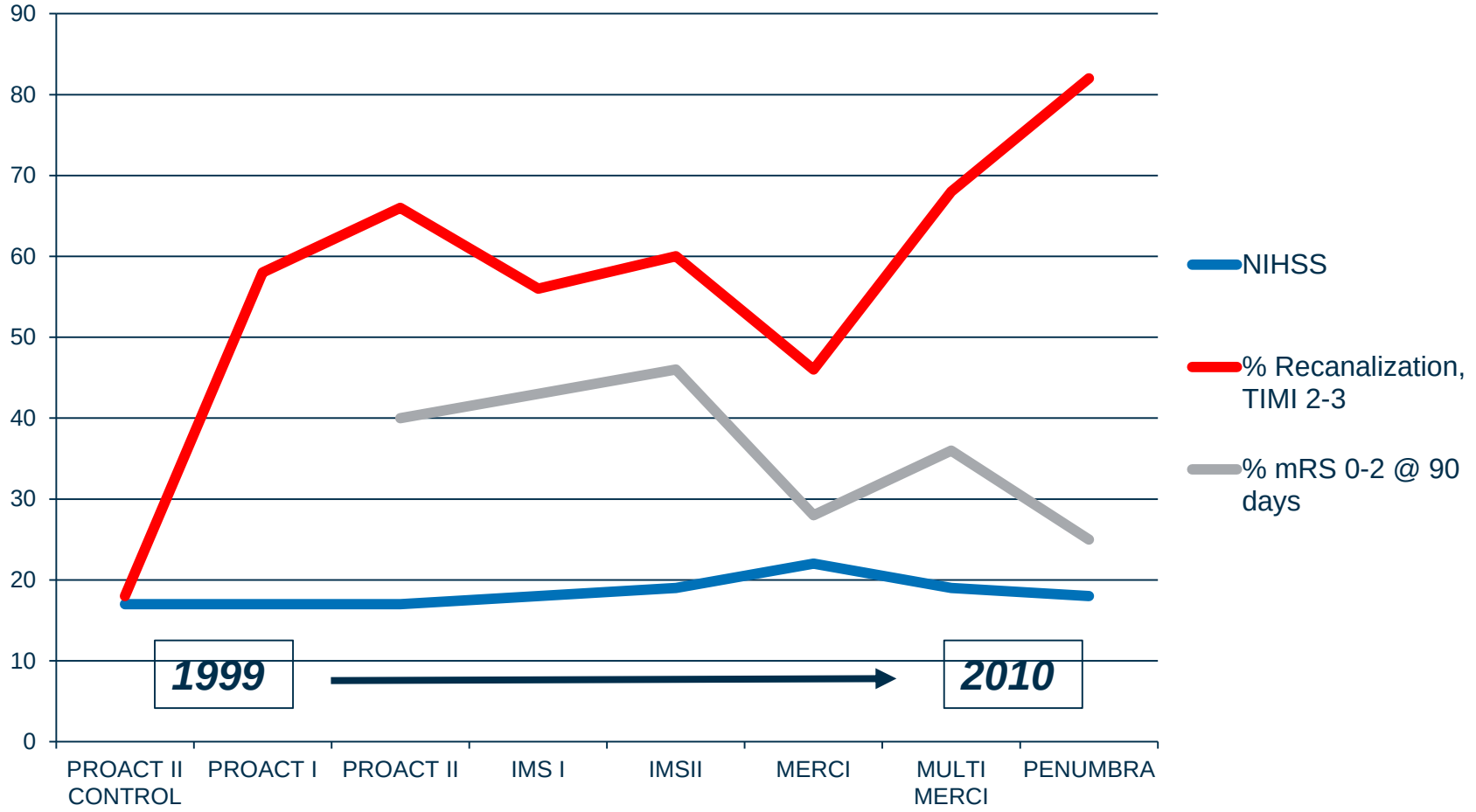
# Timing Is Critical – IMS I & II






Khatri P. Neurology 73: 1066-1072, 2009

# Outcome by NIHSS and TIMI Recan






Meyers. Circulation 123: 2591, 2011

# 6+ years in the making

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Imaging Selection and

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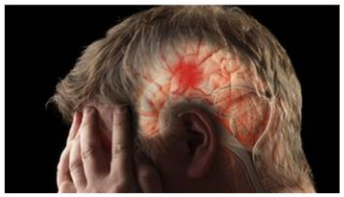
## Clot-retrieval no better for strokes

**Recovery after stroke is not improved by using a device to retrieve the clot, a US study suggests.**



More than 650 patients were studied

In a trial of more than 650 patients, standard clot-busting drugs were just as effective as using surgery to clear blockages directly.

The University of Cincinnati-led study was stopped early after it became clear that risky procedures to remove clots were having little impact.

Experts said more work was needed over clot-retrieval devices.

Presenting the findings at the International Stroke Conference, researchers said that 39% of patients treated with a clot-busting drug called tPA were living independently after 90 days.

In those who also had undergone a procedure to insert a wire through an artery to break up, remove or dissolve the clot, 41% were living independently after three months.

And 16% of patients undergoing the surgery had complications, the team reported in a paper also being published in the New England Journal of Medicine.

All patients received clot-busting tPA within three hours of their stroke symptoms.

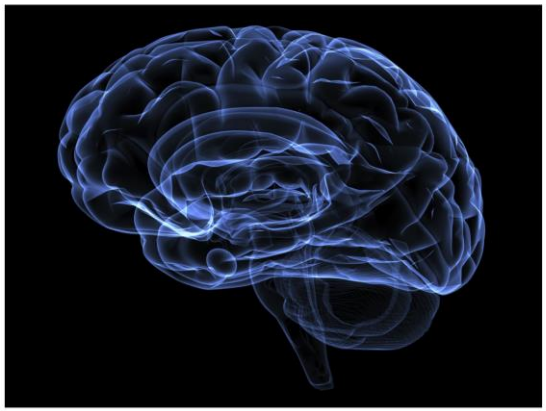
Related Stories

Stem cell 'first aid' for rat stroke

'Clot nets' help stroke recovery

Health & Science

## Long-awaited stroke studies show hopeful new treatment no better than older one



Three new studies have shown that a new approach to treating strokes is not as useful as was once thought. (istockphoto)



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travenous t-PA within
lar therapy or intrave-
sure was a modified
pendence) at 90 days
ter disability).

dified Rankin scale, ranging from 0 (no symptoms) to 6 (dead).

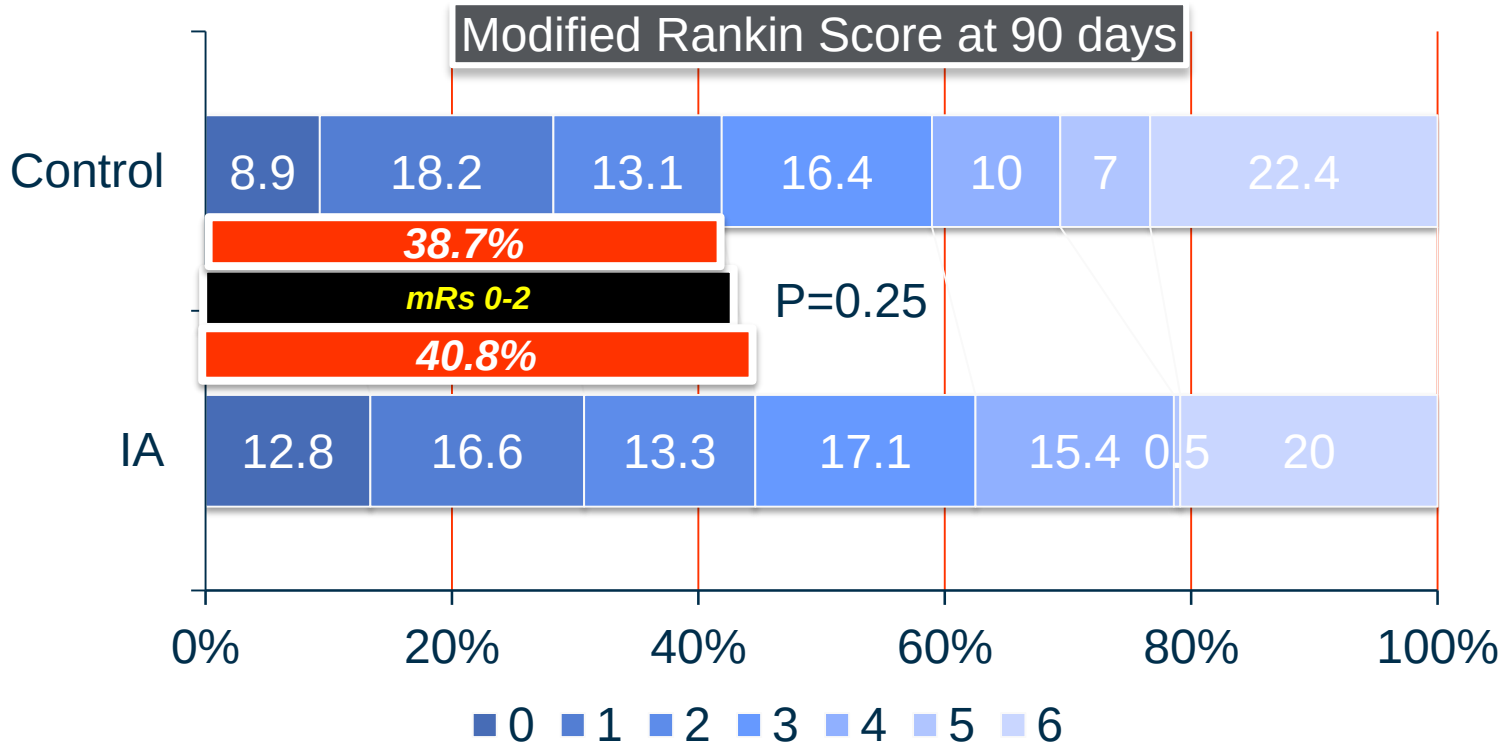
This article was published on February 7, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1214300



Broderick. NEJM 368: 893, 2013
Kidwell. NEJM 368: 914, 2013
Ciccone. NEJM 368: 904, 2013

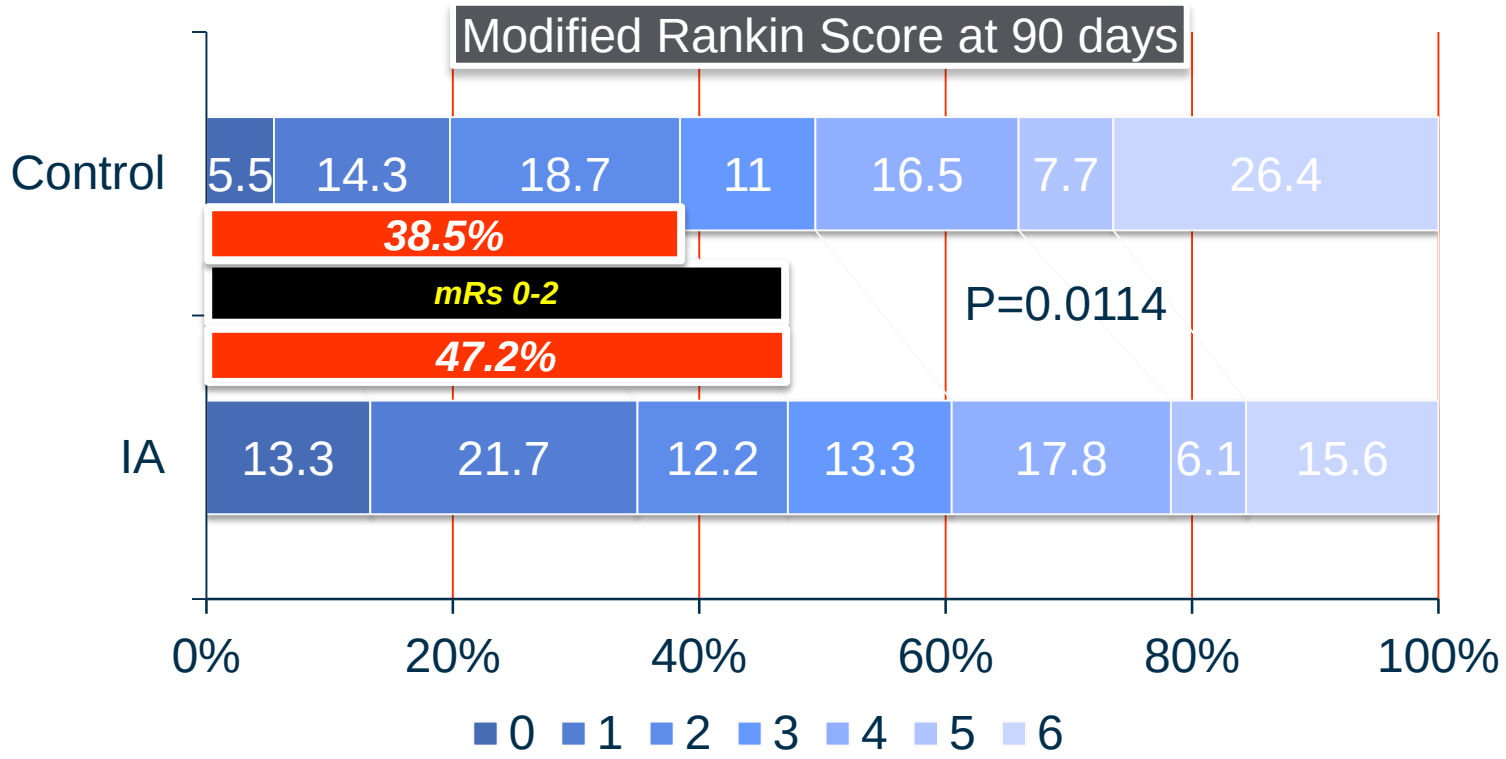
# IMS III: Primary Outcome
# No difference






Broderick. NEJM 368: 893, 2013

# IMS III: CTA documented LVO





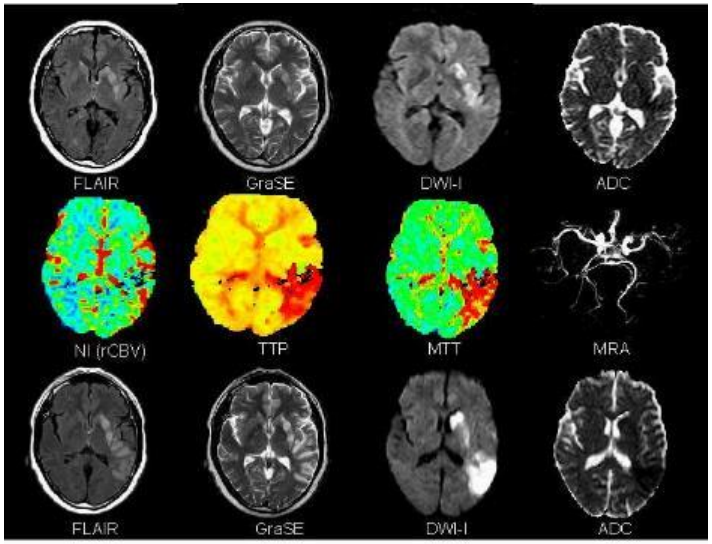

Broderick. NEJM 368: 893, 2013

# CONCLUSIONS: IMS III

- **No significant difference in functional independence with endovascular therapy after intravenous t-PA, as compared with intravenous t-PA alone**
- **No difference in safety**

# MR RESCUE: Methods

- ≤ 8 hours of onset
- Anterior circulation LVO
- Randomized to either EVT or Medical Tx
- "penumbral" pattern by CT or MRI
  - Penumbra : "Small core" (<90 cc), large penumbra
  - Non-Penumbral: Large core and small/absent penumbra

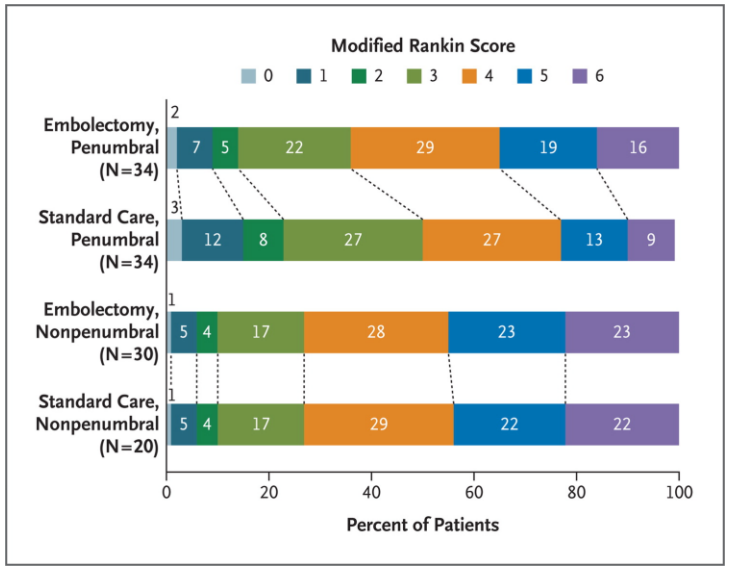





Kidwell. NEJM 368: 914-23, 2013

# MR RESCUE: 90-day mRS

- **NO DIFFERENCE IN OUTCOMES**
  - **Endovascular vs. medical therapy**
  - **Penumbra vs. no penumbra**




*p=0.23*

*p=0.32*



Kidwell. NEJM 368: 914-23, 2013

# Synthesis Expansion: Outcomes

- **Primary Outcome (mRS < 1)**
  - **30.4% EVT**
  - **34.8% IV tPA**
- **Death Rates**
  - **EVT: 14 (8%)**
  - **IV tPA: 11 (6%)**

Italian Medicines Agency (AIFA)

***"EVT is not superior to standard treatment with IV tPA"***

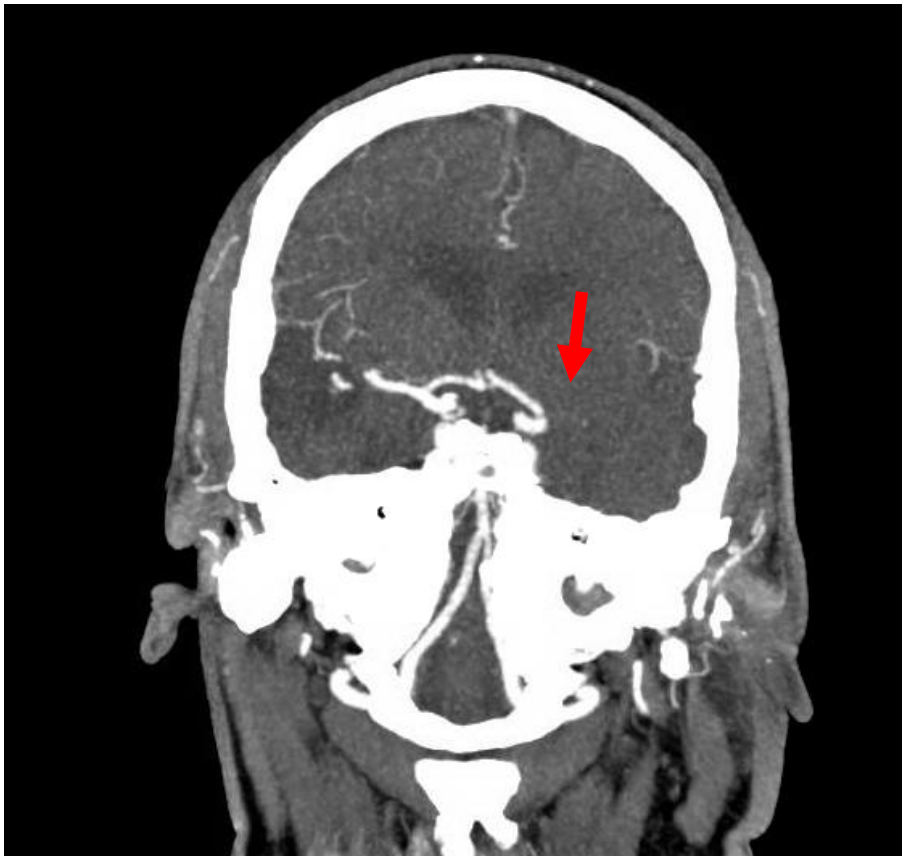
Columbia University Medical Center
Philip M. Meyers, MD



Ciccone A. NEJM 2013 Mar 7;368(10):904-13

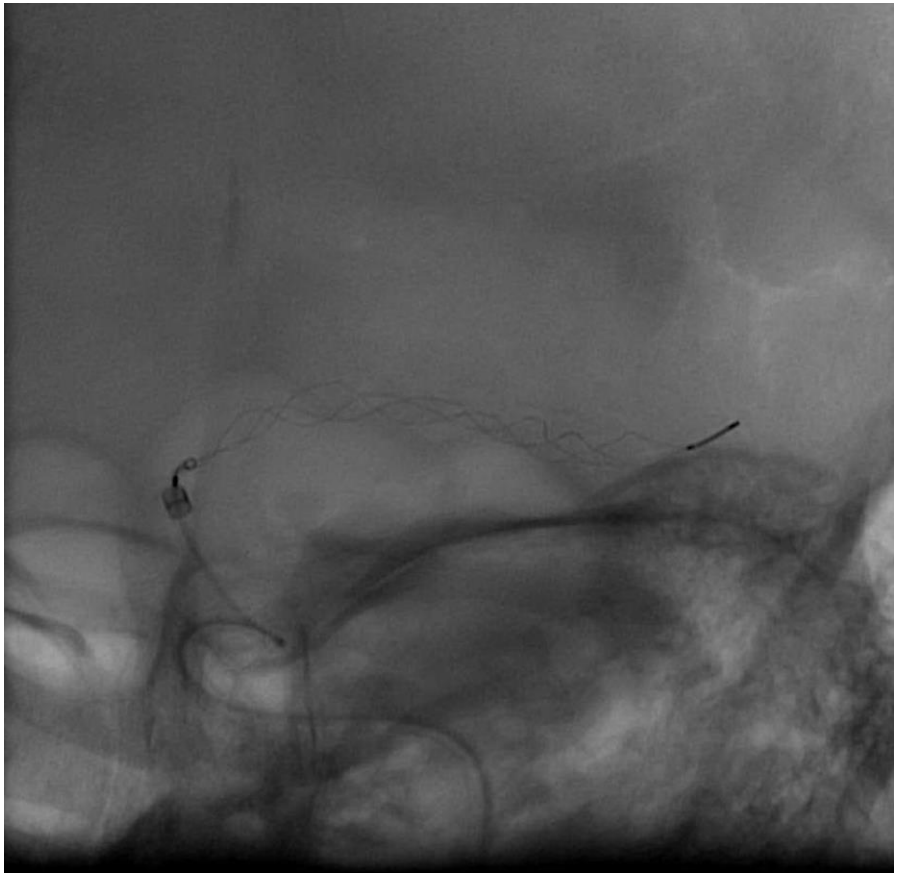
# April 2014
# Scientist, Acute Left MCA Occlusion

CT Scan

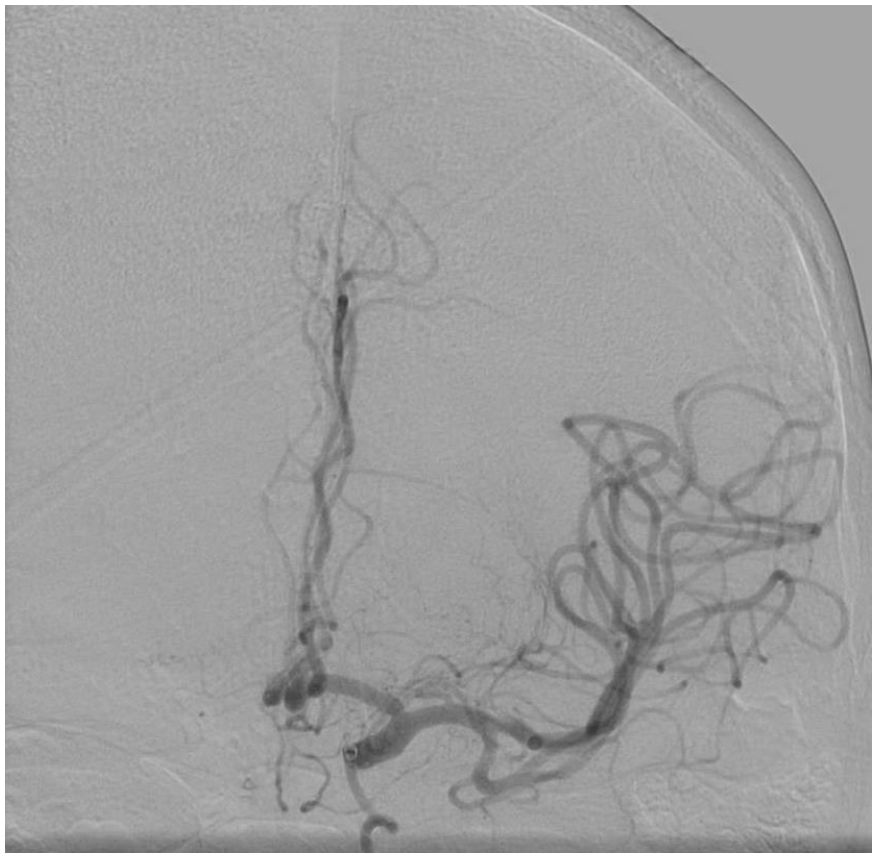


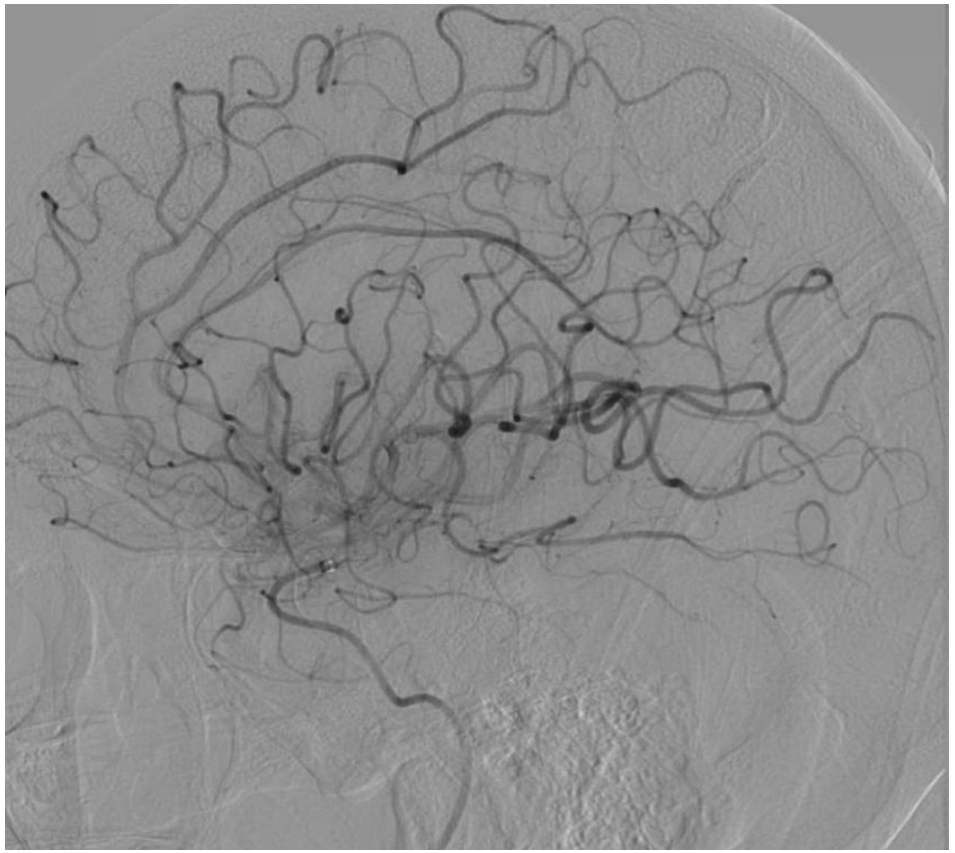
CT Angiogram

# NIHSSS 27

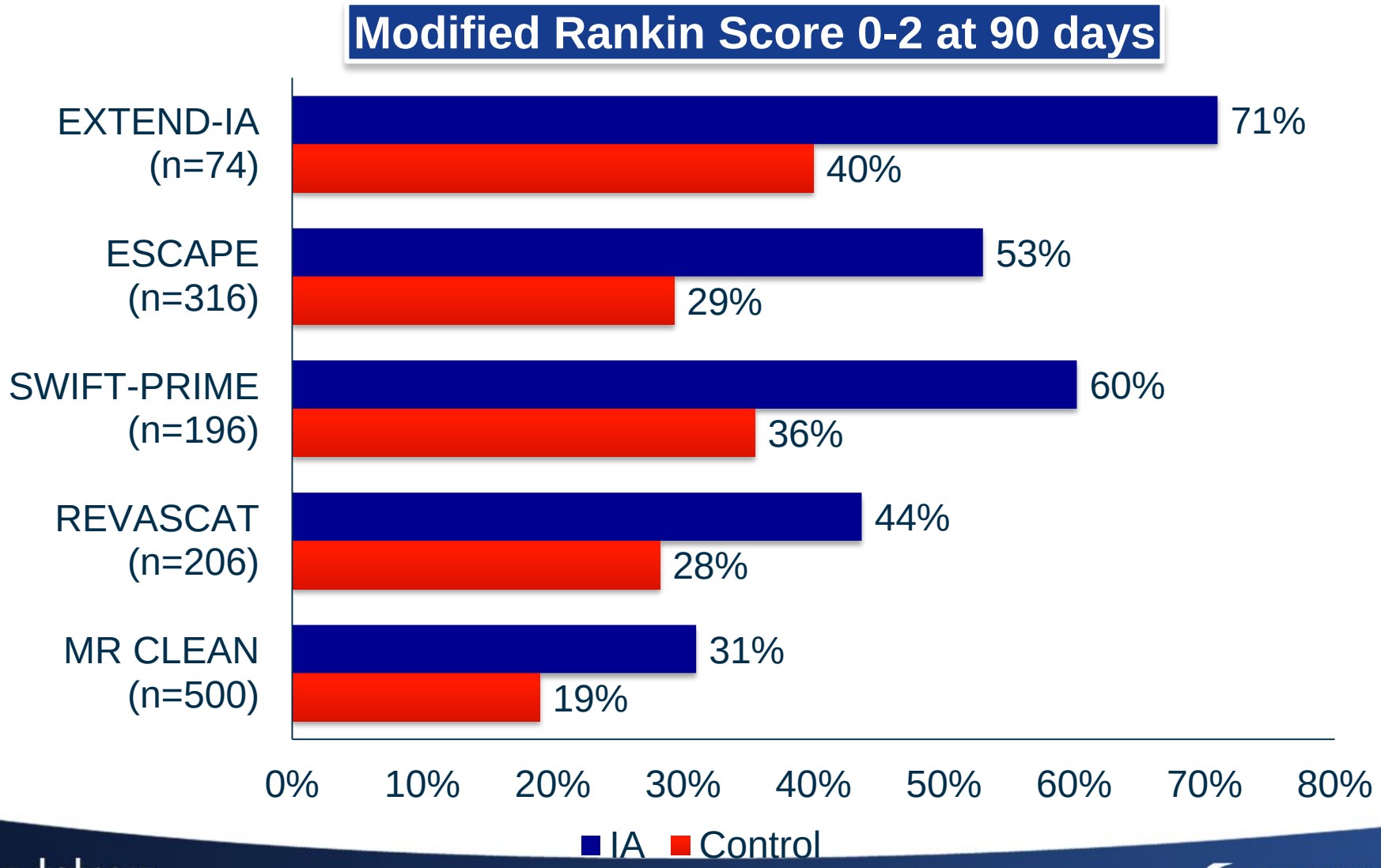


# TICI 3 (Complete) Recanalization

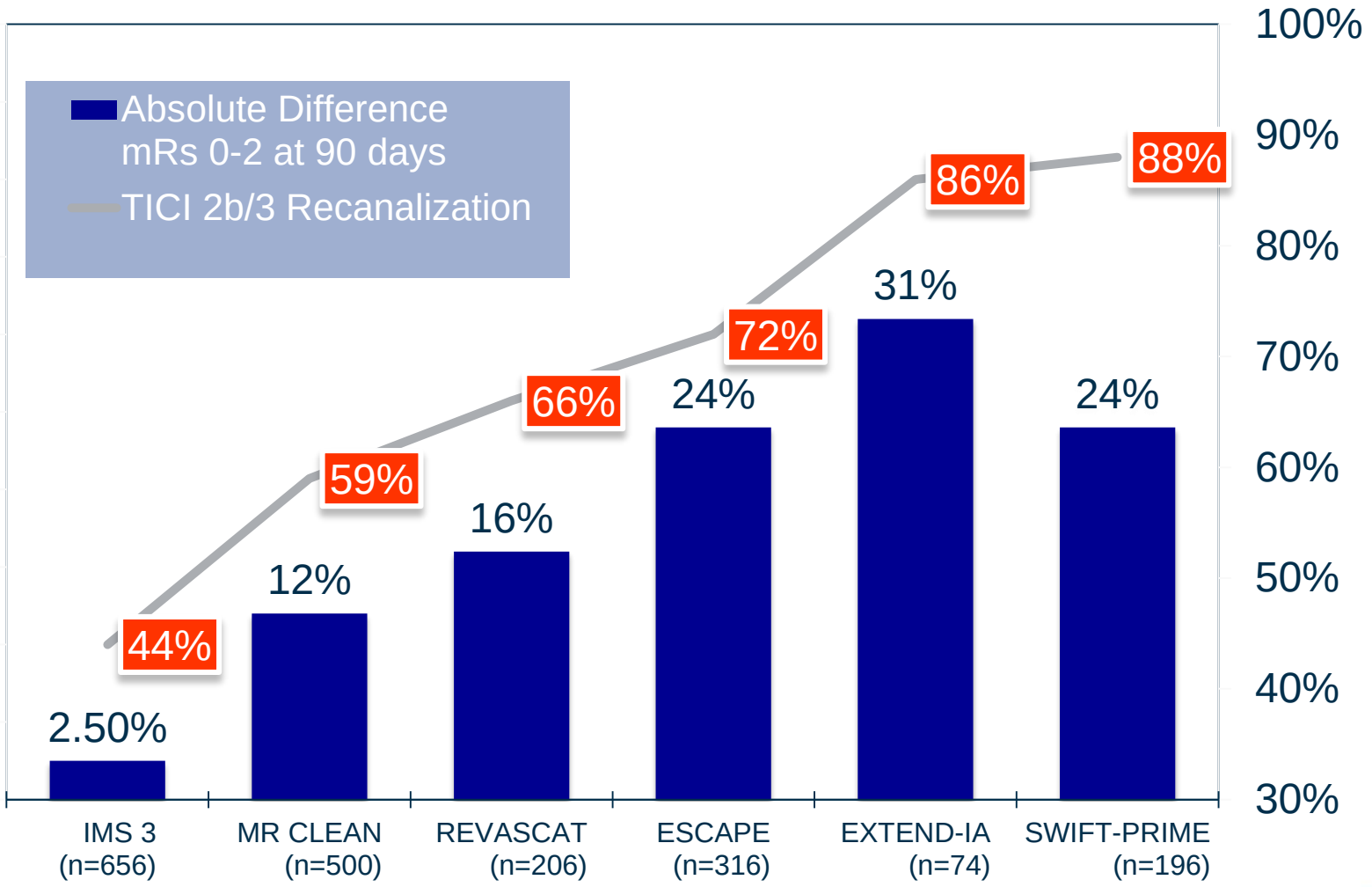




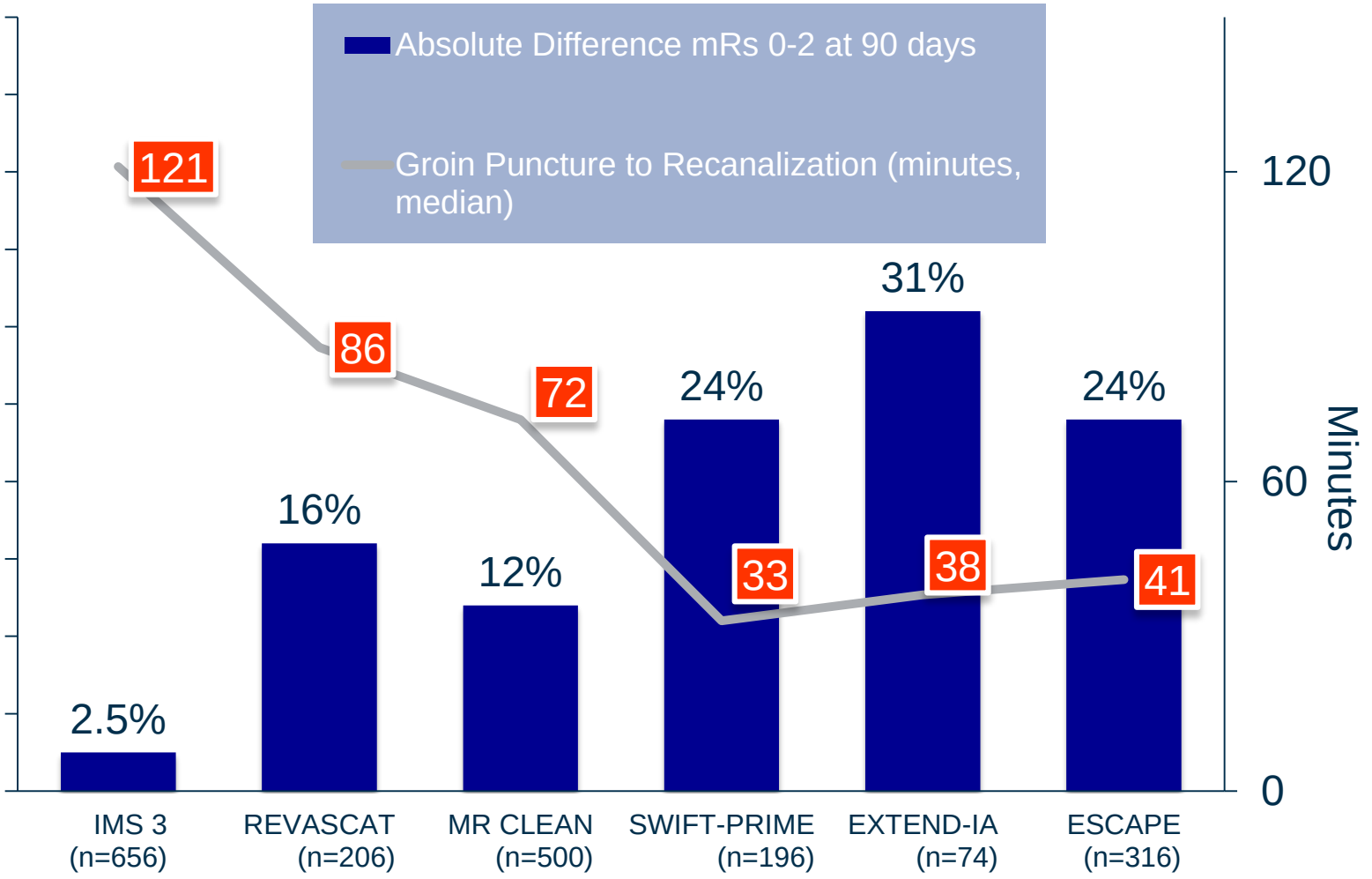
# Recent trials: Summary



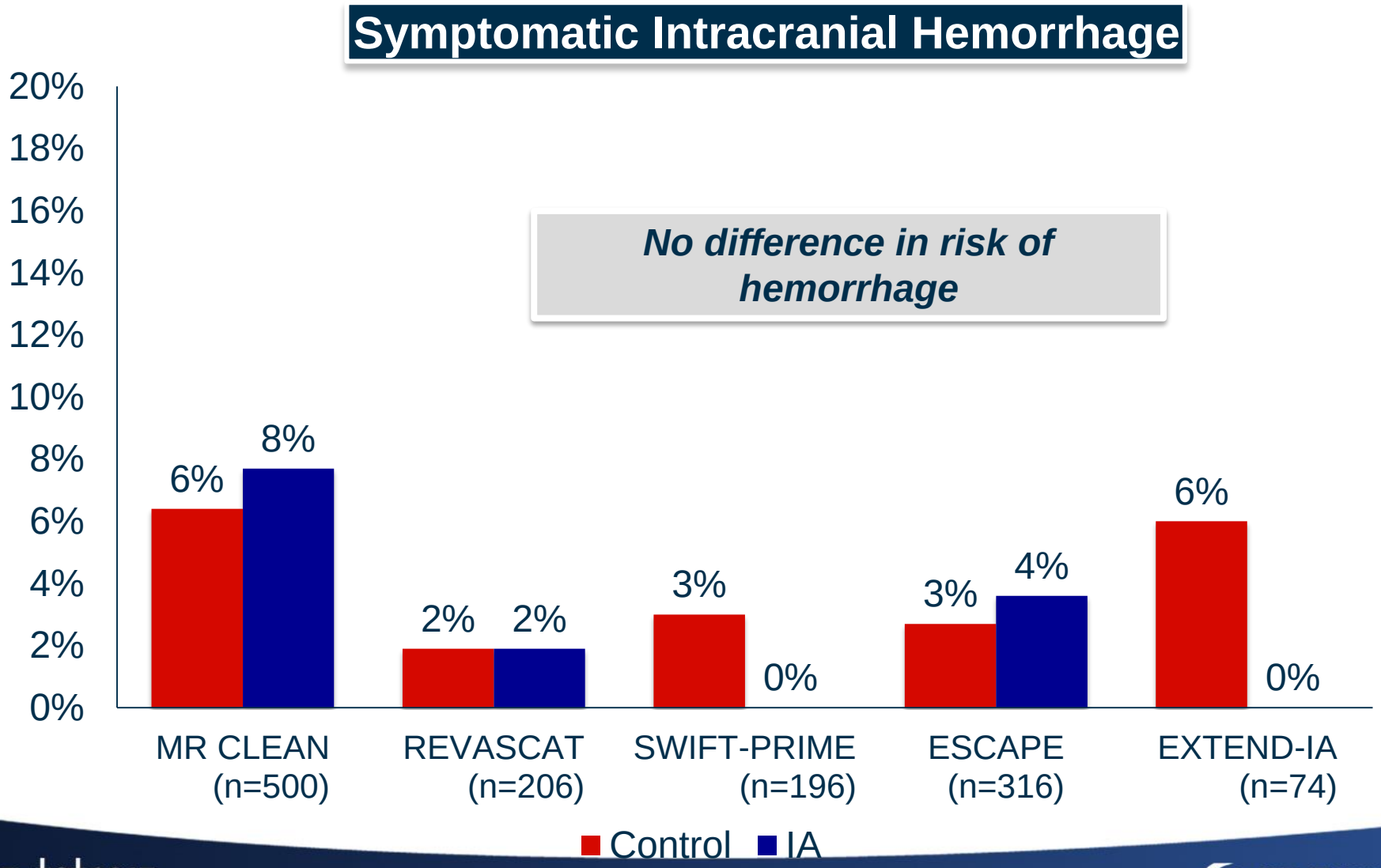
# TICI 2b-3 Recanalization and Outcome



# Time to recanalization



# Recent trials: Remarkable Safety



# Endovascular Stroke Trials Meta-analysis

**Figure 2A: Functional independence (90-day modified Rankin score of 0 to 2); analysis limited to newer trials**

| Study or Subgroup | Intervention Events | Intervention Total | Control Events | Control Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| ESCAPE 2015 | 87 | 164 | 43 | 147 | 26.1% | 2.73 [1.71, 4.37] |
| EXTEND-IA 2015 | 25 | 35 | 14 | 35 | 5.8% | 3.75 [1.38, 10.17] |
| MR CLEAN 2015 | 76 | 233 | 51 | 267 | 34.2% | 2.05 [1.36, 3.09] |
| REVASCAT 2015 | 45 | 103 | 29 | 103 | 17.1% | 1.98 [1.11, 3.53] |
| SWIFT PRIME 2015 | 59 | 98 | 33 | 97 | 16.9% | 2.93 [1.64, 5.26] |
| **Total (95% CI)** | | **633** | | **649** | **100.0%** | **2.42 [1.90, 3.07]** |
| Total events | 292 | | 170 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 2.51, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 7.22 (P < 0.00001)

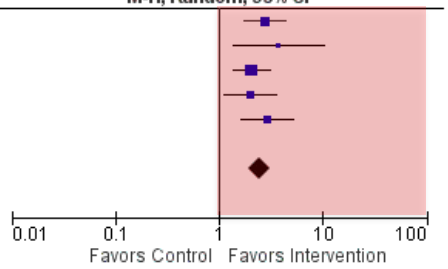



**Figure 2B: All cause-Mortality; analysis limited to newer trials**

| Study or Subgroup | Intervention Events | Intervention Total | Control Events | Control Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| ESCAPE 2015 | 17 | 164 | 28 | 147 | 23.5% | 0.49 [0.26, 0.94] |
| EXTEND-IA 2015 | 3 | 35 | 7 | 35 | 6.7% | 0.38 [0.09, 1.59] |
| MR CLEAN 2015 | 44 | 233 | 49 | 267 | 35.2% | 1.04 [0.66, 1.63] |
| REVASCAT 2015 | 19 | 103 | 16 | 103 | 20.2% | 1.23 [0.59, 2.55] |
| SWIFT PRIME 2015 | 9 | 98 | 12 | 97 | 14.5% | 0.72 [0.29, 1.79] |
| **Total (95% CI)** | | **633** | | **649** | **100.0%** | **0.80 [0.54, 1.18]** |
| Total events | 92 | | 112 | | | |

Heterogeneity: Tau² = 0.06; Chi² = 5.81, df = 4 (P = 0.21); I² = 31%
Test for overall effect: Z = 1.13 (P = 0.26)

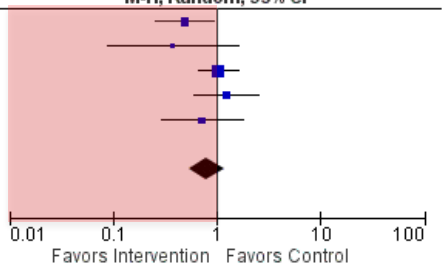
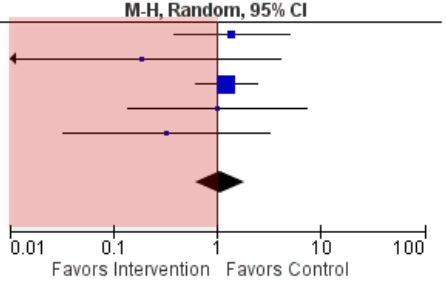



**Figure 2C: Symptomatic Intracerebral Hemorrhage; analysis limited to newer trials**

| Study or Subgroup | Intervention Events | Intervention Total | Control Events | Control Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| ESCAPE 2015 | 6 | 165 | 4 | 150 | 18.5% | 1.38 [0.38, 4.98] |
| EXTEND-IA 2015 | 0 | 35 | 2 | 35 | 3.2% | 0.19 [0.01, 4.08] |
| MR CLEAN 2015 | 18 | 233 | 17 | 267 | 64.6% | 1.23 [0.62, 2.45] |
| REVASCAT 2015 | 2 | 103 | 2 | 103 | 7.8% | 1.00 [0.14, 7.24] |
| SWIFT PRIME 2015 | 1 | 98 | 3 | 97 | 5.9% | 0.32 [0.03, 3.16] |
| **Total (95% CI)** | | **634** | | **652** | **100.0%** | **1.08 [0.62, 1.87]** |
| Total events | 27 | | 28 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)





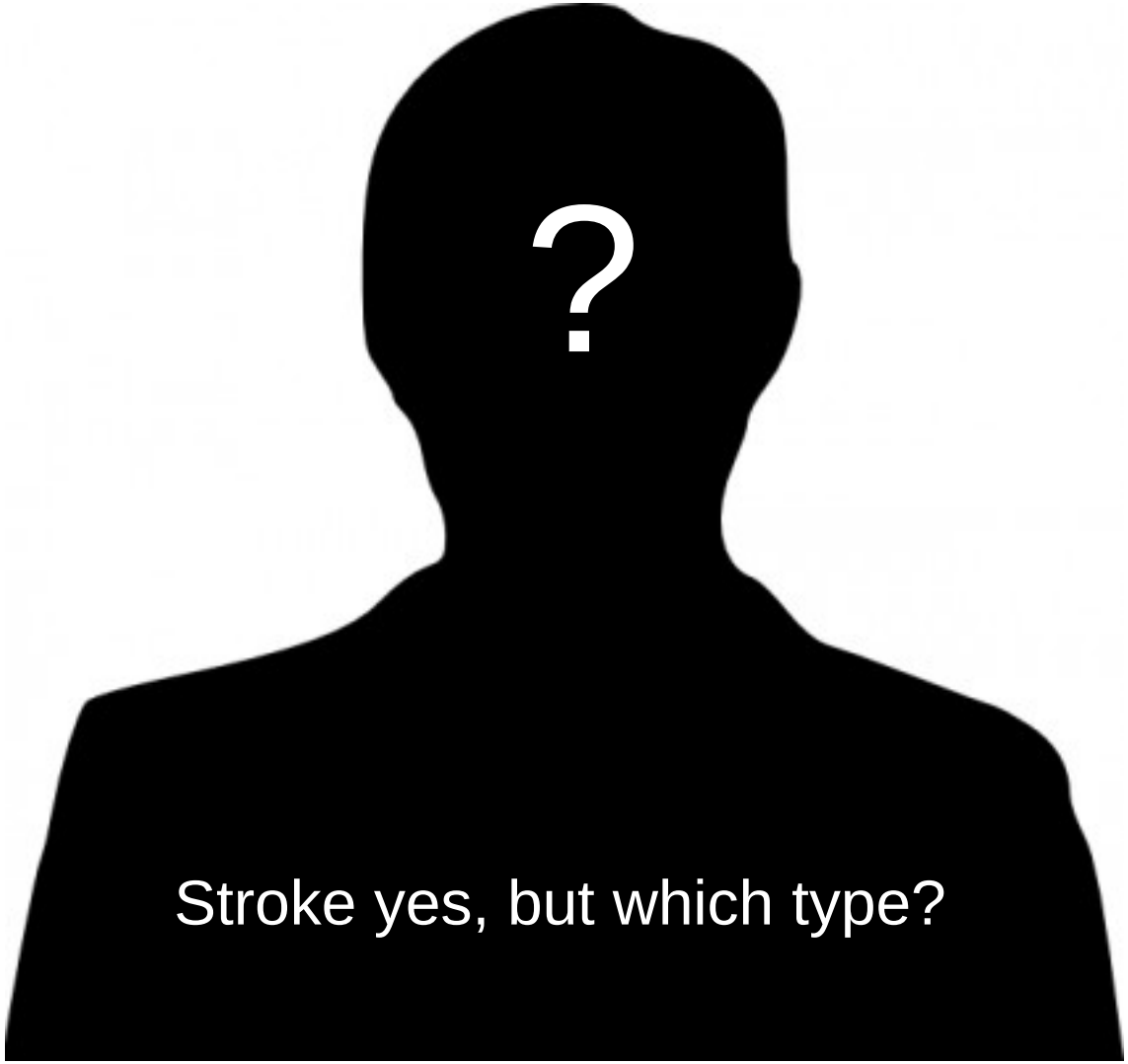

Sardar. Eur Heart Journal 36: 2373-80, 2015

# Negative trials: Why they failed

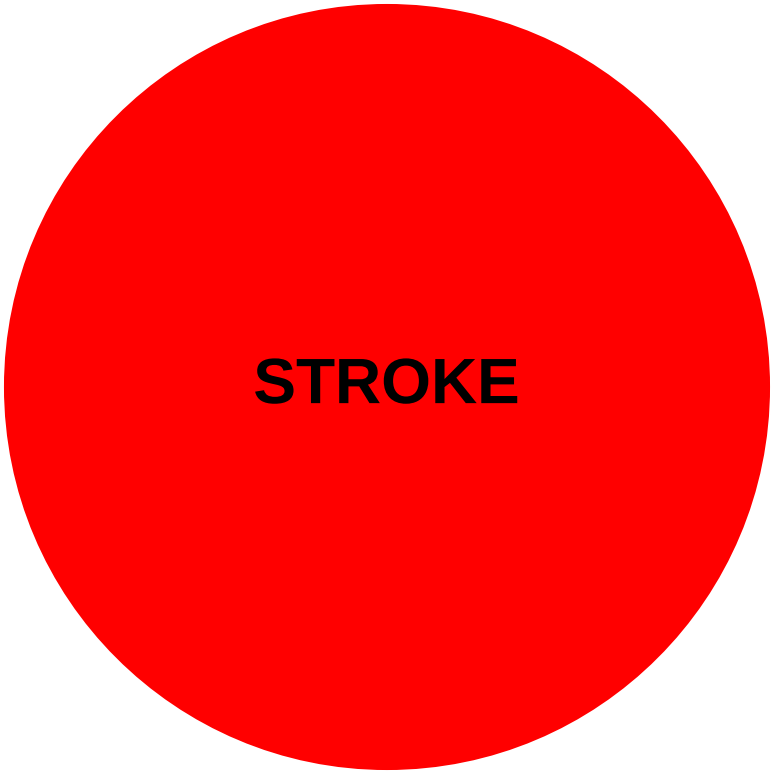
- **Rate of reperfusion:**
  - **1st and 2nd generation thrombectomy devices**
  - **27-40% vs. 58-88% TICI 2b-3**
- **Less specific vascular imaging requirement**
  - **No Large vessel occlusion**
  - **Less discrimination of infarct and collaterals**
- **Longer time to reperfusion:**
  - **No difference in time to treatment (3.1-3.5 hr)**

➔ **Reperfusion occurs more quickly with new devices**
**5.4 hr (IMS-III) vs. 4.0-4.2 hr**

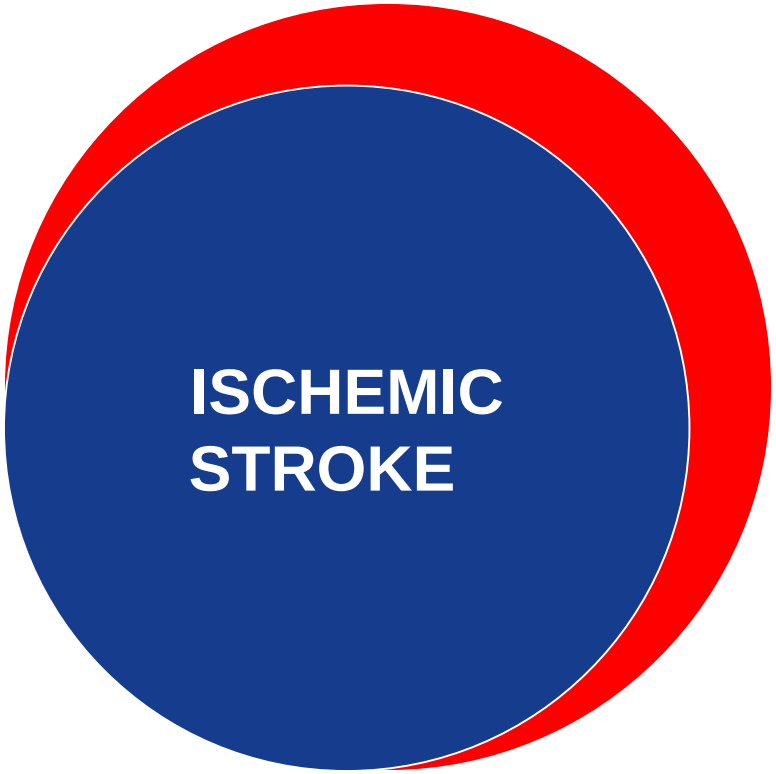
# Game of Probabilities



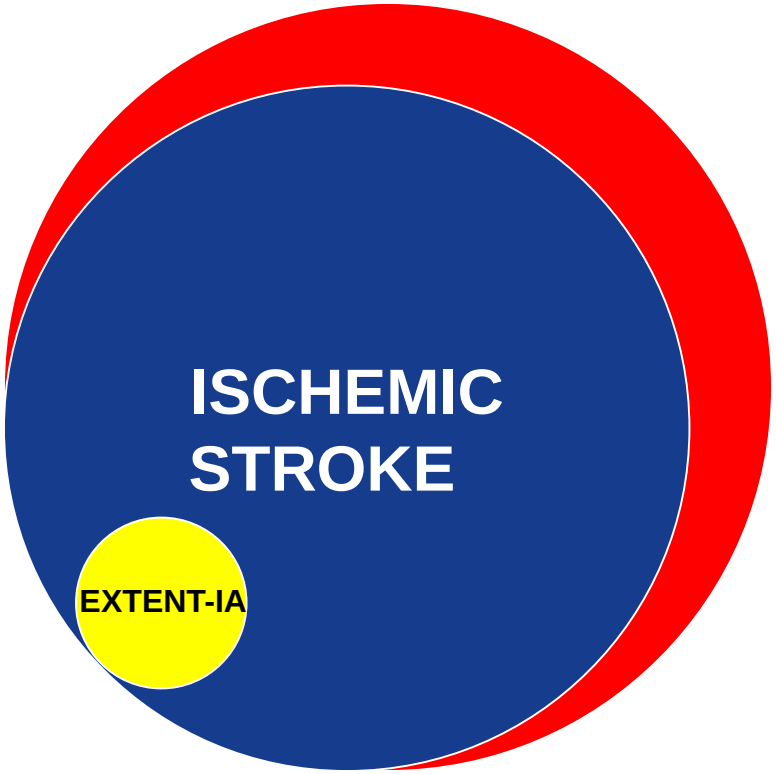
# Highly selected subpopulation



# Highly selected subpopulation

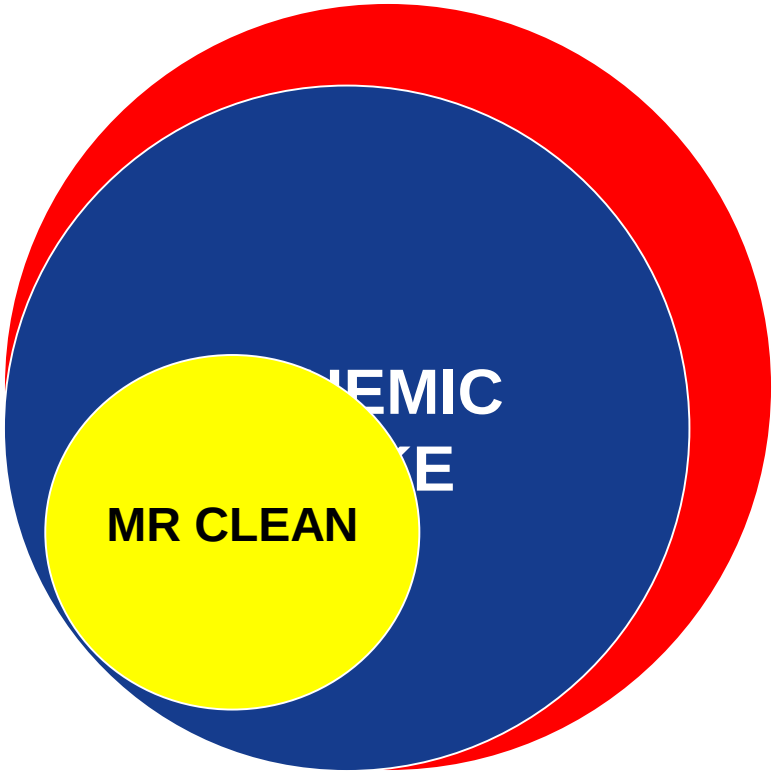


# Highly selected subpopulation




Only **8.5%** of stroke patients treated with IV rt-PA were eligible for randomization

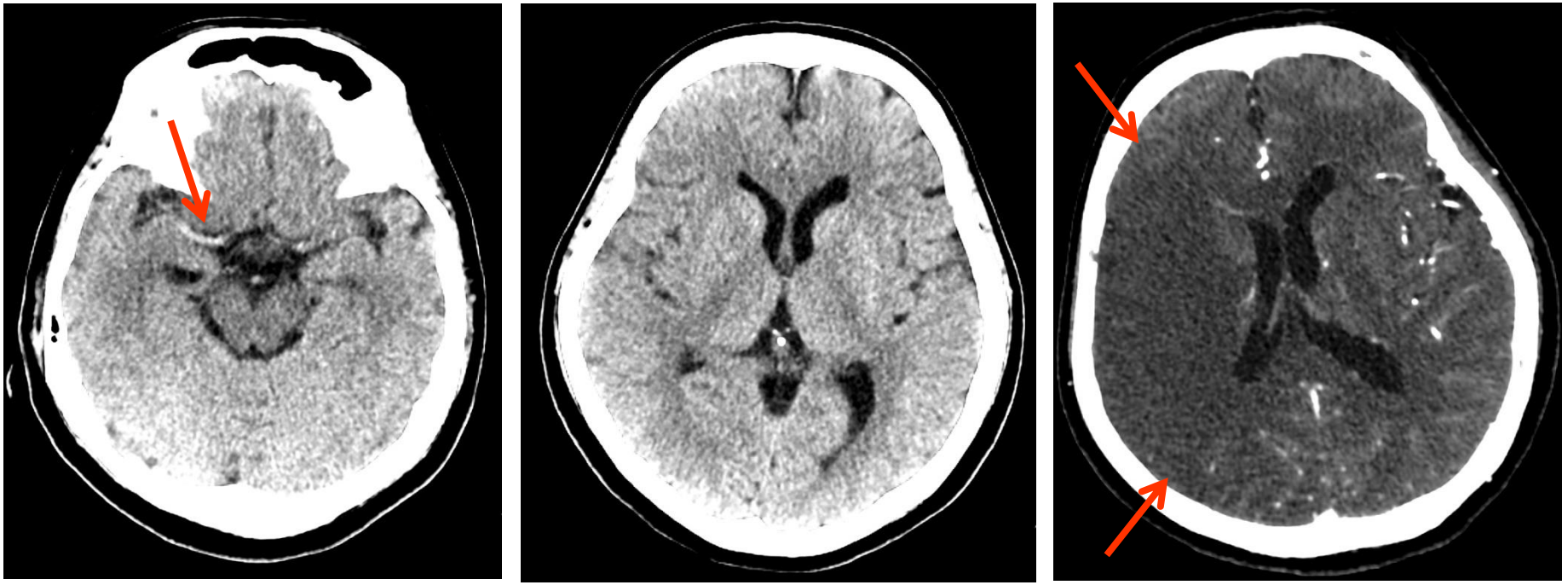
# Highly selected subpopulation




Enhanced selection based on imaging to benefit of intervention:
19.1% mRS 0-2
vs. 35-40% in prior trials

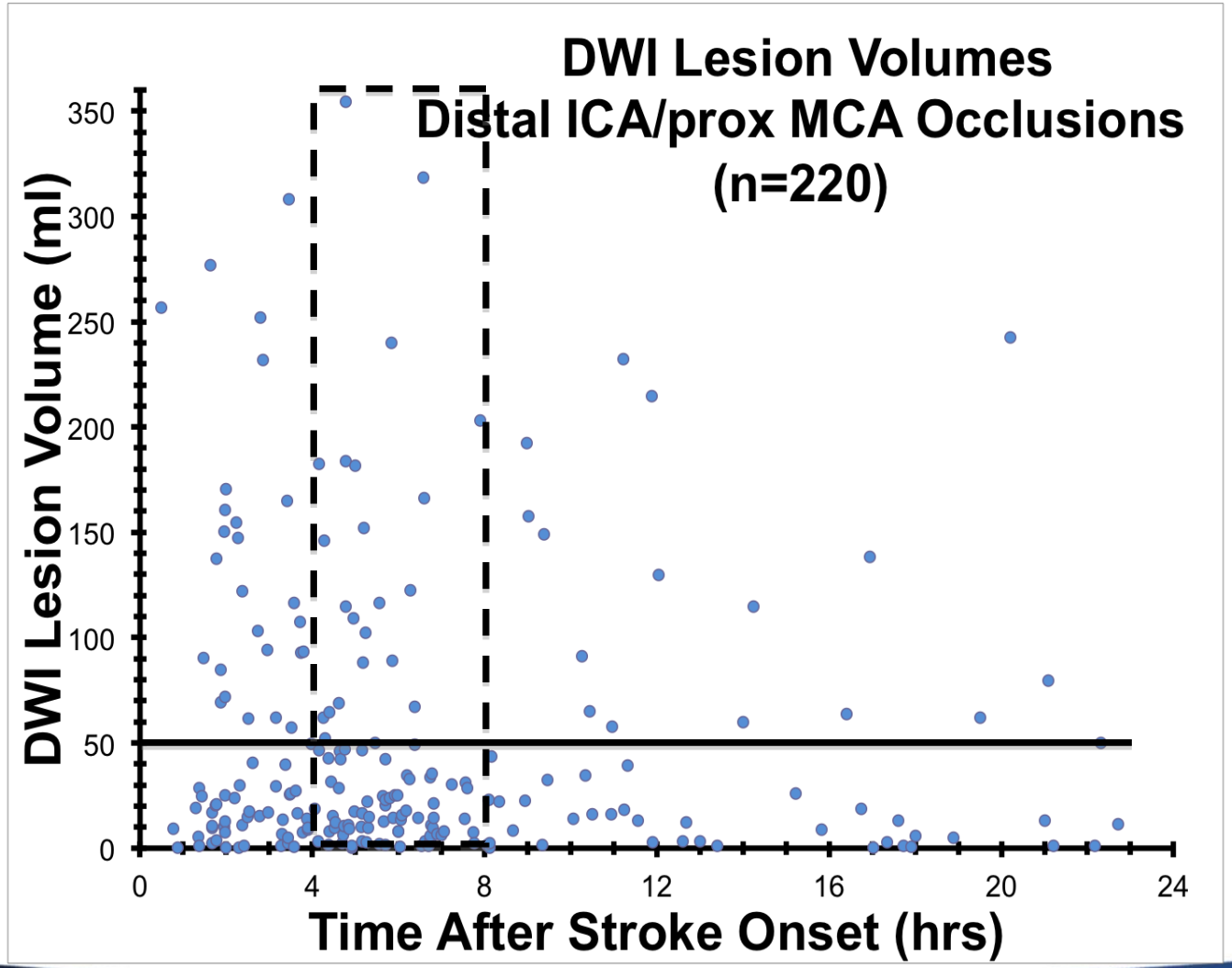
# Witnessed Stroke

## Severe ischemic pattern



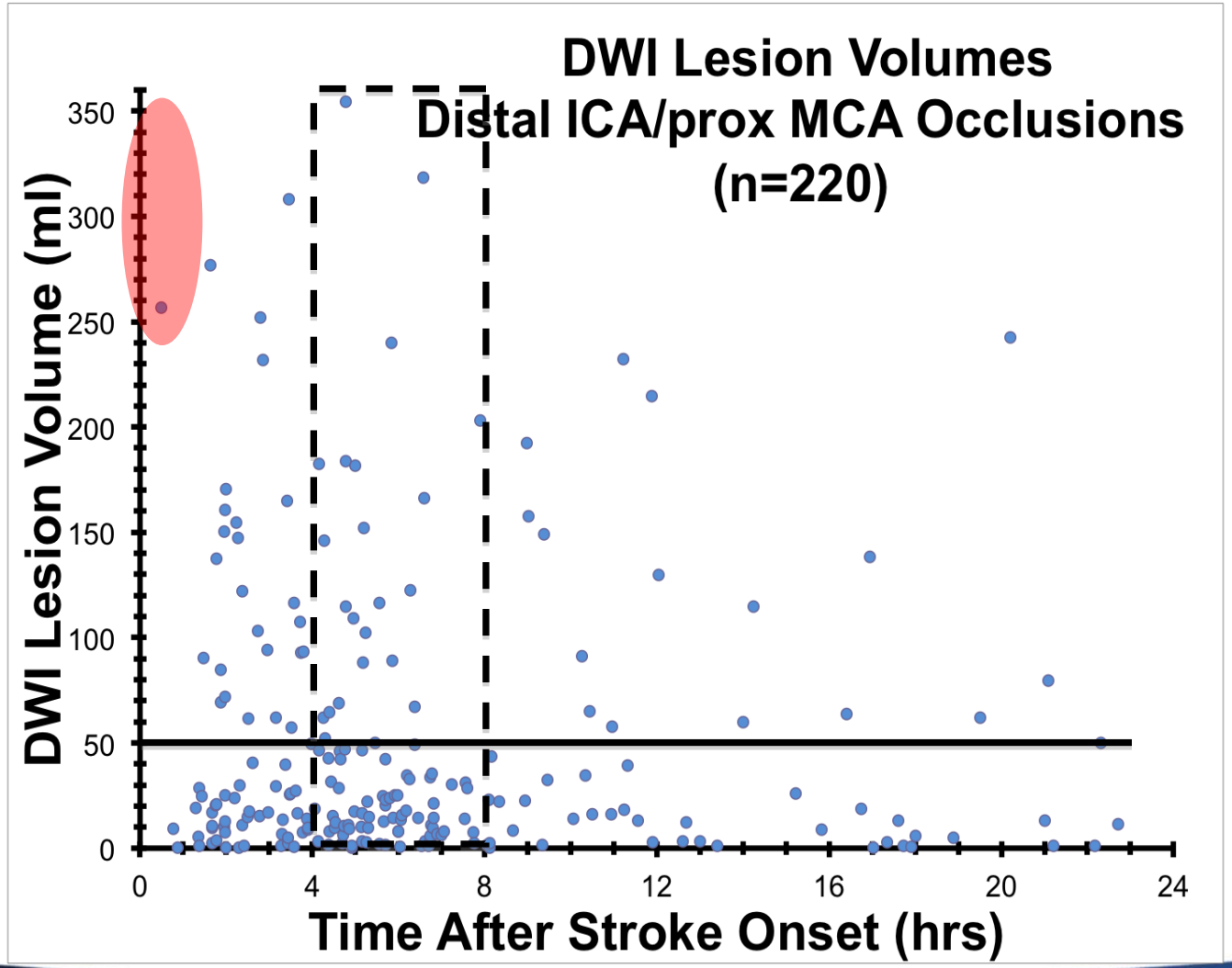
6:02 PM → IV rtPA → 6:26 PM

# Distal ICA/Proximal MCA Occl + DWI volume < 50ml




Courtesy of G.Gonzalez, MD PhD
Massachusetts General Hospital

# Distal ICA/Proximal MCA Occl + DWI volume < 50ml



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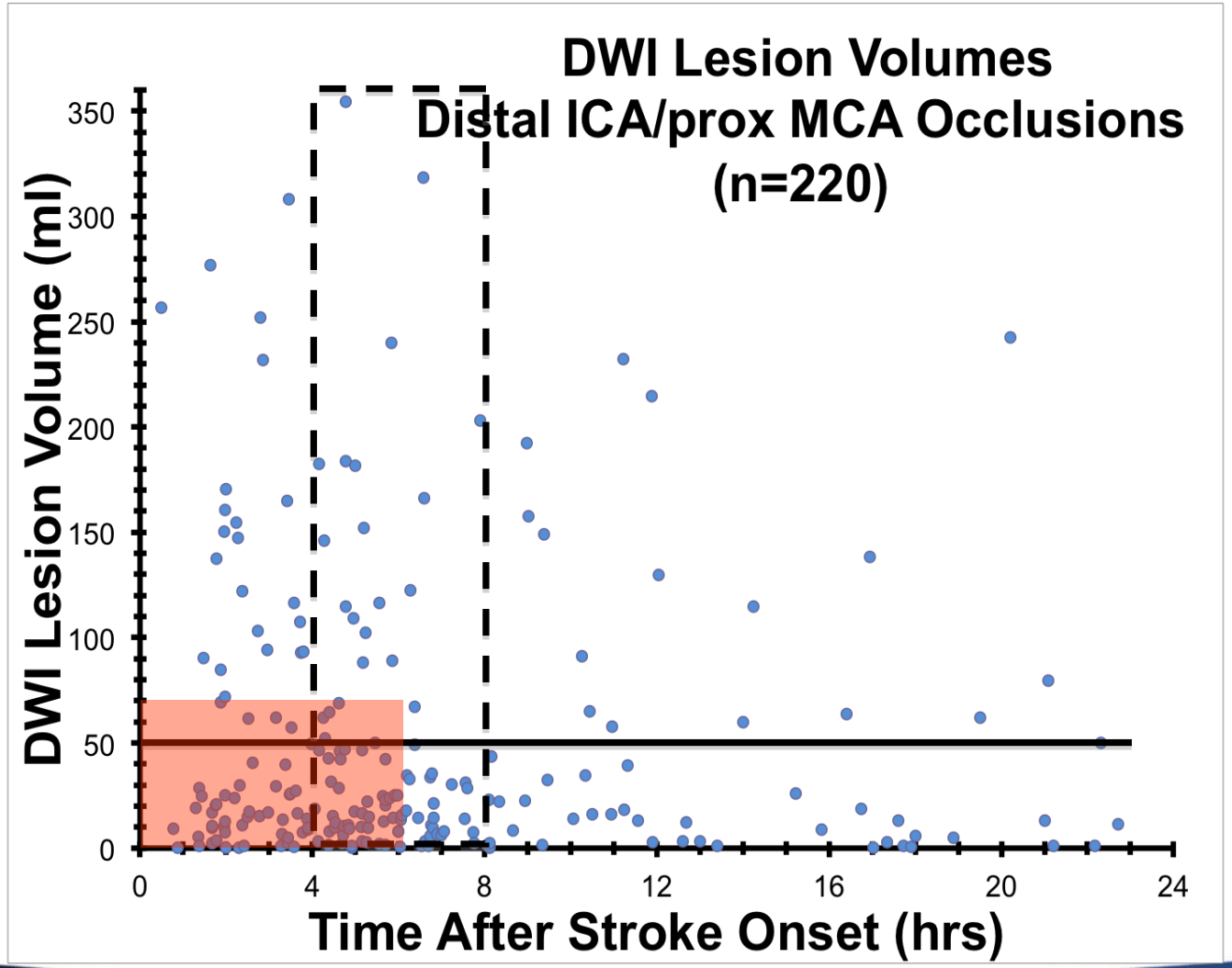
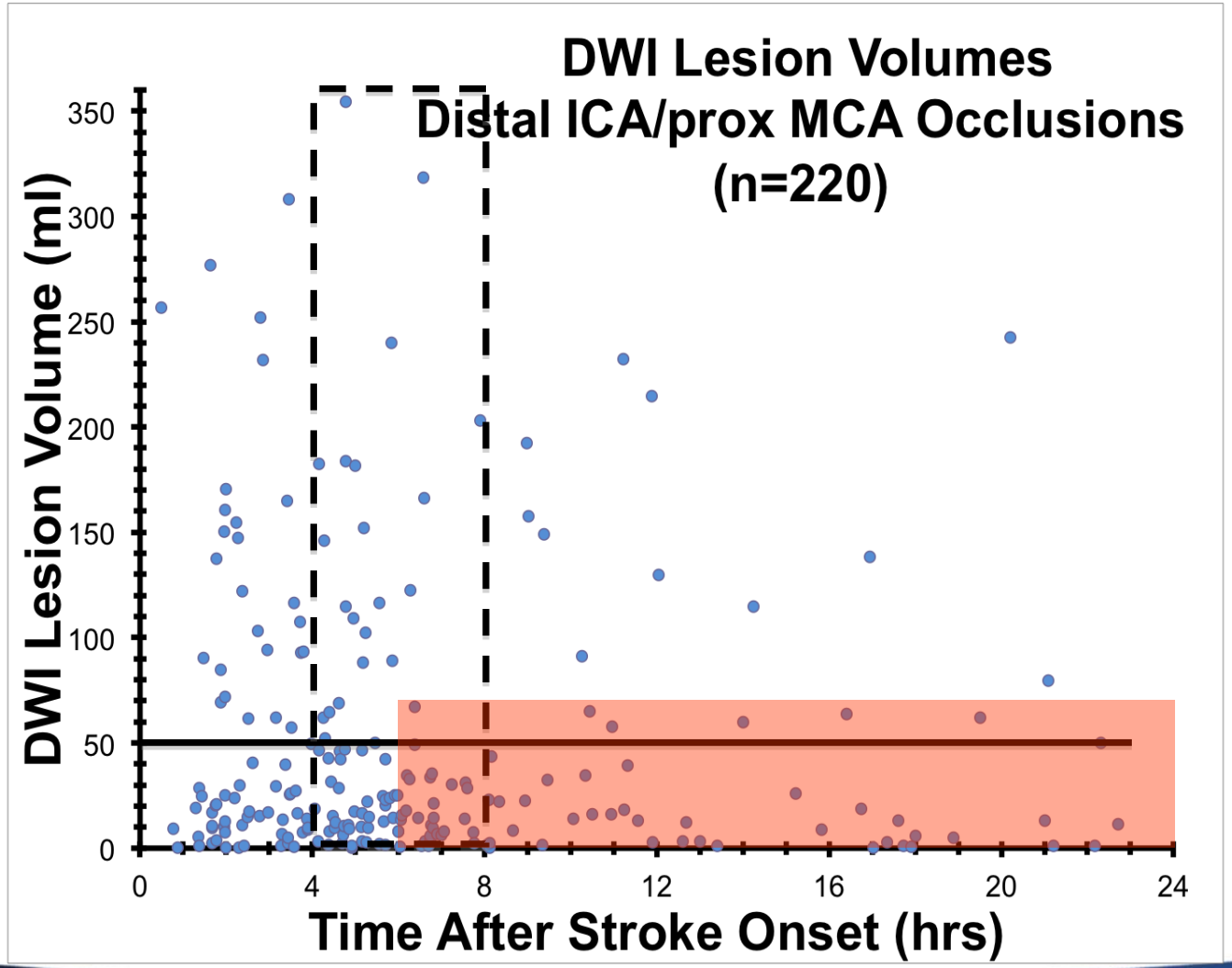
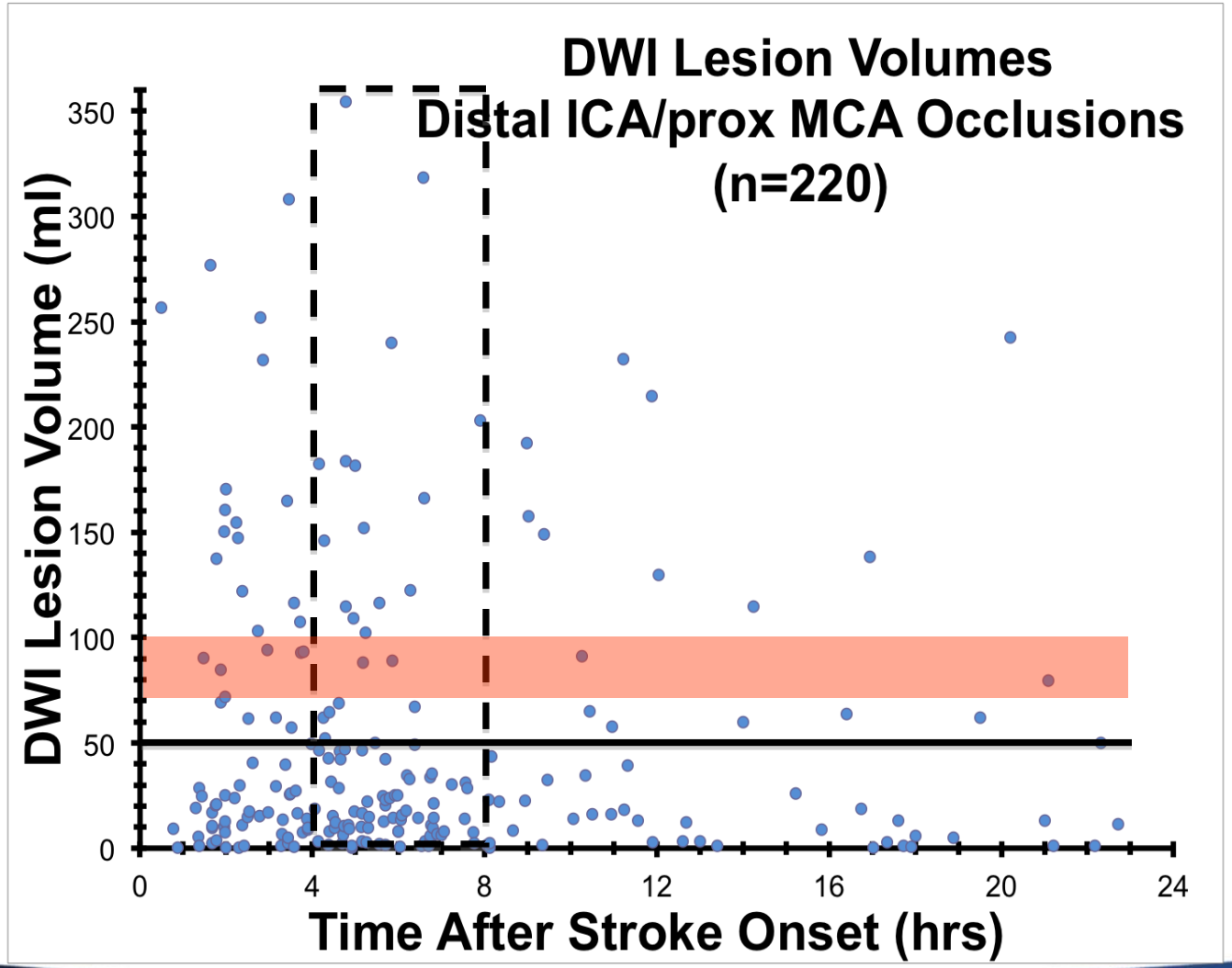


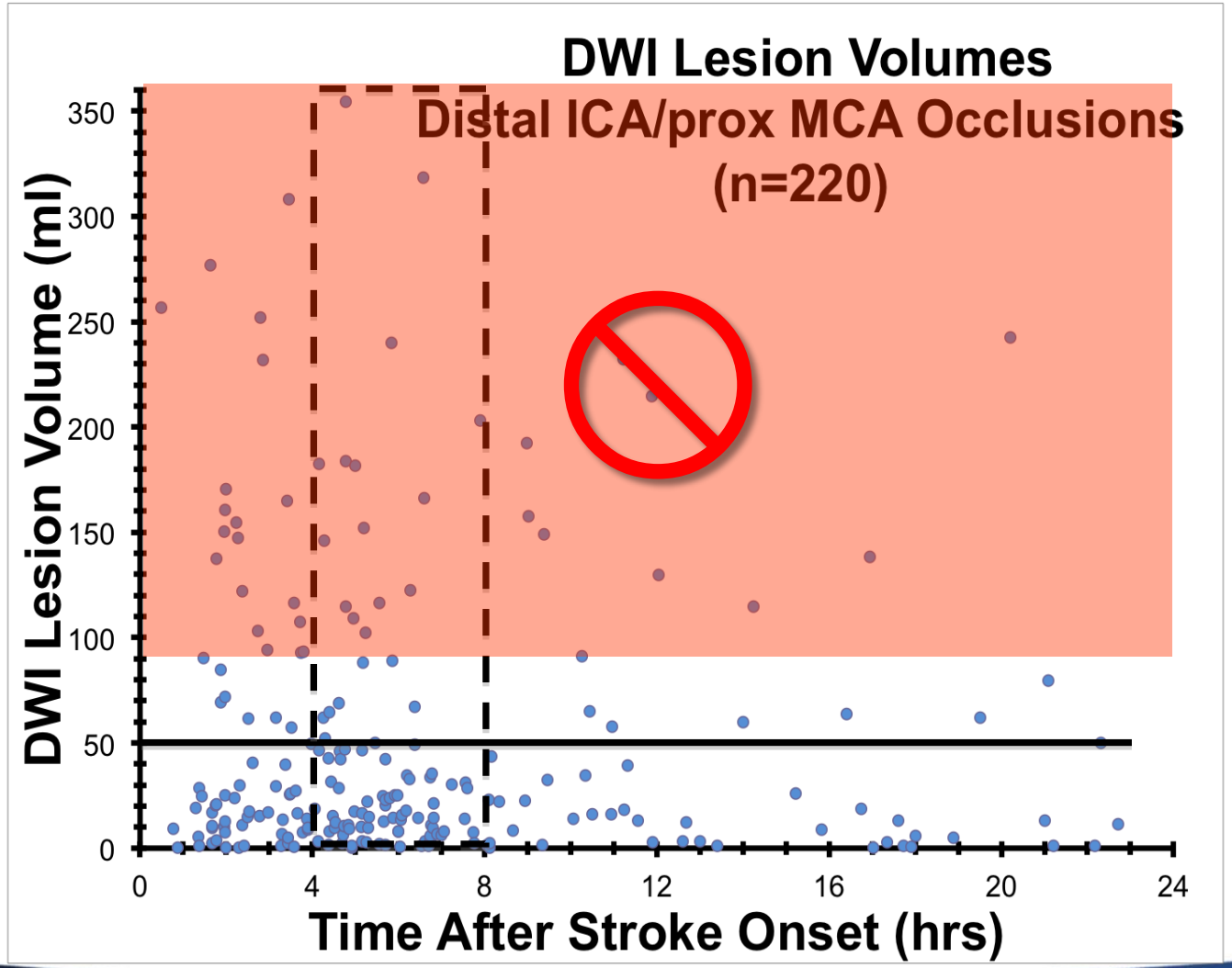
# Distal ICA/Proximal MCA Occl + DWI volume < 50ml



# Distal ICA/Proximal MCA Occl + DWI volume < 50ml

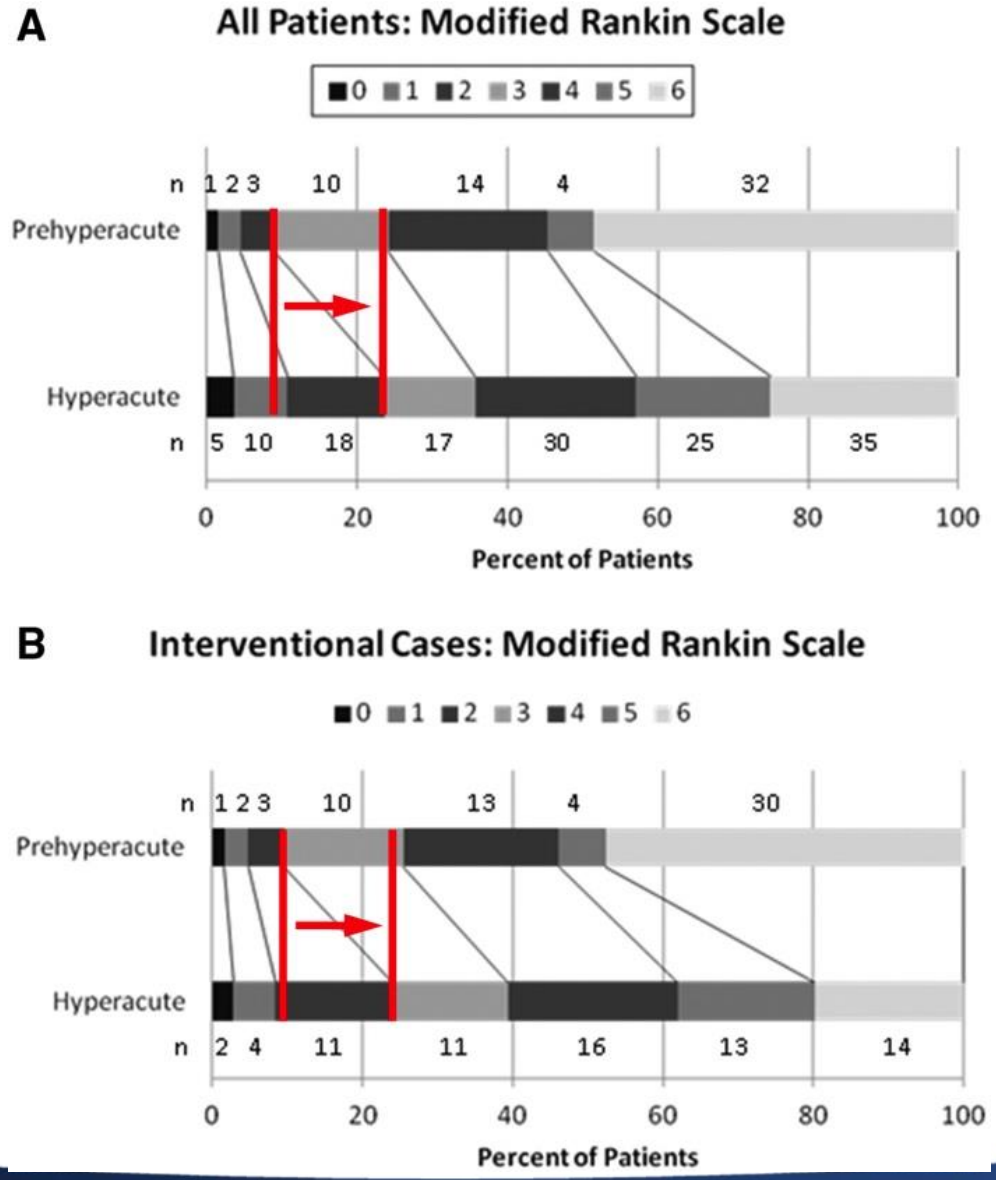


# Distal ICA/Proximal MCA Occl + DWI volume < 50ml



# Going in with guns blazing

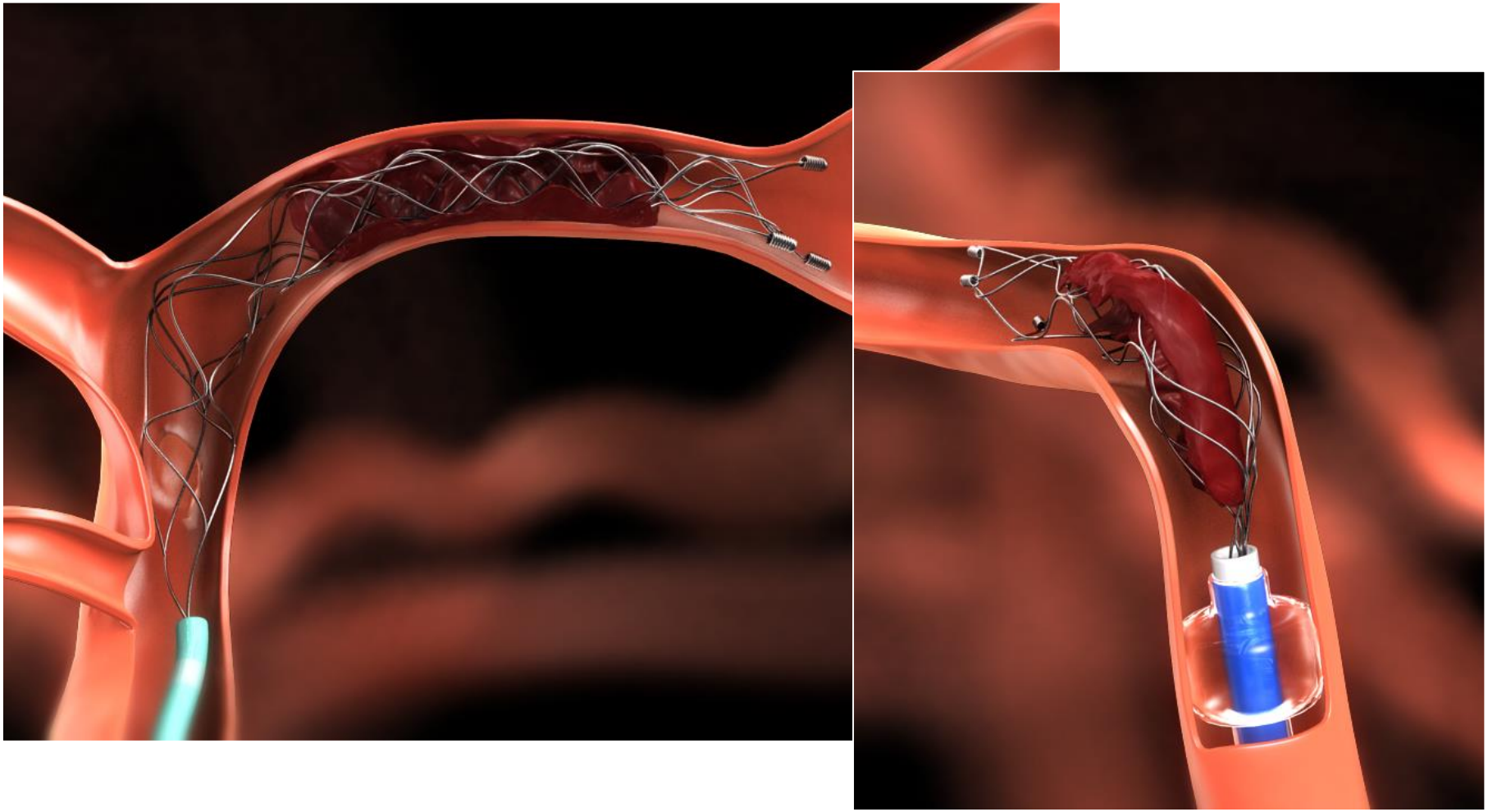
# Better outcomes, DWI < 70 mL



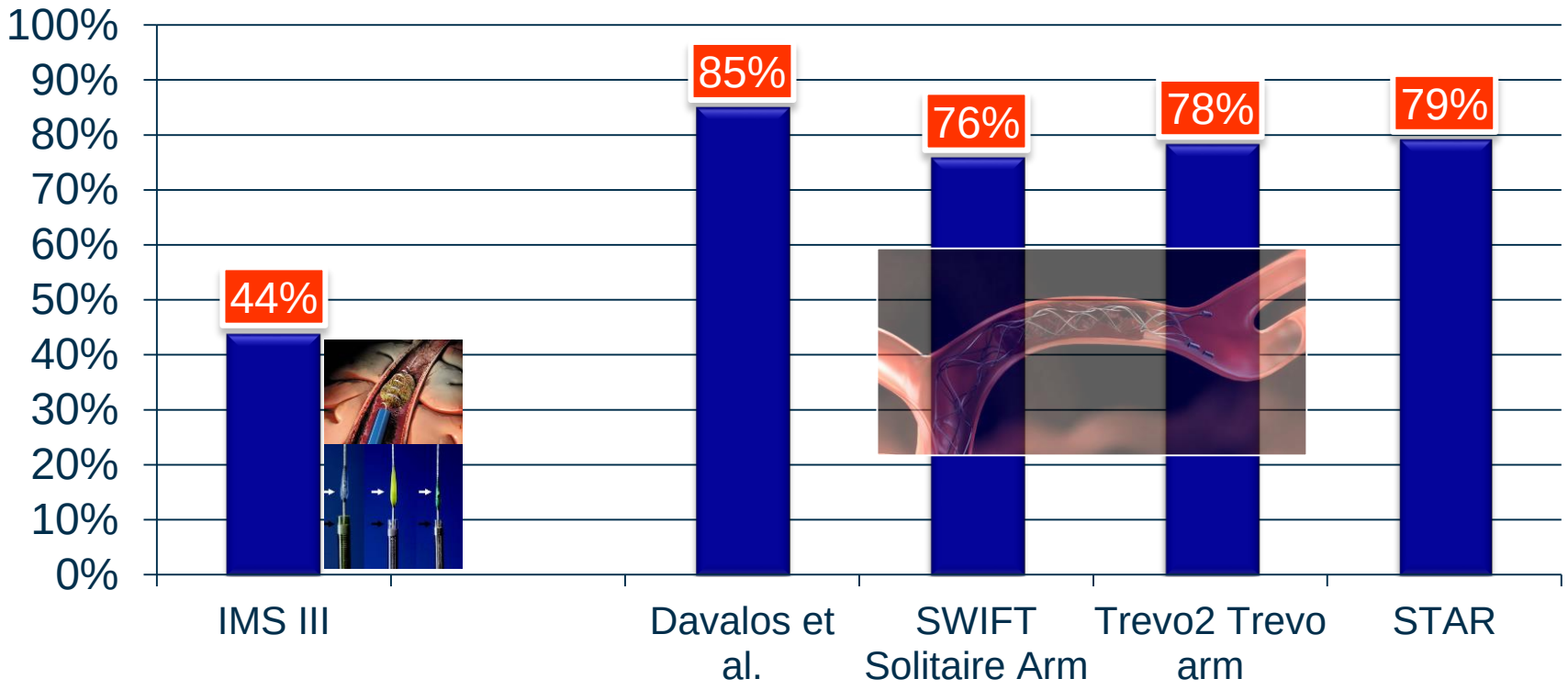



Wisco. Stroke 45: 467-72, 2014

# Stent-retrievers: A better tool



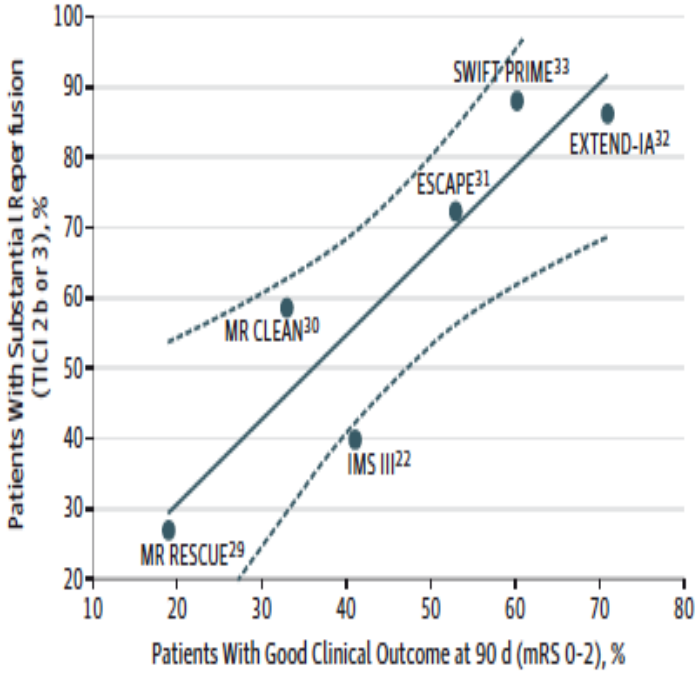
# Recanalization Rates: Stent-Retriever vs. Older Technology

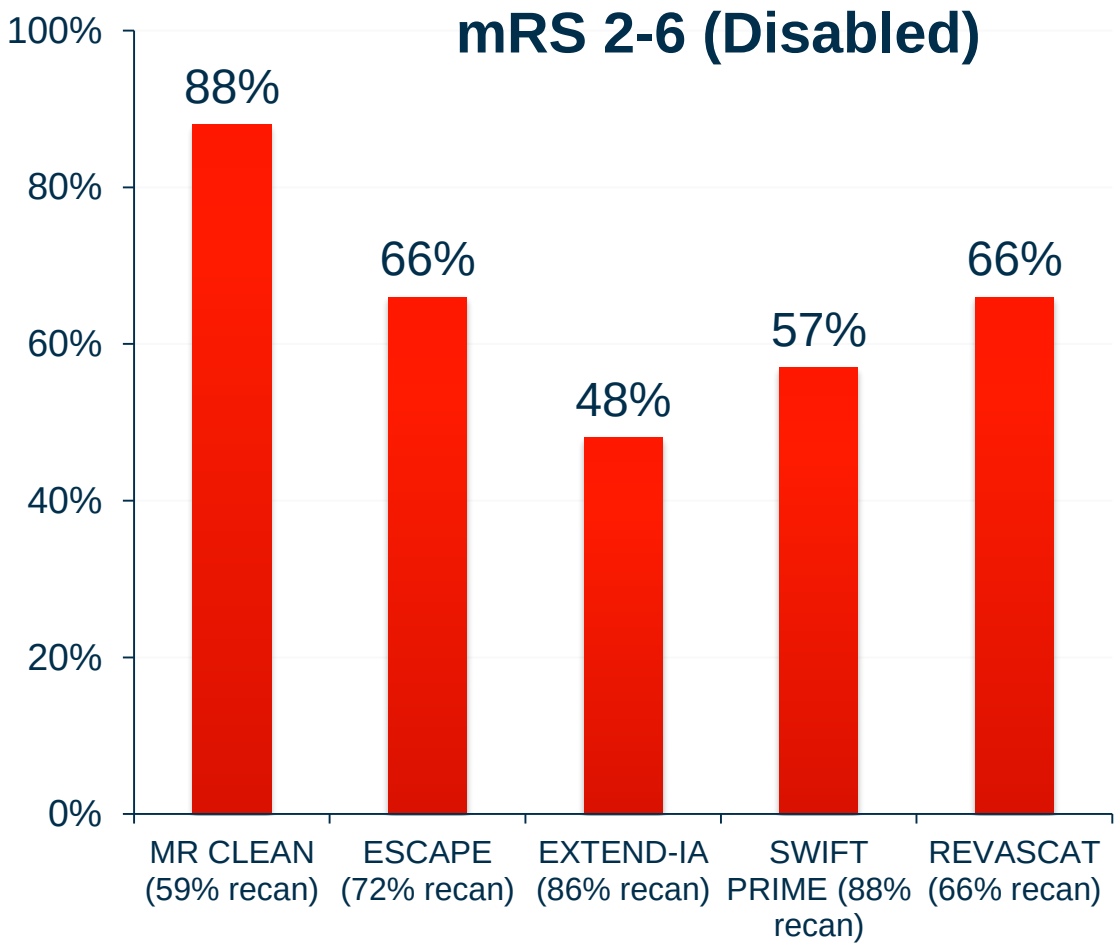




Dávalos. Stroke. 43: 2699, 2012
Saver. Lancet 380:1241-1249, 2012
Broderick. NEJM 388: 893, 2013

# Substantial Rates of Poor Outcomes





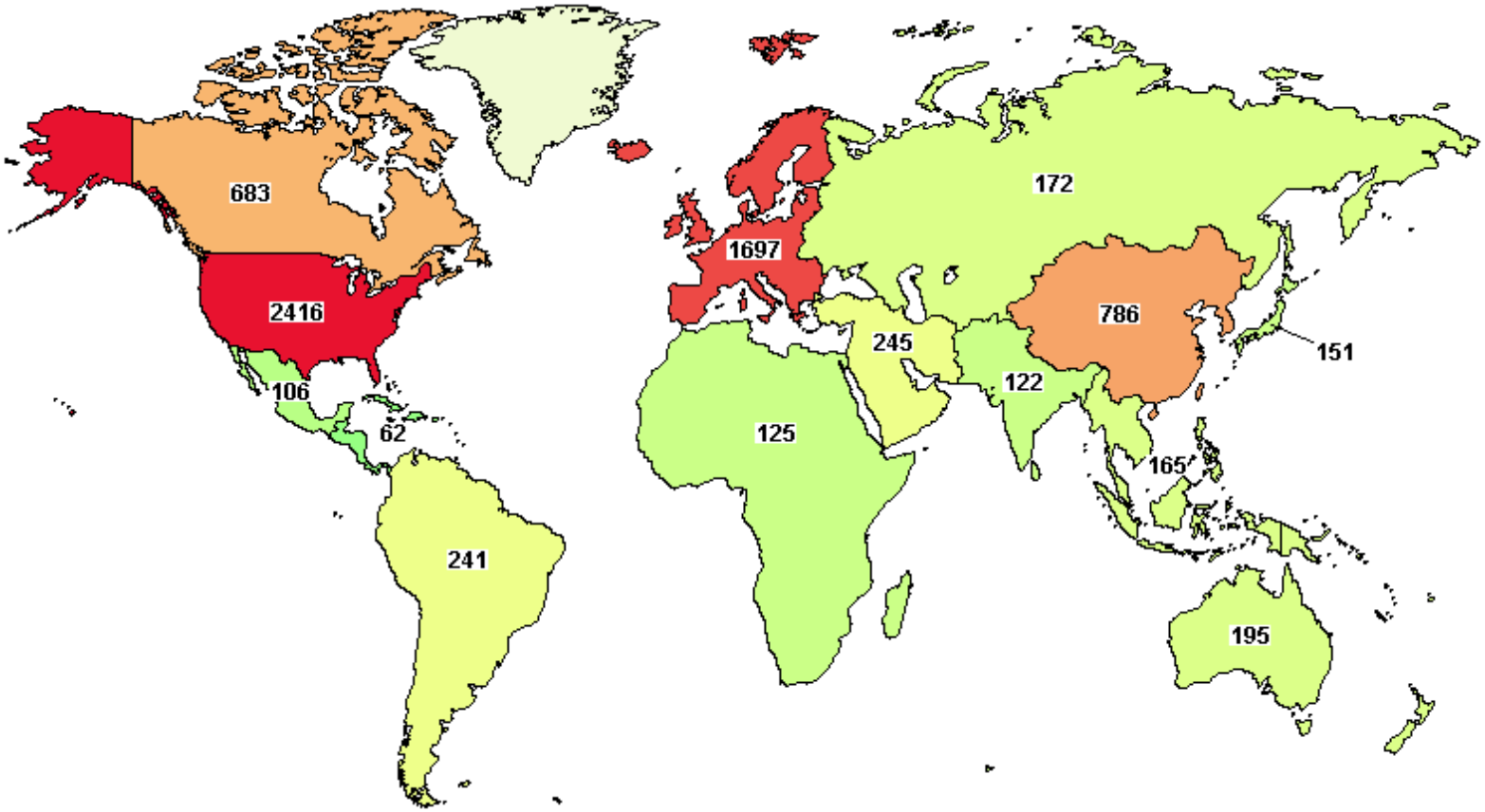

Prabhakaran S. JAMA 313: 1451- 62, 2015

# Financial Challenges
## Maldistribution of Reimbursement

- QALY analysis shows benefit
- Acute care reimbursement limited
  - National In-patient Sample (2008)
    - Up to $24,000 deficit per patient
  - IMS III data (2013)
    - Losses in 75% of patients treated with thrombectomy
  - Procedure: 25-50% of MS-DRG 23, 24

Ganesalingam Stroke 46:2591, 2015
Leppert. Stroke 46:1870, 2015
Brinjikji. Stroke 42:3271, 2011
Simpson. Stroke 45:1791, 2014
Kass-Hout. Intervent Neurol 3:107, 2014

# Map of Stroke Studies




Accessed Sept 3, 2015

# Endovascular Stroke Trials

ReStore Thrombectomy Trial for Flow Restoration in Acute Ischemic Stroke Patients
Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE)
Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE)
Solitaire FR Thrombectomy for Acute Revascularisation (STAR)
Percutaneous Recanalization in Ischemic Stroke Management in Europe Observational Registry (PRIISM2)
POSITIVE Stroke Clinical Trial
Penumbra Imaging Collaborative Study (PICS)
ADAPT: A Direct Aspiration, First Pass Technique for the Endovascular Treatment of Stroke
A Randomized, Concurrent Controlled Trial to Assess the Safety and Effectiveness of the Separator 3D as a Component of the Penumbra System in the Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke
Feasibility Study of IV rtPA vs. Primary Endovascular Therapy for Acute Ischemic Stroke (EARLY)
Intra-arterial Magnesium Administration for Acute Stroke
Swiss Intravenous and Intra-arterial Thrombolysis for Treatment of Acute Ischemic Stroke Registry (SWISS)
Wake up Symptomatic Stroke - Benefit of Intravenous Clot Busters or Endovascular Intervention (WASSABI)
Study of ALD-401 Via Intracarotid Infusion in Ischemic Stroke Subjects
Sedation Versus General Anesthesia for Endovascular Therapy in Acute Stroke - Impact on Neurological Outcome (ANSTROKE)
Basilar Artery International Cooperation Study (BASICS)
A Safety and Dose Finding Study of Plasmin (Human) Administered Into the Middle Cerebral Artery of Stroke Patients
Autologous Bone Marrow Stem Cells in Ischemic Stroke
Hypothermia in Acute Ischemic Stroke - Surface Versus Endovascular Cooling (HAIS-SE)
International Multicenter Registry for Mechanical Recanalization Procedures in Acute Stroke (ENDOSTROKE)
Computed Tomography Perfusion (CTP) to Predict Response to Recanalization in Ischemic Stroke Project (CRISP)
Imaging Guided Patient Selection for Interventional Revascularization Therapy (START)
Endovascular Acute Stroke Intervention Trial - the EASI Trial

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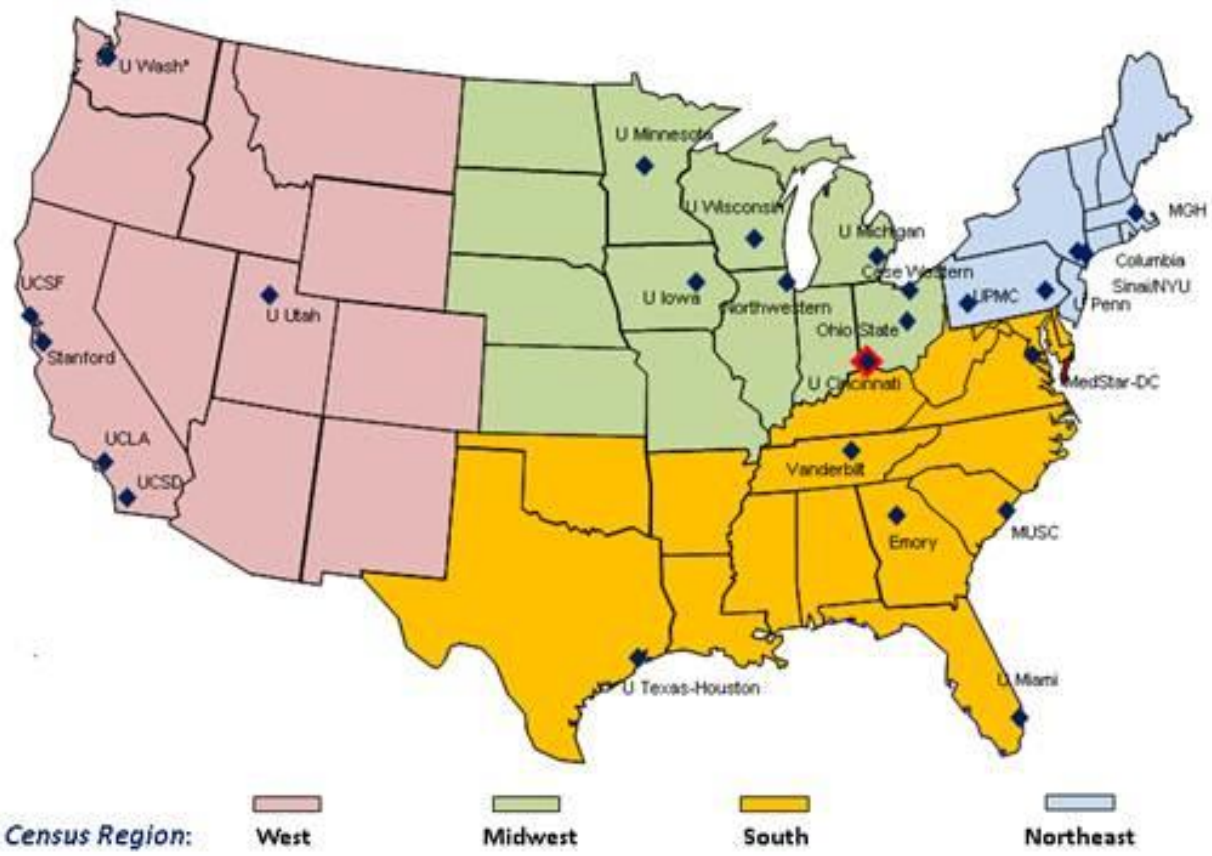
NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

Funded by a Grant from the National Institutes of Health

# National and Regional Coordinating Centers

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# StrokeNET

- Purpose: create efficient research network
- Feasibility shown by SPOTRIAS, NeuroNext, NETT
- Network
  - National coordinating center: U. Cincinnati (J. Broderick)
  - Data coordinating center: MUSC
  - Regional clinical centers: >200 hospitals
- All multi-center trials will be considered through StrokeNet
- All StrokeNet studies will use central coordination

# StrokeNet Trials

- **Primary and Secondary Stroke Prevention Trials**
  - **CREST 2**
- **Acute Stroke Intervention Trials – Intracerebral hemorrhage**
  - **MISTIE-III**
  - **I-DEF**
  - **DEFUSE 3 – imaging guidance for late stroke intervention, 6-16 hours**

# Conclusions

- **Proven benefit: thrombectomy for severe stroke with LVO up to 6 hours**
- **Areas for development**
  - **Pre-hospital systems of care**
  - **Comprehensive stroke centers**
  - **Ongoing interventional research**
    - **Image-guided selection**
    - **Extending time window in subgroups**
    - **Direct to IA without IV rtPA**