Current Status of Acute Ischemic Stroke trials
Trials, Tribulations and Practical Issues

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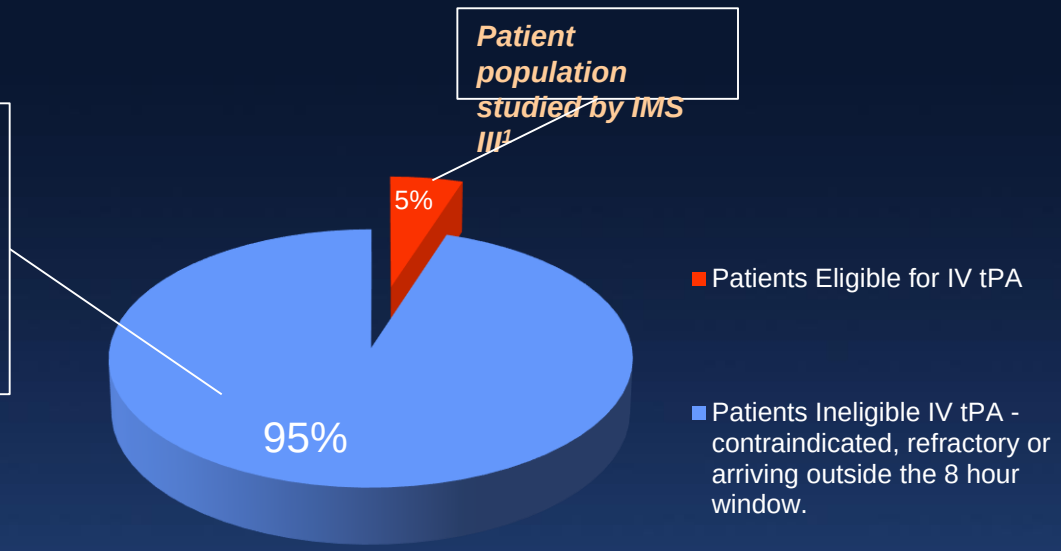
- **Consultant:** *Codman & Shurtleff, Inc., Stryker, Covidien Vascular Therapies, Microvention, Penumbra, GuidePoint Global Consulting, Abbott Vascular, Blockade, Lazarus, Pulsar, Neuroavi, Reverse Medical, Silkroad Medical, Syntervention, Medina Medical*
- **Honoraria:** *Genentech, Neocure Group LLC, American Association of Neurological Surgeons' courses, an Emergency Medicine Conference, Abbott Vascular, Covidien and Codman & Shurtleff, Inc. for training other neurointerventionists for carotid stent training and for training physicians in endovascular stenting for aneurysms, Covidien for Pipeline proctorship*
- *No consulting salary arrangements. All consulting is per project and/or per hour.*

Large Vessel Occlusions, Natural History and the Patient Population: 95% – 98%[1] of these patients have limited treatment options

Natural History of Patients with LVO within 8 hours of stroke onset (ICA + MCA Occlusions)*

Mortality: ***39.7%***
90-day mRS: ***20.4%***

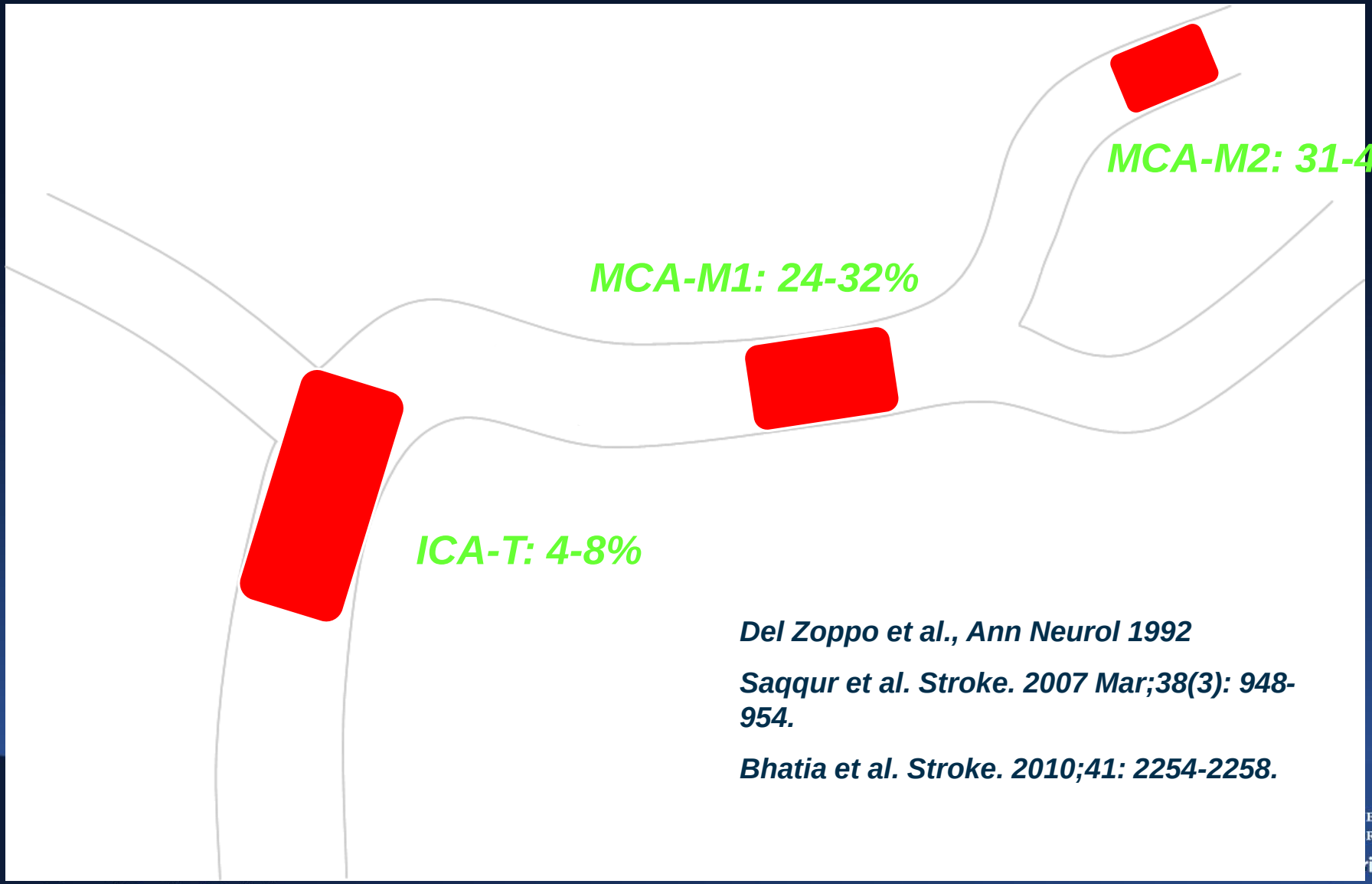


Because IV tPA is only approved to 3 hours from onset, it is critical to provide a therapy that is better than the natural history of the disease for the majority of patients with large vessel occlusions.**

****FIRST Trial: Preliminary Results. Presented at ISC 2013 by Dr. Vallabh Janardhan***
*****IV-rTPA Instructions for Use***

[1] *de Los Ríos la Rosa, F., et al. Eligibility for Intravenous Recombinant Tissue-Type Plasminogen Activator Within a Population: The Effect of the European Cooperative Acute Stroke Study (ECASS) III Trial. Stroke, 2012. 43(6): p. 1591-5.*

IV rt-PA Has a Limited Effect Over Proximal Arterial Occlusions!



Del Zoppo et al., Ann Neurol 1992

Saqqur et al. Stroke. 2007 Mar;38(3): 948-954.

Bhatia et al. Stroke. 2010;41: 2254-2258.

Proximal Arterial Occlusions: Low Rates of rt-TpA Recanalization and Poor Natural History

- **Mortality rates**
  - ICA-T: 53% Jansen, 1995
  - MCA: 30-35% Chambers, 1987
  - Basilar: 89-92% Brückmann H, 1986 & Brandt, 1996
- **Good outcome rates**
  - ICA-T: 17% Georgiadis, Neurology 2004
  - MCA: Furlan, JAMA 1997

Occlusion Site	Pts	rpro-UK	Control	Absolute Δ	p
All	180	40%	25%	15%	0.043
M1 Occl	111	34%	22%	12%	0.162
M2 Occl	55	54%	38%	16%	0.261

IV rt-PA Has a Limited Effect Over Proximal Arterial Occlusions!

The Importance of Size

Successful Recanalization by Intravenous Thrombolysis in Acute Anterior Stroke Depends on Thrombus Length

Christian H. Riedel, MD; Philip Zimmermann, MD; Ulf Jensen-Kondering, MD; Robert Stingele, MD; Günther Deuschl, MD; Olav Jansen, MD

Background and Purpose—We hypothesize that in acute middle cerebral artery stroke, thrombus lengths measured in thin-slice nonenhanced CT images define a limit beyond which systemic thrombolysis will fail to recanalize occluded arteries.

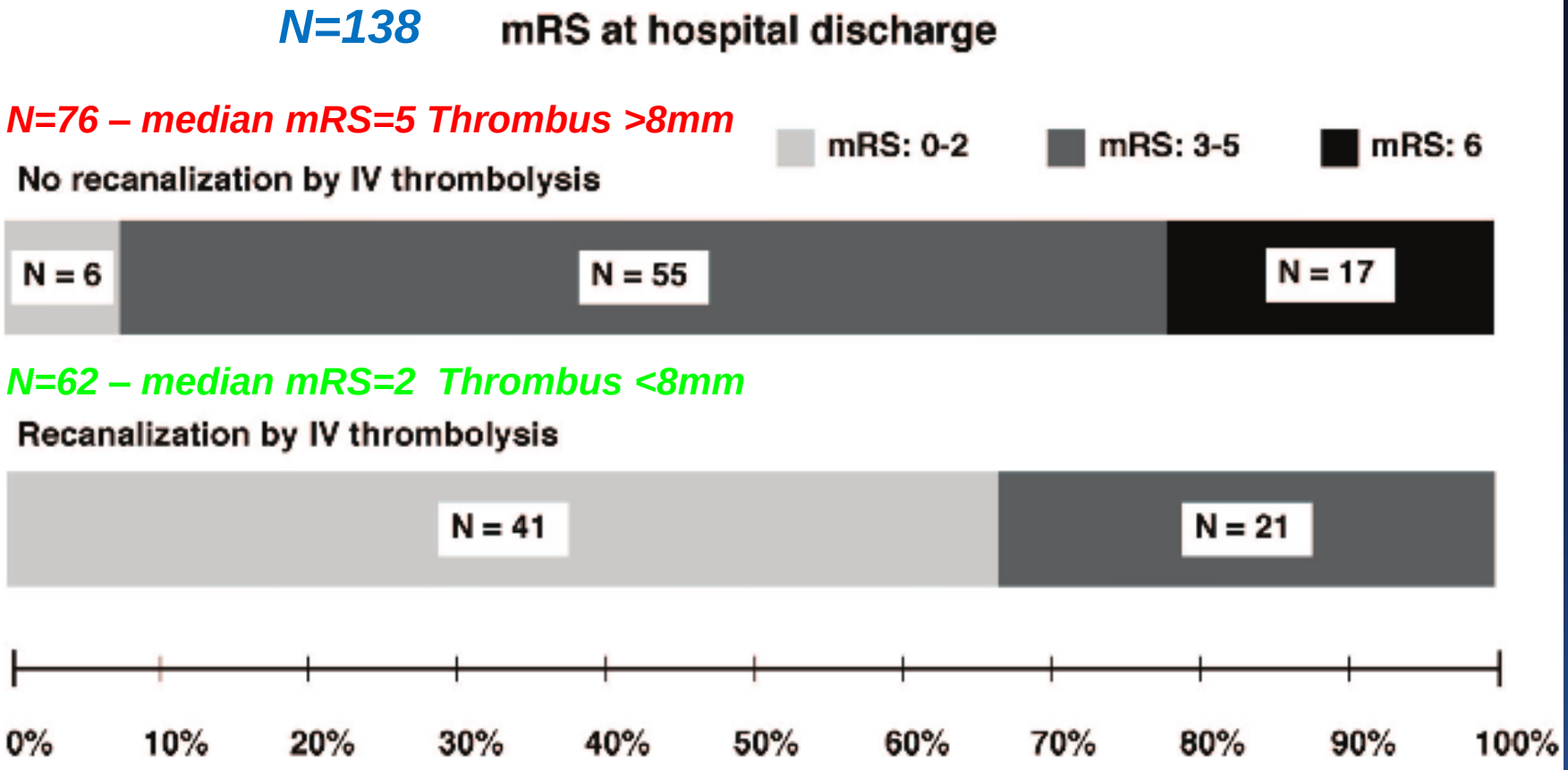
Methods—In 138 patients who presented with acute middle cerebral artery stroke and who were treated with intravenous thrombolysis (IVT), we measured lengths of thrombotic clots depicted as arterial hyperdensities in admission nonenhanced CT images with 2.5-mm slice width. Vascular recanalization was investigated after thrombolysis and recanalization results were related to thrombus lengths by logistic regression.

Results—In 62 patients, IVT resulted in recanalization; among these patients, no thrombus length exceeded 8 mm. The median modified Rankin scale score at hospital discharge was 2. In the remaining 76 patients, thrombus lengths mostly exceeded 8 mm and IVT failed in recanalization. These patients were discharged with a median modified Rankin scale score of 5.

Conclusions—This study shows that in acute middle cerebral artery stroke, IVT has nearly no potential to recanalize occluded vessels if thrombus length exceeds 8 mm. (***Stroke***. **2011;42:1775-1777.**)

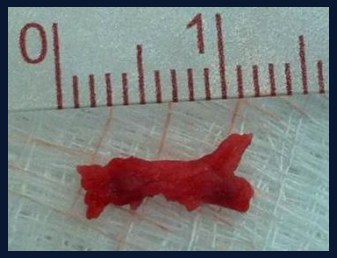
Key Words: cerebral ischemia ■ computed tomography ■ ischemic stroke

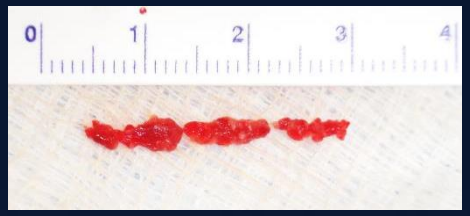
IV rt-PA Has a Limited Effect Over Proximal Arterial Occlusions!

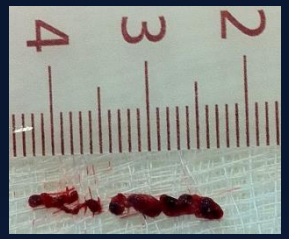


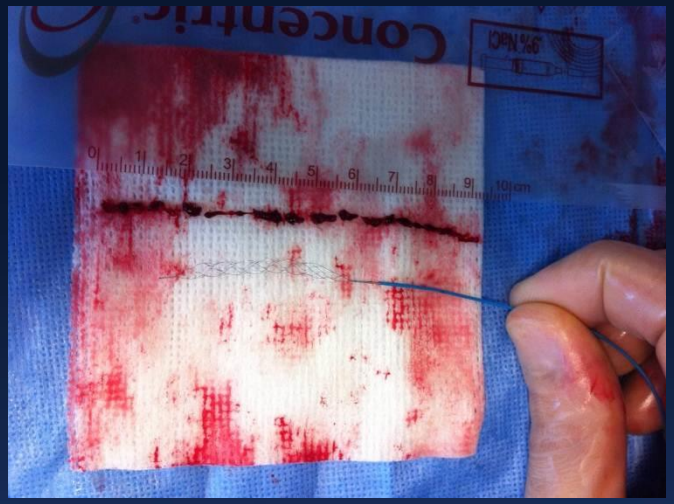
Riedel et al. Stroke. 2011;42: 1775-1777

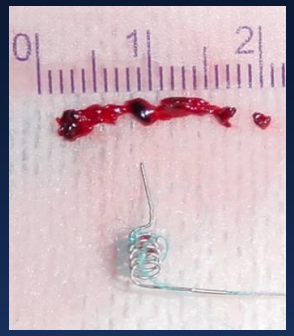
Reperfusion in AIS: Size Matters!

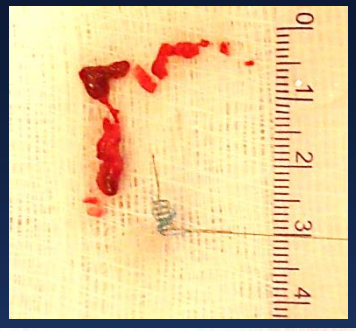


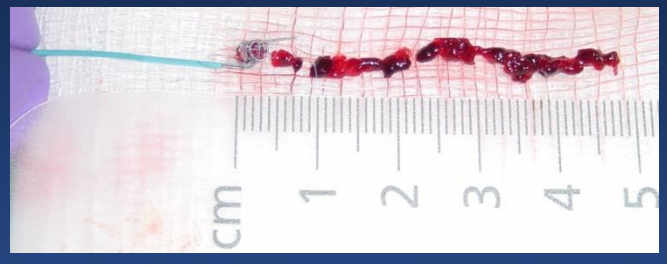


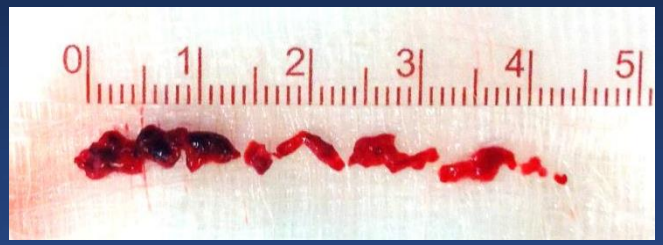


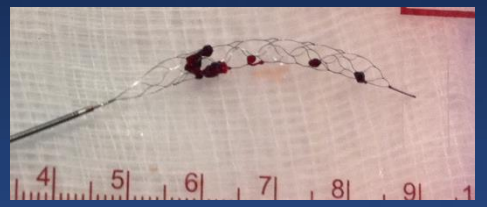






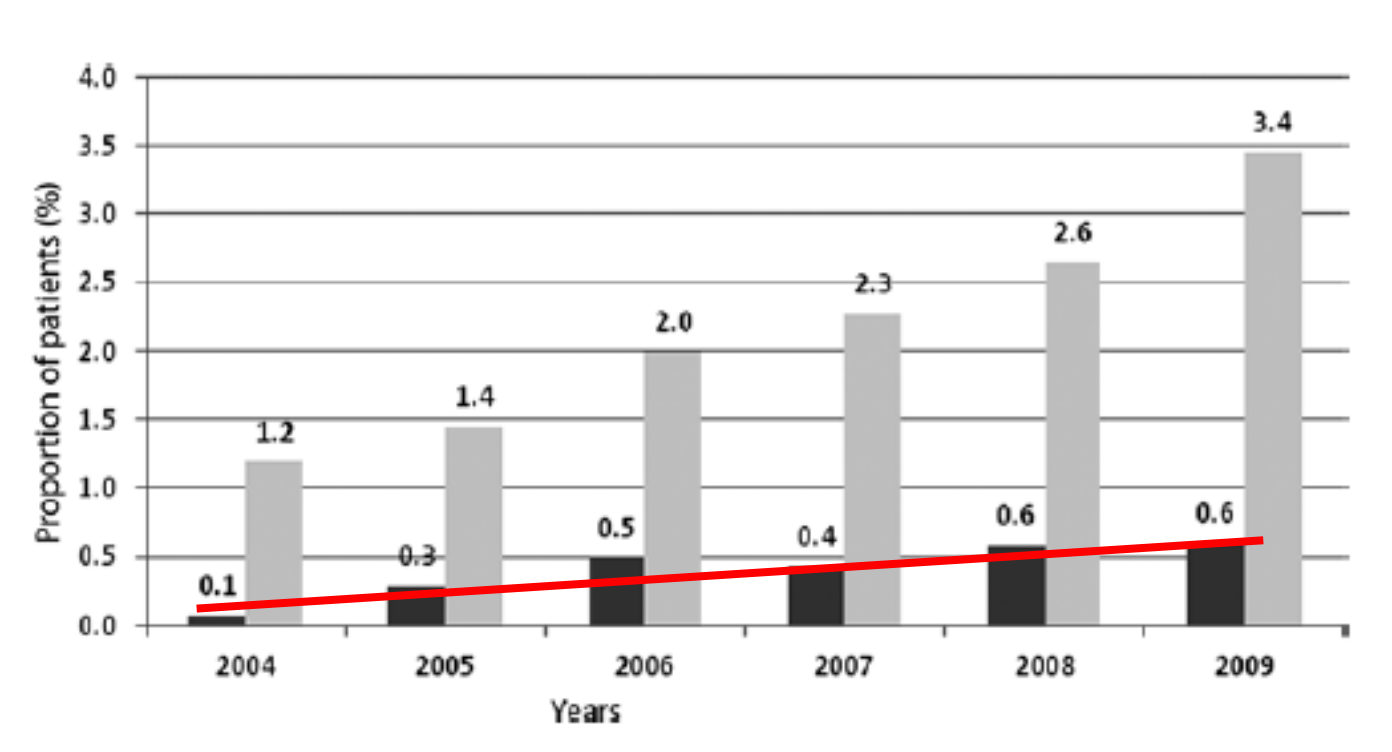






How many IA stroke interventions do we do?

- Less than 1% of all strokes
- NOT ENOUGH!!!



Stroke. 2012;43:3012-3017

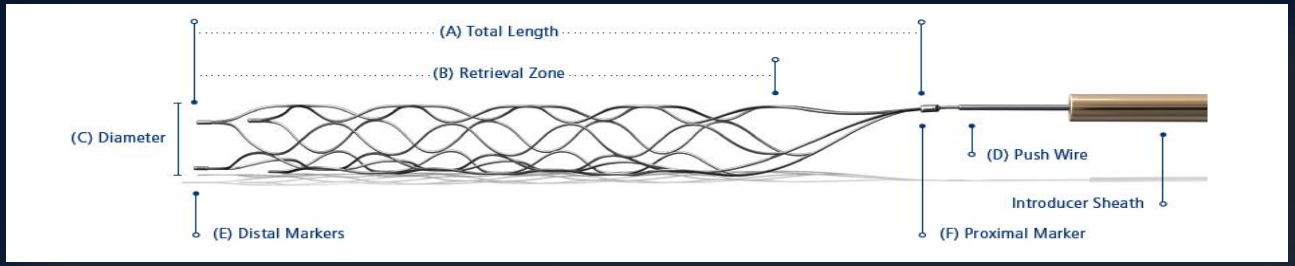
Endovascular Intra-arterial therapies

510(k) clearance for recanalization of cerebral vessels in patients with acute ischemic stroke:

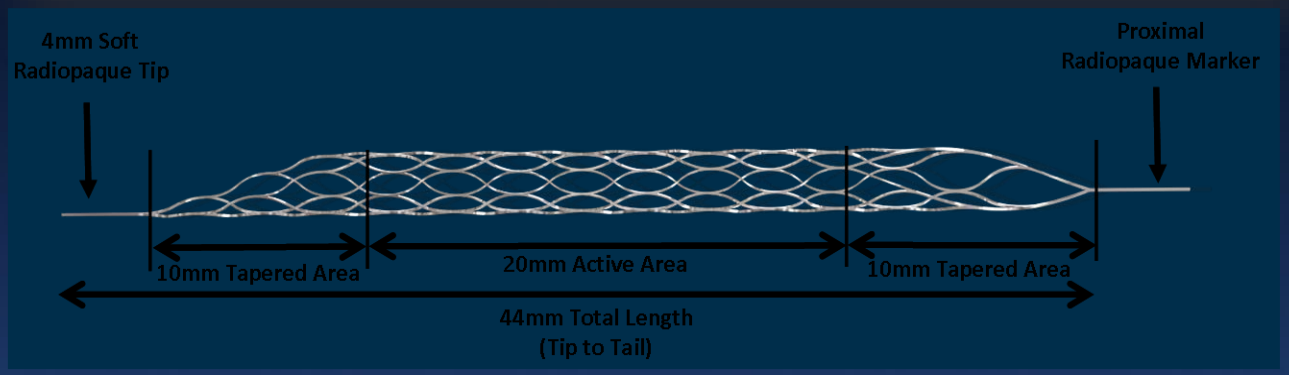
1. Solitaire Flow Restoration (FR) device - approved in March 2012 (ev3/Covidien Vascular Therapies)
2. Trevo Pro Retriever (Stryker Corp.) – approved in April 2012
3. Penumbra device - in 2008 (Penumbra Inc.)
4. Merci device - in 2004 (Concentric Medical)

Newer Technologies = Better Outcomes

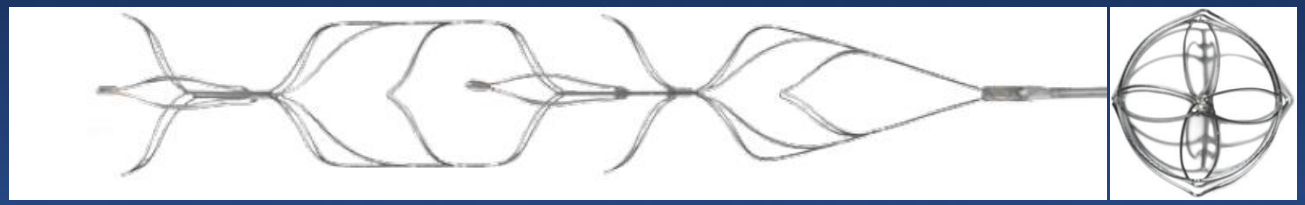
Solitaire FR



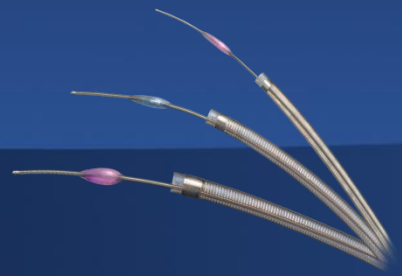
Trevo



Separator 3-D

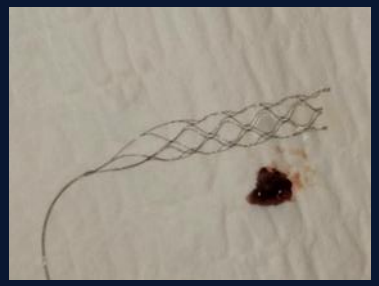


Penumbra Max System



Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial

Jeffrey L Saver, Reza Jahan, Elad I Levy, Tudor G Jovin, Blaise Baxter, Raul G Nogueira, Wayne Clark, Ronald Budzik, Osama O Zaidat, for the SWIFT Trialists



- **Recanalization Rate:**
  - TIMI 2/3 achieved in 69% of Solitaire cases versus 30% with Merci
- **Good Neurologic Outcome:**
  - Defined as mRS ≤2 or improvement in NIHSS score ≥10 points at 3-month follow up
  - Achieved in 58% of patients with Solitaire versus only 33% of patients treated with the Merci

Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial

Raul G Nogueira, Helmi L Lutsep, Rishi Gupta, Tudor G Jovin, Gregory W Albers, Gary A Walker, David S Liebeskind, Wade S Smith, for the TREVO 2 Trialists

- **Trial design similar to SWIFT: Merci versus Trevo in patients with acute stroke within first 8 hours**
- **Results**
  - **final TICI≥2: 92% with Trevo vs 77% with Merci**
  - **3 months mRS of 0-2: 40% with Trevo vs 22% with Merci**

"Real-world" post FDA approval UBNS experience with stentrievers

NEUROSURGERY
THE REGISTER OF THE NEUROSURGICAL MEME

Neurosurgery. 2013 Feb 25. [Epub ahead of print]

Solitaire FR Thrombectomy for Acute Ischemic Stroke: Retrospective Multicenter Analysis of Early Postmarket Experience after FDA Approval.

Mokin M, Dumont TM, Veznedaroglu E, Binning MJ, Liebman KM, Fessler RD 2nd, To CY, Turner RD 4th, Turk AS, Chaudry MI, Arthur AS, Fox BD, Hanel RA, Tawk RG, Kan P, Gaughen JR Jr, Lanzino G, Lopes DK, Chen M, Moftakhar R, Billingsley JT, Ringer AJ, Snyder KV, Hopkins LN, Siddiqui AH, Levy EI.

1Departments of Neurosurgery and Radiology, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY 2Capital Health, Trenton, NJ 3St. John Providence Health System, Detroit, MI 4Departments of Neurosurgery and Radiology, Medical University of South Carolina, Charleston, SC 5Semmes-Murphey Neurologic and Spine Institute, Memphis, TN 6Department of Neurosurgery, Mayo Clinic, Jacksonville, FL 7University of South Florida, Department of Neurosurgery and Neuroradiology, Tampa, FL 8Department of Neurosurgery, Mayo Clinic, Rochester, MN 9Department of Neurosurgery, Rush University Medical Center, Chicago, IL 10Department of Neurosurgery, Mayfield Clinic, University of Cincinnati, Cincinnati, OH.

- At 30 days, 38% of patients had favorable outcome (mRS≤2)
- If using SWIFT trial definition of "good" outcome -), the rate of good outcome reached 47% at 30 days

ISCHEMIC PENUMBRA- THE NEW THERAPEAUTIC TARGET

- The concept of identifying the therapeutic target (the ischemic penumbra) and having an estimation of the size and location of the core is driving neuroimaging research at a fast pace.
- This has provided a second overlay over the time of stroke onset to decide on reperfusion strategies and adjunctive measures to improve AIS outcomes

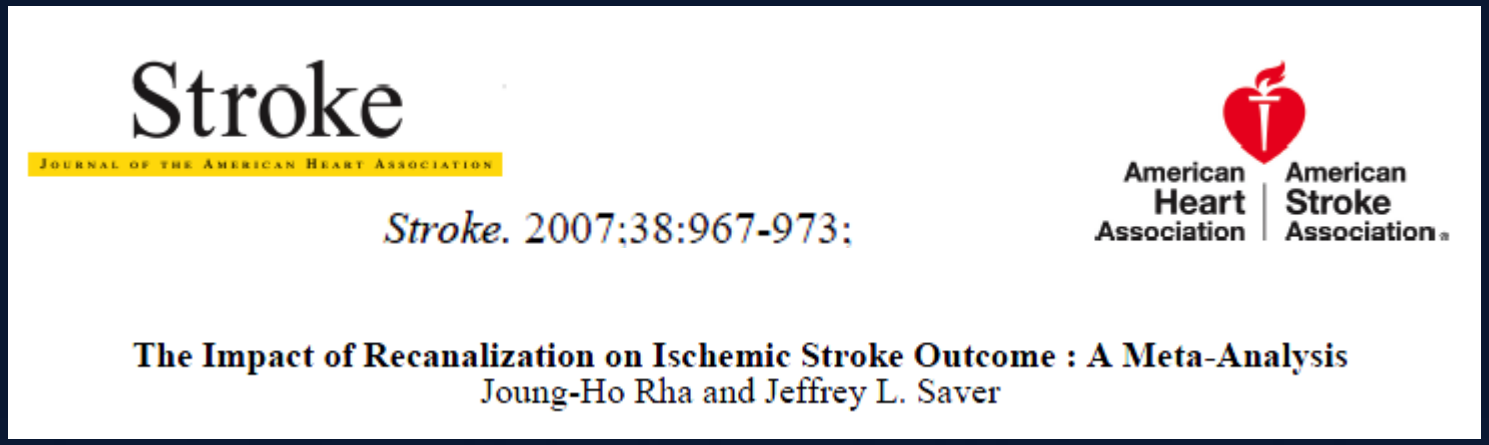
Cortical CBV loss is predictive of poor clinical outcomes

ORIGINAL RESEARCH

Correlation between cerebral blood volume values and outcomes in endovascular therapy for acute ischemic stroke

Maxim Mokin,[1,2] Simon Morr,[1,2] Andrew A Fanous,[1,2] Hussain Shallwani,[1,2] Sabareesh K Natarajan,[1,2] Elad I Levy,[1,2,3,4] Kenneth V Snyder,[1,2,3,4,5] Adnan H Siddiqui[1,2,3,4,6]

J Neurointerv Surg. 2014 Aug 21



- Meta-analysis of articles published during 1985 - 2002 that assessed vessel recanalization
- Included 53 studies, total 2066 patients
- Conclusion: *Recanalization is strongly associated with improved functional outcomes and reduced mortality*

Newer devices achieved higher recanalization rates and improved outcomes

Trial	TICI/TIMI 2 or 3 revascularization	Good outcome (mRS 0–2) at 90 days (%)	Mortality at 90 days (%)
NINDS,* 1995[2]	NR	43	17
	NR	27	21
PROACT II, 1999[11]	66%‡	40	25
IMS I, 2004[10]	56%	43	16
MERCI, 2005[14]	46%	28	44
IMS II, 2007[12]	73% ‡	46	16
Multi-MERCI, 2008[13]	55%	36	34
Penumbra, 2009[15]	82% ‡	25	33
RECOST, 2011[16]	88%	54	12
SARIS, 2009,[6] 2011[7]	100%‡	55†	35†
SWIFT, 2012[17 19]	80%‡	36	17
START, 2012[8]	86%‡	48	29
TREVO, 2012[9]	92%‡	55	22
TREVO 2, 2012[18 20]	86%‡	40	33

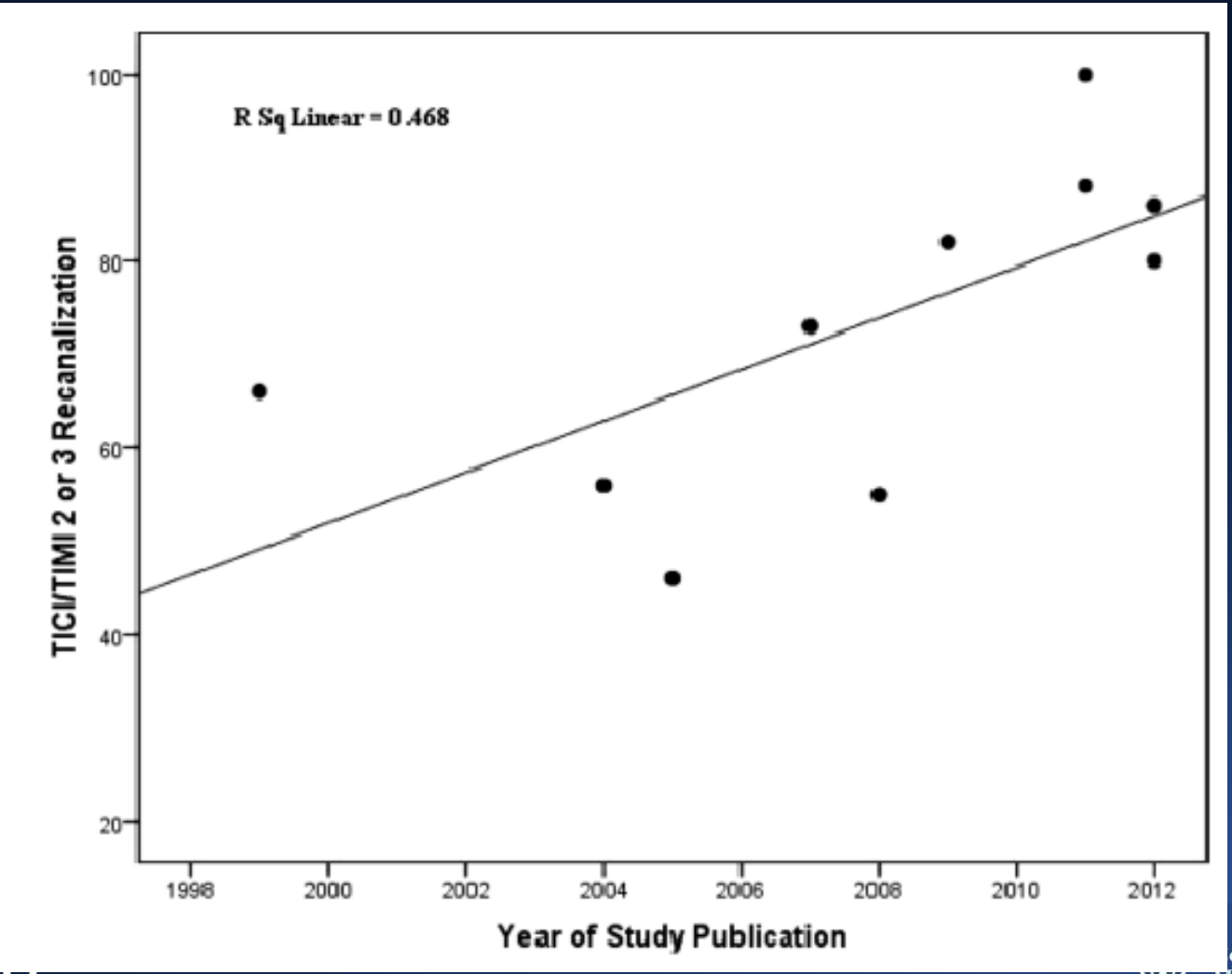
REVIEW

Journal of NEUROINTERVENTIONAL SURGERY

Improvements in recanalization with modern stroke therapy: a review of prospective ischemic stroke trials during the last two decades

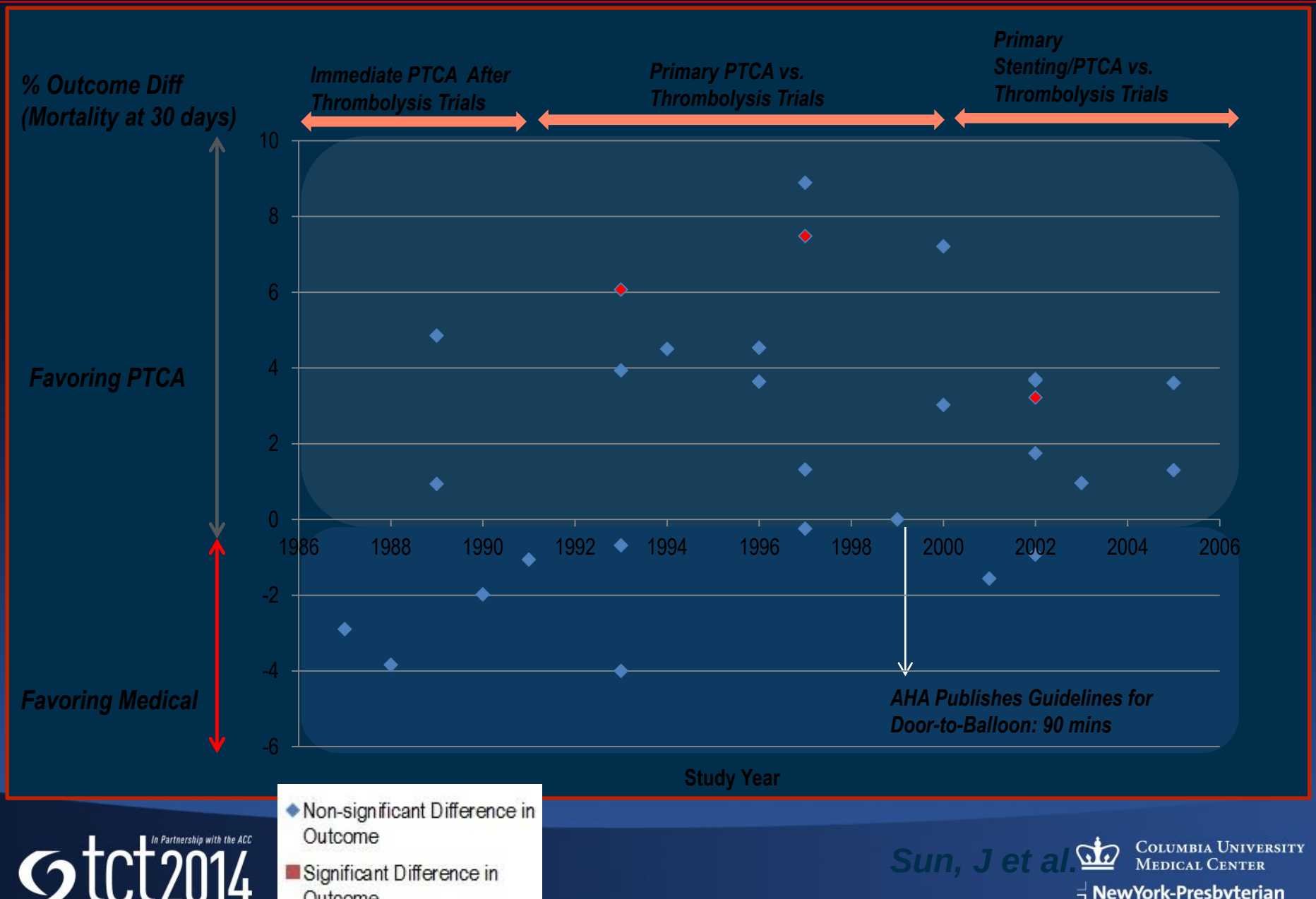
Kyle M Fargen,[1] Philip M Meyers,[2] Pooja Khatri,[3] J Mocco[4]

Improvement in recanalization rates of neuroendovascular trials



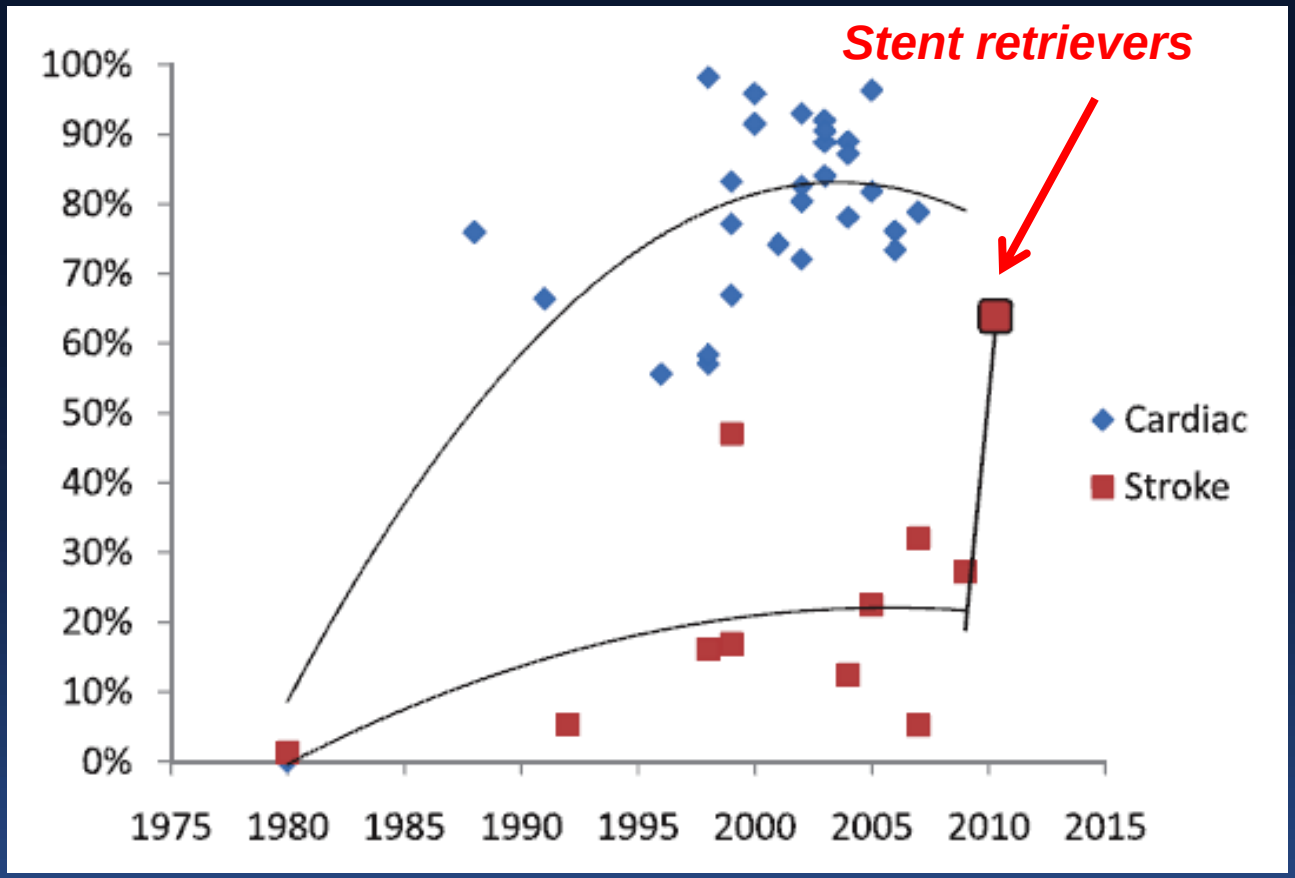
JNIS 2012 Fargen et al.

Lessons from Coronary Literature



Sun, J et al.

Trends in complete reperfusion rates in coronary and cerebral reperfusion trials



Saver JL, Stroke 2013;44:270-277

Interventions in Cardiology

- Current status of stroke neurointerventions reminiscent of the evolution of PCI procedures
- Once newer generation devices became available → interventional approach became the accepted treatment of acute MI

Recent Randomized Stroke Trials

- **IMS III: IV tPA vs IV tPA + IA Intervention**
- **MR RESCUE: Perfusion based medical vs IA Intervention**
- **SYNTHESIS Expansion: IV tPA vs IA Intervention**

The NEW ENGLAND JOURNAL of MEDICINE

Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

- **656 participants**
- **Endovascular group and IV tPA cohorts**
  - **Three month (mRS 0-2): (40.8% versus 38.7%)**
  - **Mortality (19.1% and 21.6%, P=0.52).**
  - **sICH (6.2% and 5.9%, P=0.83).**
  - **Sub-group analysis based on NIHSS severity (NIHSS 8-19 and NIHSS > 20) showed greater therapeutic benefit for endovascular therapy, but did not achieve statistical significance.**

IMS III

- Initially documentation of large vessel occlusion on non-invasive imaging was not required
- NIHSS≥10 was used for screening purposed

IMS III trial

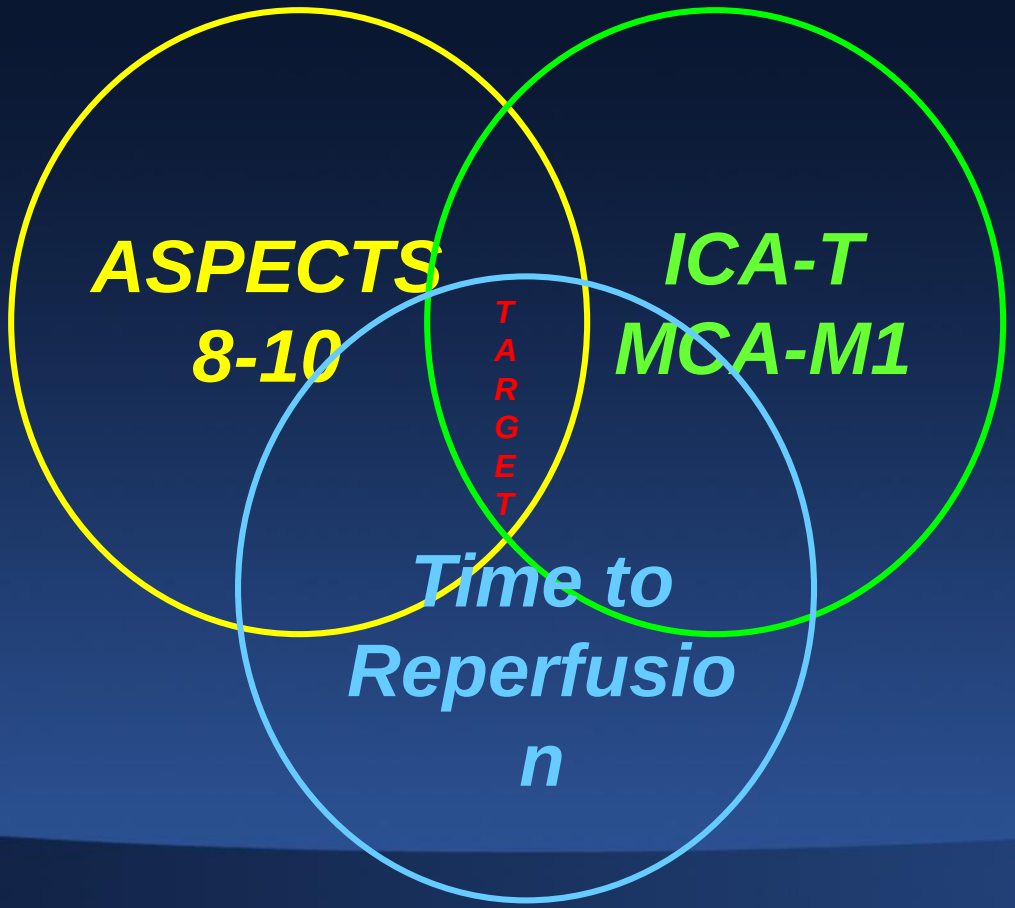
- Only after 284 participants had been enrolled, CT angiography became a part of the study.
- Only 306 of 656 participants (46.6%) had preoperative CTA, and it was not used for inclusion.
- 20% of endovascularly treated patients did not have a large vessel occlusion!!!

IMS III – Potential Reasons For Lack of Benefit

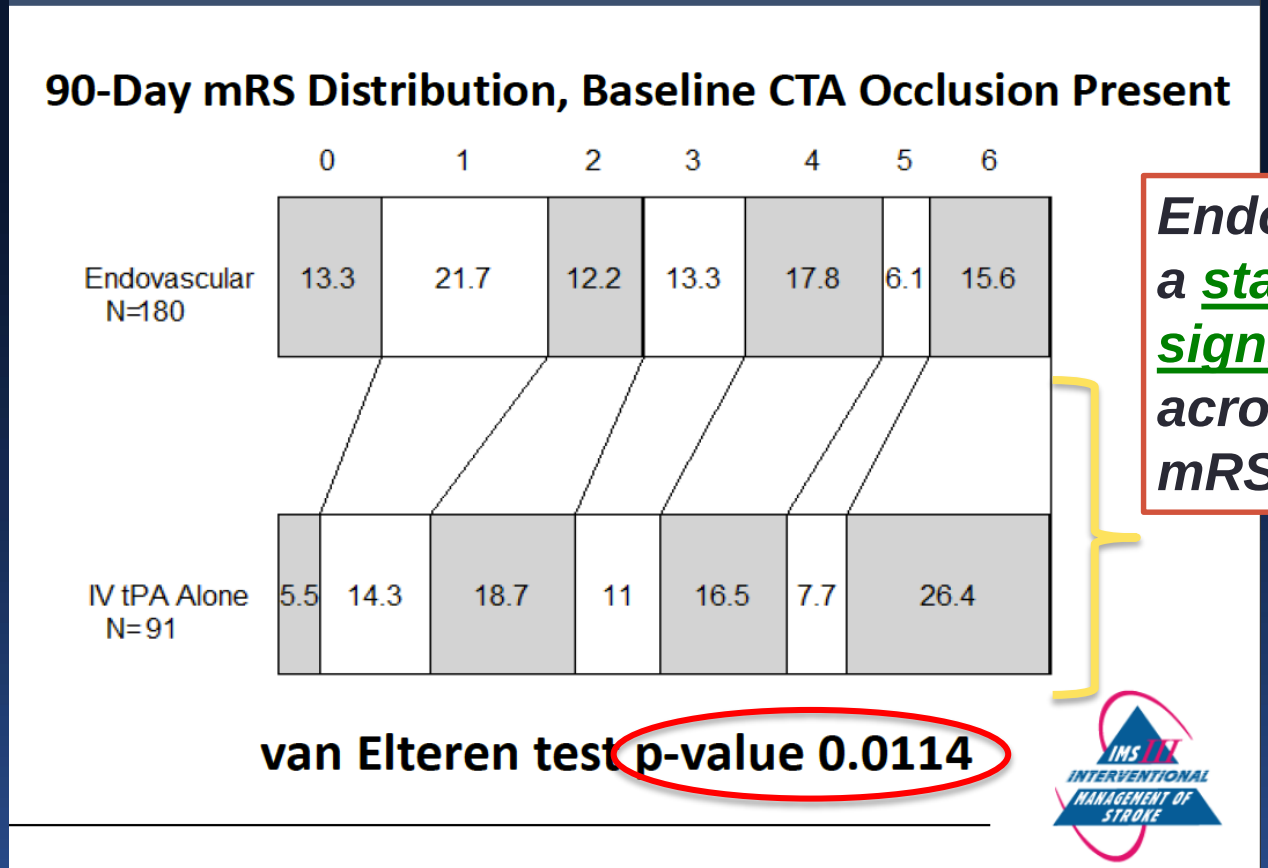
- IV rt-PA Considerations
  - IV t-PA works and patients who recanalized with t-PA were not excluded
  - IA Arm = Lower tPA dosage
- IA Therapy Considerations
  - IA Lytics > 1st Generation Mechanical > Last Generation Mechanical
- Lack of Target Occlusion
  - No CTA/MRA required = Distal/Perforator Occlusions = Better Responses to IV tPA
- Lack of Target Penumbra
  - Many patients with ASPECT <5
- Long Times to Treatment = Less Benefit from Reperfusion
- Lack of Equipoise = many “good”/eligible patients not enrolled

IMS III – Potential Reasons For Lack of Benefit

ASPECTS			
0–7	271		1.12 (0.67–1.87)
8–10	378		1.03 (0.79–1.34)
ICA, M1, or basilar occlusion	220		1.05 (0.67–1.64)



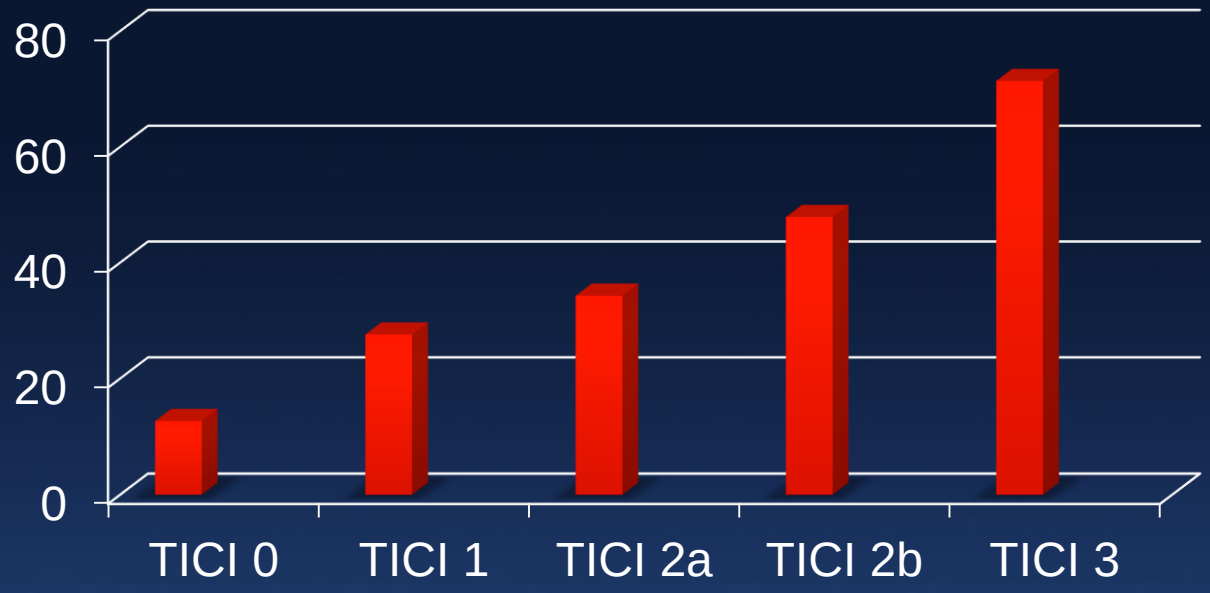
With CTA-confirmed occlusion at baseline, representative of current practice, IMS III has a statistically significant positive outcome for endovascular



Endovascular confers a statistically significant benefit across the spectrum of mRS

A. Demchuk, IMS III: Comparison of Outcomes between IV and IV/IA Treatment in Baseline CTA Confirmed ICA, M1, M2 and Basilar Occlusions, slide 20, Presented at ISC 2013, Honolulu Hawaii

Figure 9: Percentage of Patients who achieved a functional outcome in IMS III based on reperfusion result (p=0.001)



In IMS III, independent functional outcome (mRS 0-2) was strongly associated with TICI 2b-3 revascularization. Though TICI 2b-3 is the modern endovascular standard, a low percentage of patients in IMS III achieved this technical result due to older, inferior technologies. TICI 2a was considered a good outcome in IMS III but clearly does not translate into good clinical outcomes

IMS III

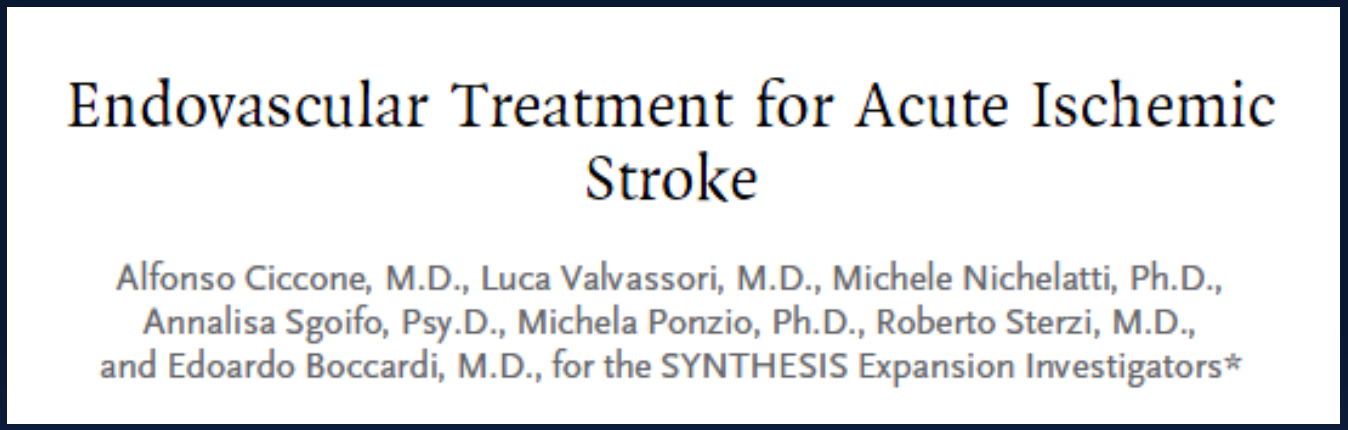
- IMS III studied a small subset of patients compared to the large volume of stroke victims suffering from large vessel occlusions.*
- IMS III showed that endovascular therapy is as safe and effective as IV tPA alone in the 0-3 hour time window. New technology, such as stentretriever devices, are approved to treat large vessel occlusions up to 8 hours from onset.*
- Due to the 6 year duration of IMS III, the data it presents is not reflective of current practice.*
- Stent retriever devices are showing fast procedure times and high recanalization rates, which are both highly correlated to improved patient outcomes.* **
- While clinical trials must continue to help better understand endovascular therapy for large vessel occlusions, mechanical thrombectomy is an important and potentially beneficial therapy for patients with no other options.

**IMS3 data presented at ISC 2013 by Dr. Joseph Broderick*
***Dávalos A, Mendes Pereira V, Chapot R, et al; Retrospective Multicenter Study of Solitaire FR for Revascularization in the Treatment of Acute Ischemic Stroke. Stroke. 2012;43:2699-2705.*

IMS III trial

- Attempt to stay abreast of rapidly evolving endovascular stroke technology was unsuccessful
- of the 334 patients randomized to and receiving IA therapy, only 5 were treated with stentretrievers

SYNTHESIS Expansion trial



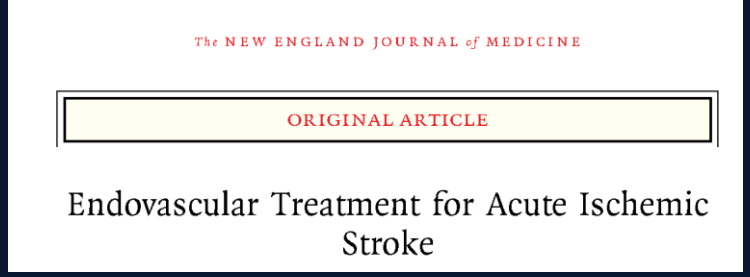
Endovascular Treatment for Acute Ischemic Stroke

Alfonso Ciccone, M.D., Luca Valvassori, M.D., Michele Nichelatti, Ph.D., Annalisa Sgoifo, Psy.D., Michela Ponzio, Ph.D., Roberto Sterzi, M.D., and Edoardo Boccardi, M.D., for the SYNTHESIS Expansion Investigators*

- **IV tPA versus IA Endovascular treatment**
- **Again, confirmation of large-vessel occlusion by noninvasive imaging was not required**

NEJM 2013 ;368(10):904-13.

"SYNTHESIS" Trial



- Italian, randomized trial comparing IV t-PA to "Endovascular" Treatment (1:1 randomization)
- 362 patients enrolled with symptom onset within 4.5 hrs
- Median NIHSS was 13 in both arms, ranging from (2-26) → *patients with NIHSS of 2 were randomized to "endovascular therapy"*
- In patients with a neurologic deficit *but no corresponding occlusion*, the endovascular procedure involved injecting t-PA into the vascular area that was presumably affected. The amount of drug to be injected, which again did not exceed 0.9 mg per kilogram (maximum, 90 mg for patients weighing ≥100 kg), was at the operator's discretion.
- IV t-PA
  - 181 patients, Median time to treat 2.75 hrs
  - Given 0.9 mg/kg (max 90mg), with 10% as initial bolus, remainder over 60 min, Median dose 66mg
  - Did not require documenting vessel occlusion with imaging (CTA, MRA, Perfusion)
- "Endovascular" Treatment
  - 181 patients, 163 patients completed (18 excluded – lack of occlusion, clinical improvement, etc.), Median time to treat 3.75 hrs
  - 109 patients (67%) received intra-arterial t-PA as MONO THERAPY (0.9mg/kg given over 1hr, median dose 40mg) → NOT approved for use in the US.
  - ONLY 56 patients (34%) received adjunctive mechanical thrombectomy
    - 23 stent-treivers -------→ *ONLY 14 % of the "endovascular" arm received current treatment*
    - 5 Merci, 9 Penumbra

Major Concern - IA thrombolysis was allowed even in cases when angiography showed no occlusion

micro-guidewire to facilitate disintegration of the thrombus, systems to capture and extract the thrombus, or more complex systems to crush and aspirate it.

In patients with a neurologic deficit but no corresponding occlusion, the endovascular procedure involved injecting t-PA into the vascular area that was presumably affected. The amount of drug to be injected, which again did not exceed 0.9 mg per kilogram (maximum, 90 mg for patients weighing ≥100 kg), was at the operator's

Such patients are inappropriate for IA therapy!!

NEJM 2013 ;368(10):904-13.

SYNTHESIS Expansion

- Of 165 patients treated with IA approach, 109 received only pharmaceutical agents or wire manipulation
- Only 56 patients received advanced mechanical thrombectomy
- Stentretrievers were used in patients 13% of patients

"MR Rescue" Trial


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

- 22 sites in North America
- Randomized to either Mechanical thrombectomy (Merci or Penumbra) or standard medical care → ZERO stent-trievers
- All patients underwent pre-treatment multimodal CT or MRI and stratified based on presence or absence of 'favorable' penumbral pattern vs. non-penumbral (core infarct) pattern.
  - Ischemic penumbra is brain tissue with reduced blood flow that is at risk for infarction if flow is not restored.
  - The hypothesis was that some patients have substantial regions of salvageable brain (penumbral pattern) within several hours after a stroke and would benefit from reperfusion, whereas patients with non-penumbral pattern would not benefit or even be harmed by reperfusion.
- Symptom onset had to be less than 8 hours.

MR RESCUE

- 118 patients within 8 hours, anterior circulation stroke. Penumbral versus non-Penumbral profile. Primary outcome was 3-month mRS
- Embolectomy and standard medical care (3.9 vs. 3.9, P = 0.99)
- Embolectomy was not superior to standard medical care in patients with either a favorable penumbral pattern (mean score, 3.9 vs. 3.4; P = 0.23) or a nonpenumbral pattern (mean score, 4.0 vs. 4.4, P=0.32).
- Patients with adequate reperfusion DID demonstrate mean improvements in 3-month mRS (3.2 [2.6-3.8] versus 4.1 [3.7-4.5], P=0.04) and median absolute infarct growth (9.0 versus 72.5 mL, P<0.001).

"MR Rescue" Trial


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

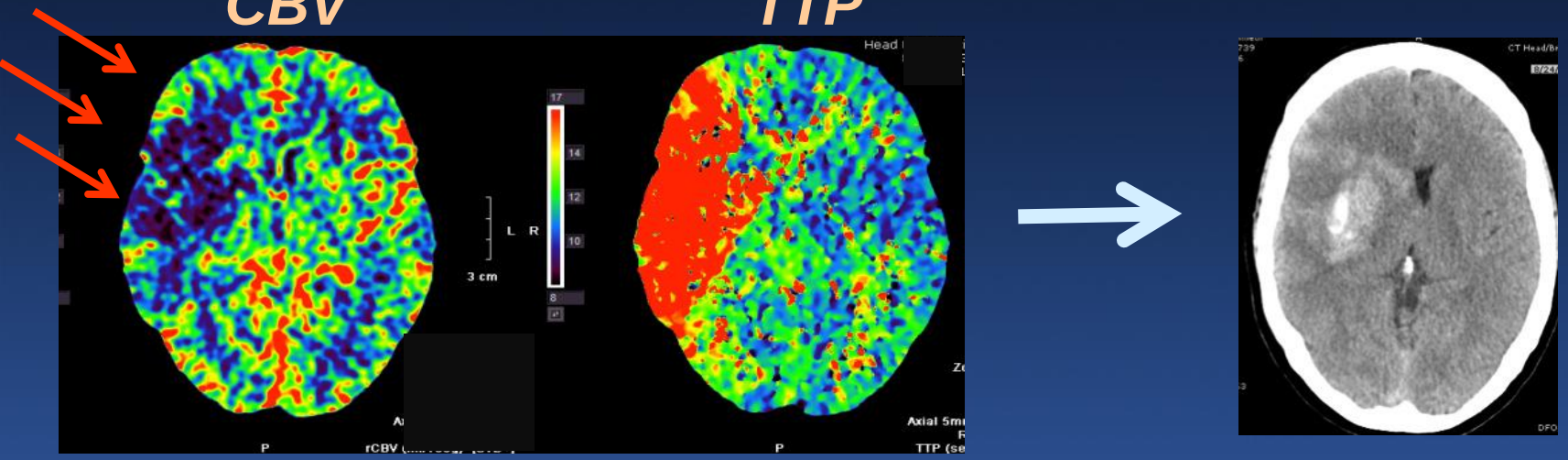
- **Potential explanations for the 'neutral' results (excluding imaging-selection hypothesis)**
  - **There was a relatively low rate of substantial revascularization (TICI 2A-3), "perhaps related to use of first-generation embolectomy devices" → ZERO stent-trievers utilized. Possible that newer-generation devices would show a benefit owing to higher recanalization and lower complication rates.**
  - **Extended time from imaging to embolectomy…Mean time from imaging to groin puncture was 2 hours and 4 minutes.**
  - **Mean time from last known well to groin puncture was 6 hours and 21 minutes, longer than mean time in most prior endovascular stroke trials.**
  - **Procedure could not extend beyond 9 hours after symptom onset.**
  - **Embolectomy times beyond 2 hours were 'discouraged'.**

MR RESCUE trial

- Hypothesis: favorable neuroimaging ('penumbral') pattern can identify patients with benefit from endovascular treatment
- Randomization of patients with an infarct core volume as large as 90 ml was permitted – core was TOO LARGE
- Such high volumes of infarcted core are associated with poor outcomes

Example of “bad” penumbra – real world case

- There is mismatch but core is too large
- This patient had large stroke and ICH despite achieving TICI2



MR RESCUE trial

- Only 27% of patients were able to achieve TICI2b-3 score
- This is UNACCETABLY LOW reperfusion result according to current standards

MR RESCUE trial

- Only 20 to 34 patients were included in each group (4 arms total)
- Very low number – unlikely to achieve any statistical significance
- And finally…. stent-retrievers were NOT included in the endovascular arm

- *In the IMS-III and SYNTHESIS trials assessing "endovascular" stroke therapy*
  - *51% of patients (251/497) receiving "endovascular" therapy received IA t-PA as MONO therapy → not approved for use in the US*
- *In all 3 trials assessing "endovascular" stroke therapy*
  - *Only 6.6% of patients (37/561) receiving "endovascular" therapy were treated with 'current' technology (i.e. stent-trievers)*

- **All 3 of previous trials did show no difference in safety with 'endovascular' therapy vs. 'standard' therapy.**

- **All 3 trials pointed out that assessment of stent-trievers technology could not be made from the current literature, and emphasized the need for randomized clinical trials assessing the efficacy of the stent-triever technology.**

- **IMS-III and SYNTHESIS acknowledge that because imaging confirmation of vessel occlusion was not mandated in the IV t-PA group…one can not exclude that endovascular therapy is superior to IV t-PA in cases of large vessel occlusion.**

SUMMARY OF LIMITATIONS OF RECENT TRIALS

- Long period of enrollment- Not keeping in pace with technology
- Small number of patients per center per year
- No angiographic confirmation of large vessel occlusion
- No evaluation of salvageable brain tissue
- First generation endovascular technology

SUMMARY OF LIMITATIONS OF RECENT TRIALS

- Good start, many lessons learned
- We need to move forward
- Ignore those who state “these trials showed no benefit of endovascular therapy”..

SUMMARY OF LIMITATIONS OF RECENT TRIALS

- **What did those trials show?**

- Endovascular therapy has no benefit in poorly selected patients with outdated technology…DAH!!

Good Summary of Potential Challenges and Solutions

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

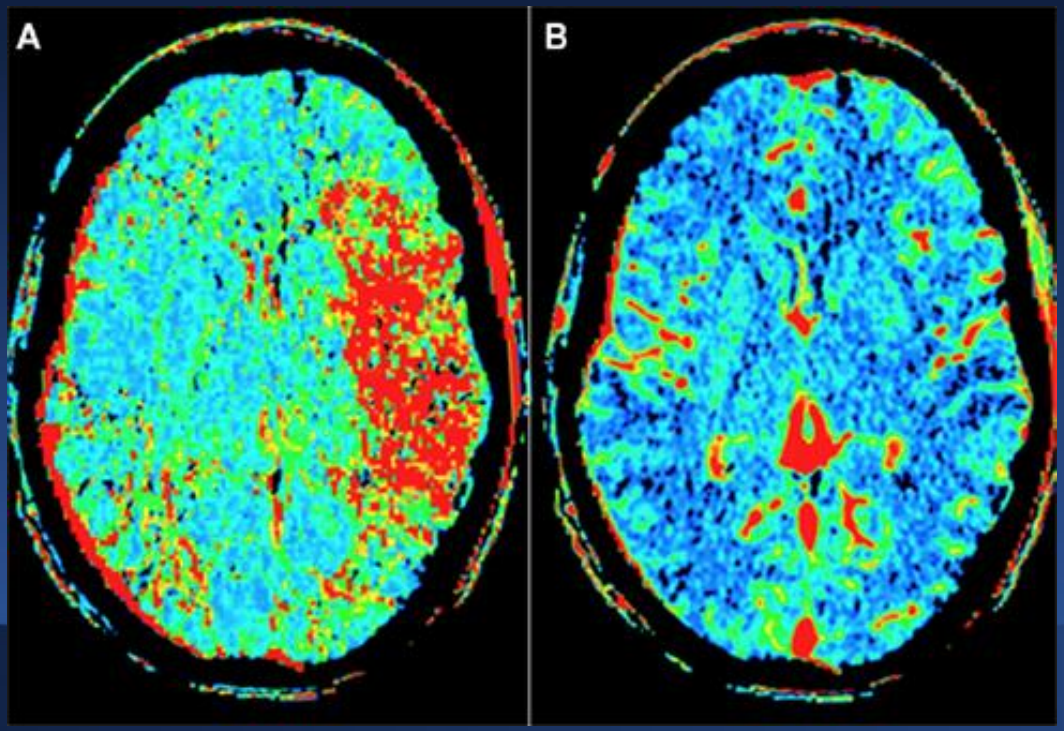
Challenges of Acute Endovascular Stroke Trials

Mayank Goyal, Mohammed Almekhlafi, Bijoy Menon, Michael Hill, Kyle Fargen, Mark Parsons, Oh Young Bang, Adnan Siddiqui, Tommy Andersson, Vitor Mendes, Antoni Davalos, Aquilla Turk, J Mocco, Bruce Campbell, Raul Nogueira, Rishi Gupta, Sean Murphy, Tudor Jovin, Pooja Khatri, Zhongrong Miao, Andrew Demchuk, Joseph P. Broderick and Jeffrey Saver

Stroke. published online August 28, 2014;

Challenges

We need to figure out who we should treat



Core?

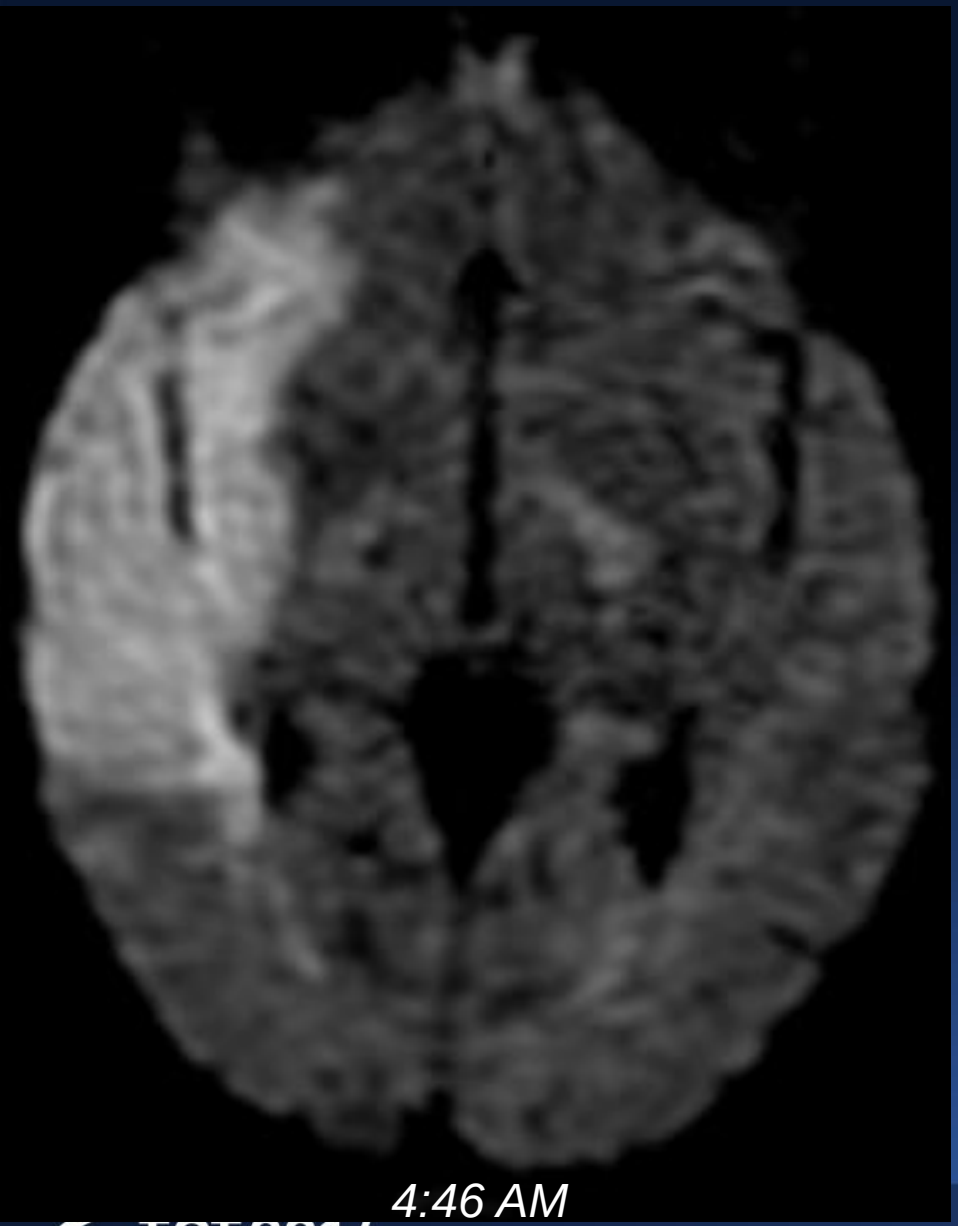
29 y.o. female

24 weeks pregnant

Last normal = 2 am

NIHSS 17 -> Thrombectomy -> NIHSS 5

Pre and Post MRI on the same 1.5 Tesla unit



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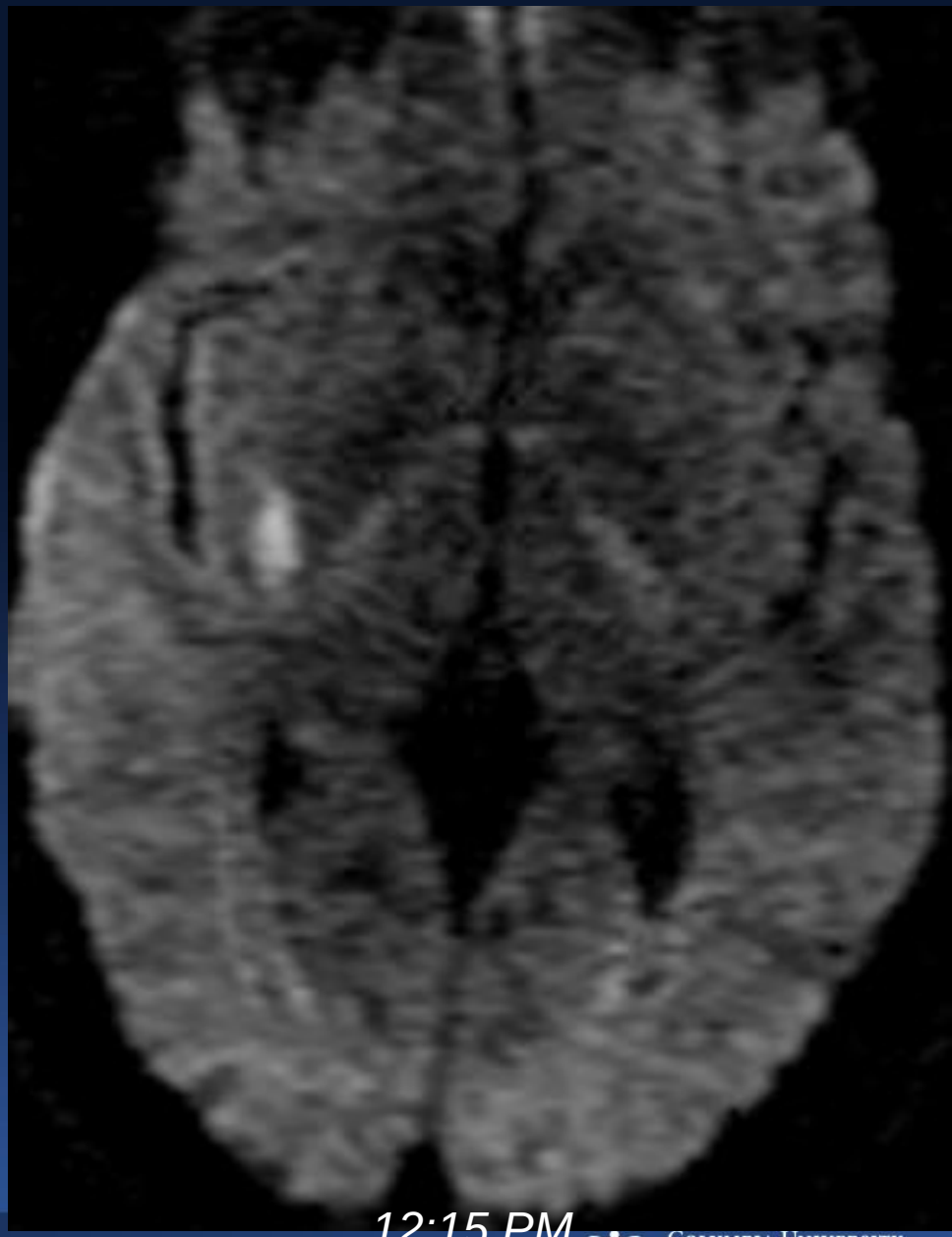

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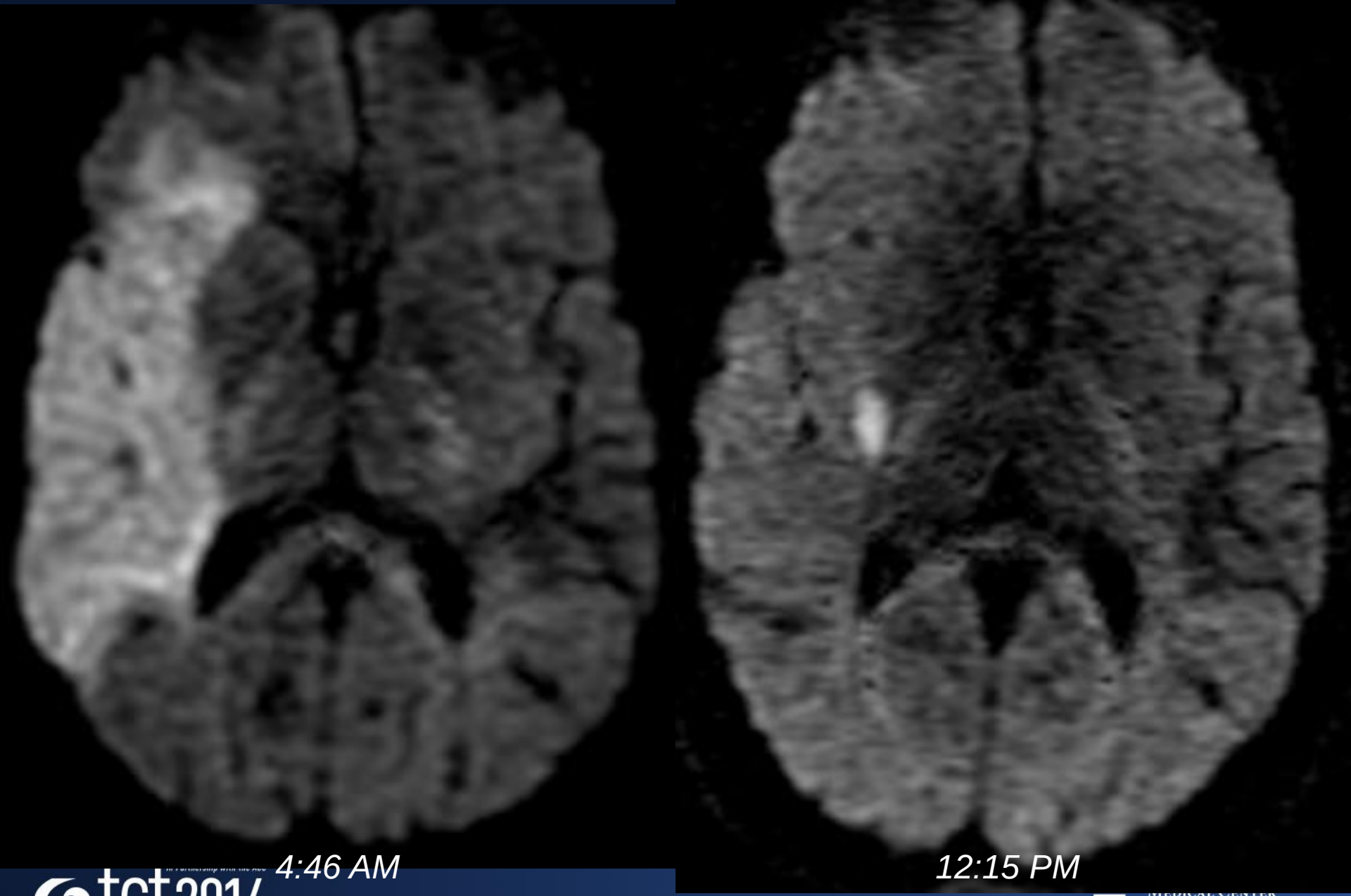
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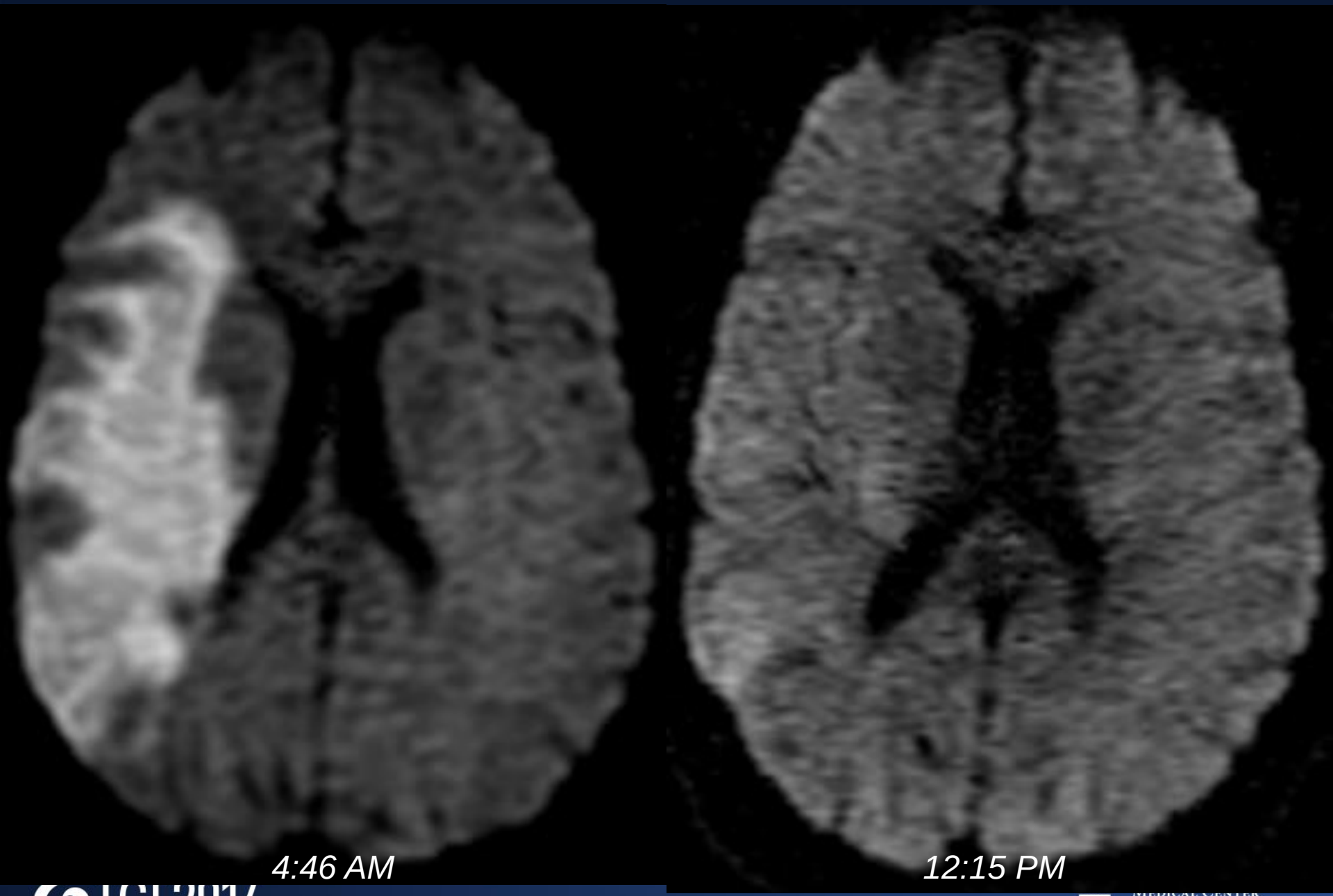
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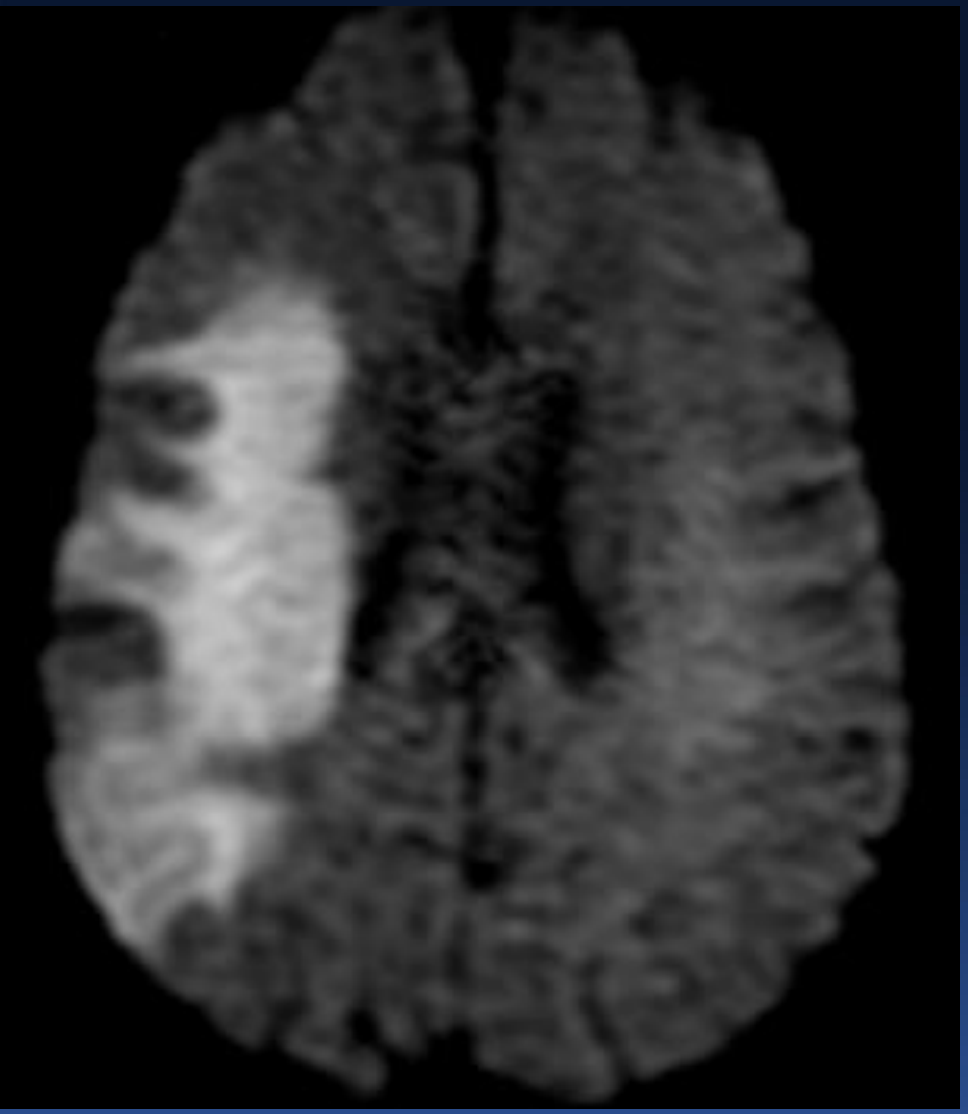

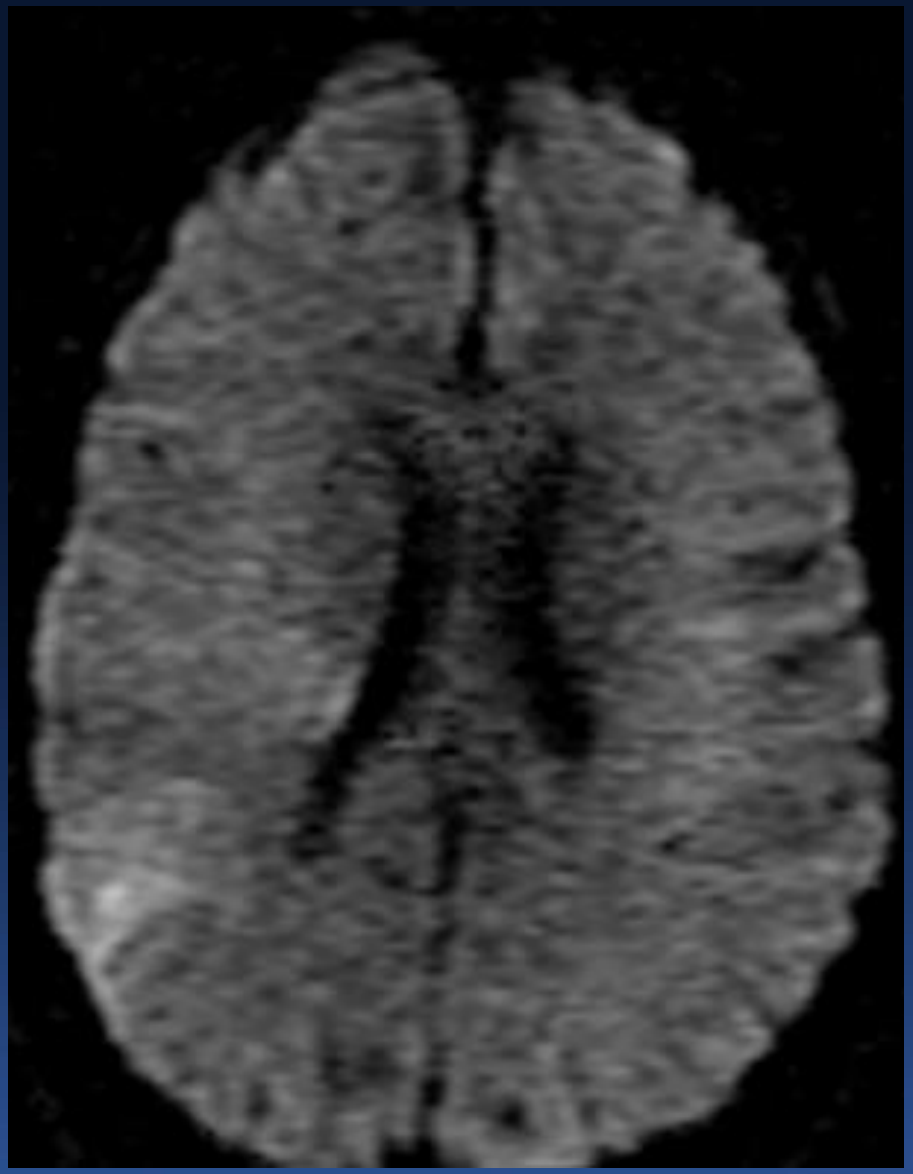

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Endpoints	≤8 hours (N=173)	>8 hours (N=74)	P-value
Mean Age	67 yrs	64 yrs	0.054 (NS)
Gender (M)	45.1 %	51.4 %	0.405 (NS)
Mean time to treatment	4.8 hrs	16.4 hrs	**<0.0001**
Mean NIHSS	18.7	17.2	0.069 (NS)
90-day mRS ≤ 2	42.8 %	41.9 %	1.0 (NS)
90-day mRS ≤ 3	54.9 %	55.4 %	1.0 (NS)
Mortality	24.9 %	20.3 %	0.5 (NS)
TICI 2B or 3 Recan Complete (%) None (%)	 71.7 % 28.3 %	 81.1 % 18.9 %	 0.151 (NS)
Location Anterior Circulation MCA occlusion	 92.4 % 69.6 %	 83.6 % 67.1 %	 0.062 (NS) 0.763 (NS)
Intracranial Hemorrhage	19.7 %	18.9 %	1.0 (NS)

Real world Perfusion based selection

Turk et al JNIS

Columbia University Medical Center
NewYork-Presbyterian

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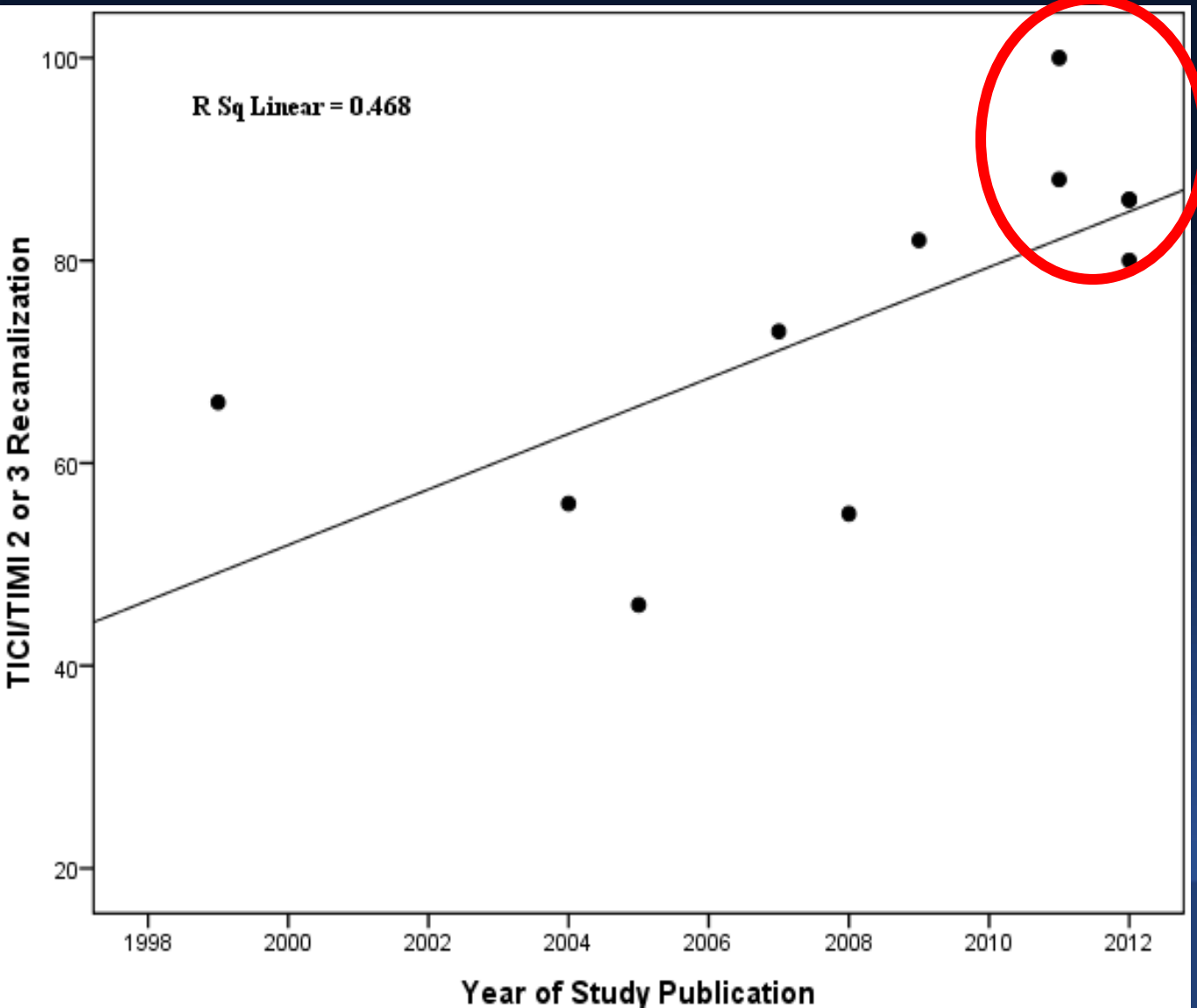
Columbia University Medical Center
NewYork-Presbyterian

How successful are we?



80-90%

How successful are we?

This means 10-20% are not achieving TICI 2b-3

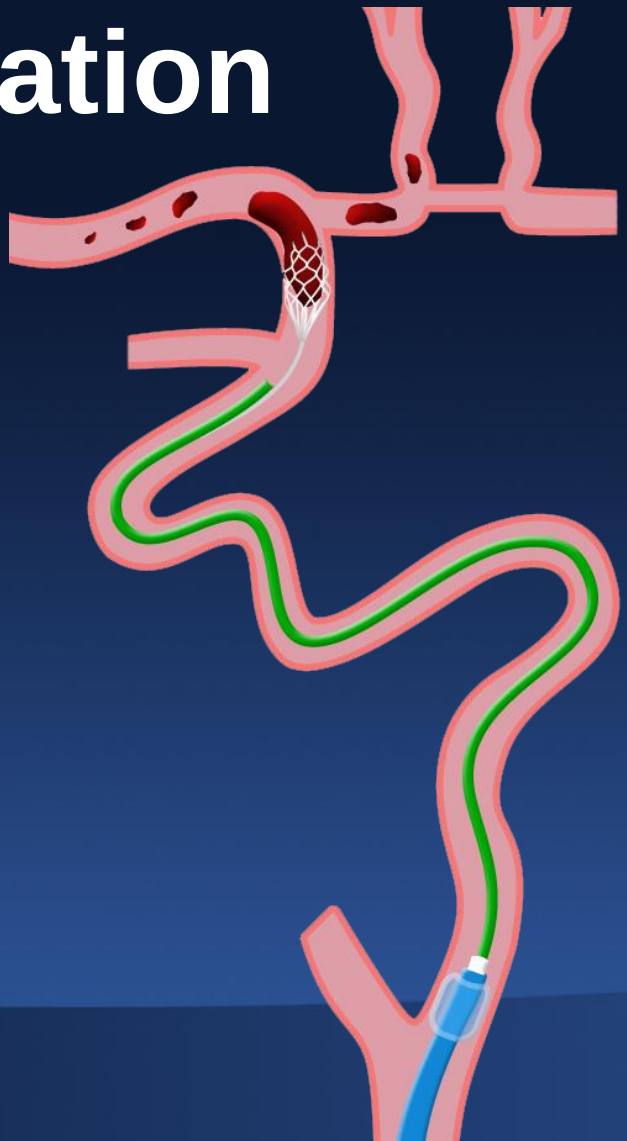
How successful are we?

This means 10-20% are not achieving TICI 2b-3

This is inadequate

How successful are we?

Distal Embolization



How successful are we?

Distal Embolization

22%[1]

7-9%[1,2]

[1] Solitaire Retrospective Study. Presented at WFITN, 2011. Costalat, Stroke (2011).
[2] Trevo 2 Trial. Presented at ESC, 2012.

How successful are we?

Frequency and relevance of anterior cerebral artery embolism caused by mechanical thrombectomy of middle cerebral artery occlusion.

Kurre W, Vorlaender K, Aguilar-Perez M, et al. AJNR Am J Neuroradiol 2013;34:1606–11

New ACA emboli in 12 of 105 (11.4%) M1 procedures

Causing ACA infarcts in 5.7% of patients

No BGC for majority of cases

How successful are we?

Distal aspiration with retrievable stent assisted thrombectomy for the treatment of acute ischemic stroke

Stent aspiration technique

5.7% ENT Rate

William Humphries, Daniel Hoit, Vinodh T Doss, Lucas Elijovich, Donald Frei, David Loy, Gwen Dooley, Aquilla S Turk, Imran Chaudry, Raymond Turner, J Mocco, Peter Morone, David Fiorella, Adnan Siddiqui, Maxim Mokin, Adam S Arthur Humphries W, et al. J NeuroInterv Surg 2014;0:1–5. doi:10.1136/neurintsurg-2013-010986

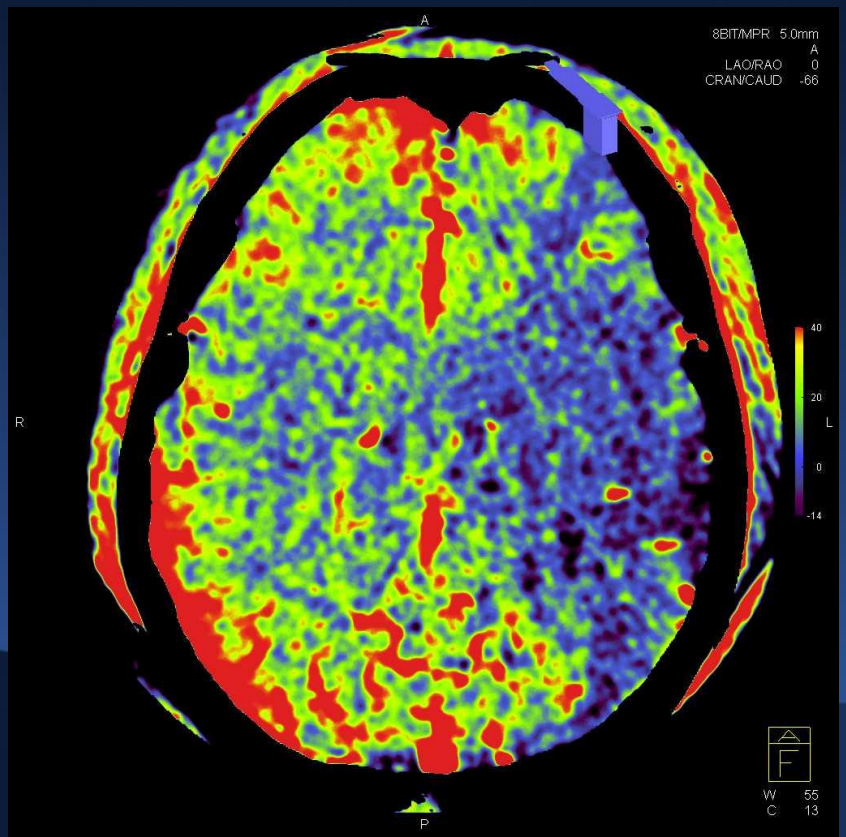
How do we improve?

New technology is critical

How do we improve?

New technology is critical

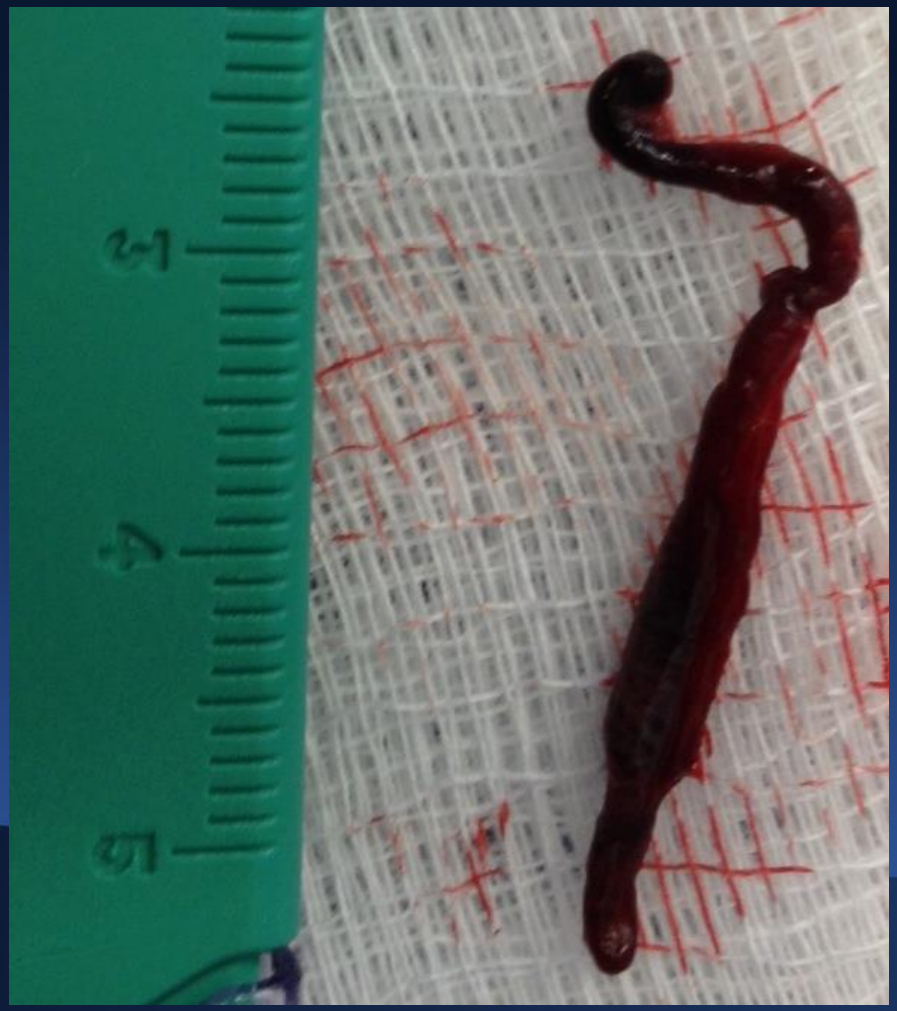
Dyna CBV



Improved imaging paradigms

How do we improve?

New technology is critical

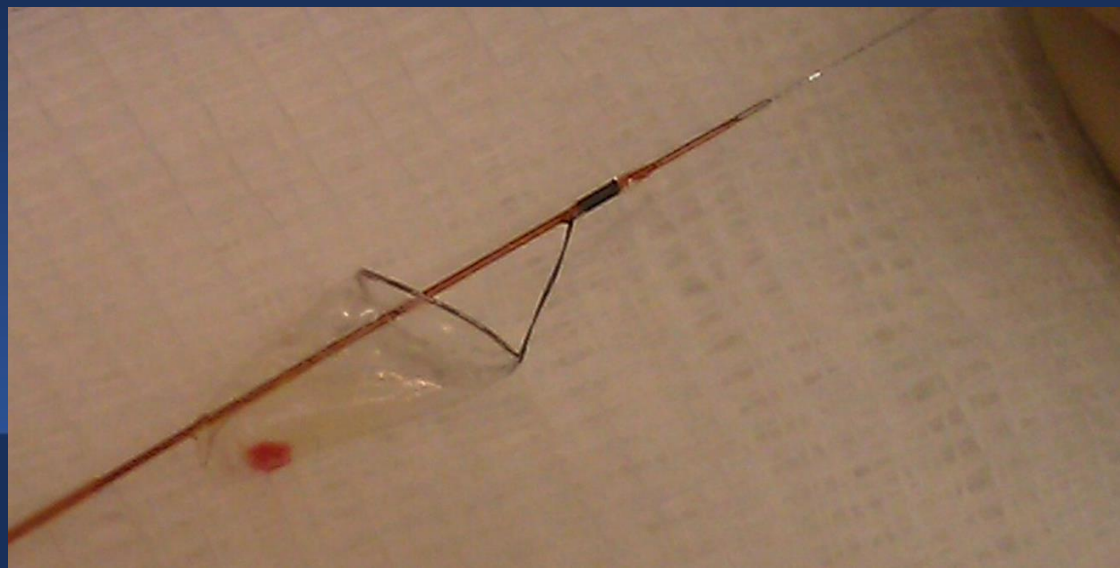


Aspiration based thrombectomy to prevent fragmentation

How do we improve?

New technology is critical

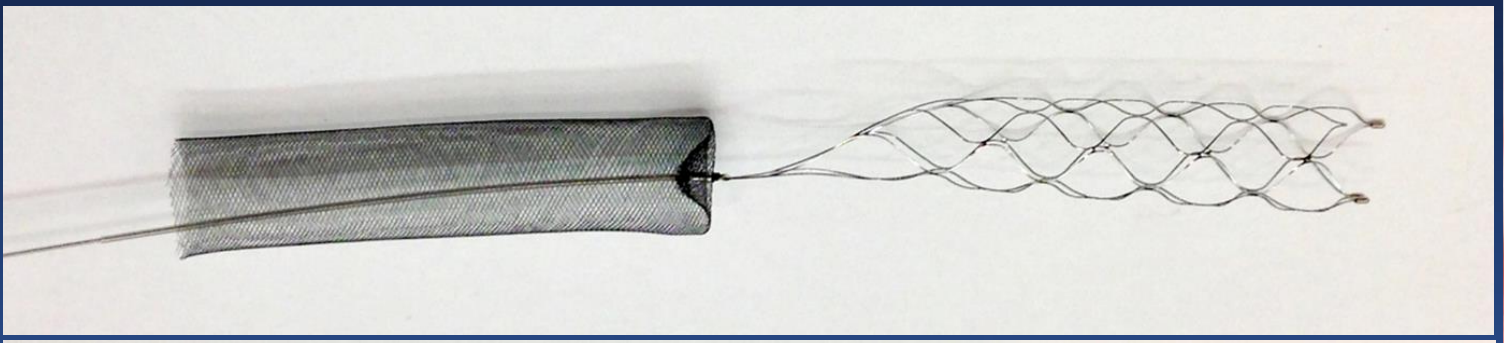
Emboli protection devices

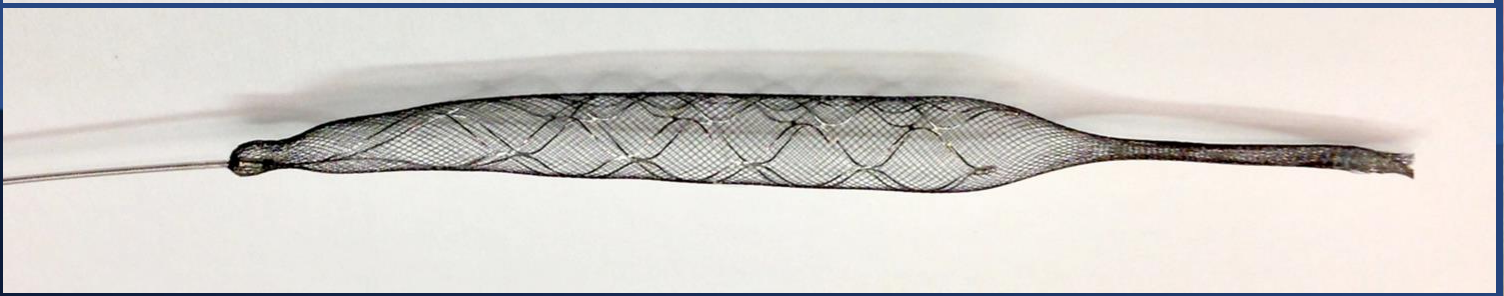


How do we improve?

New technology is critical

Emboli protection devices





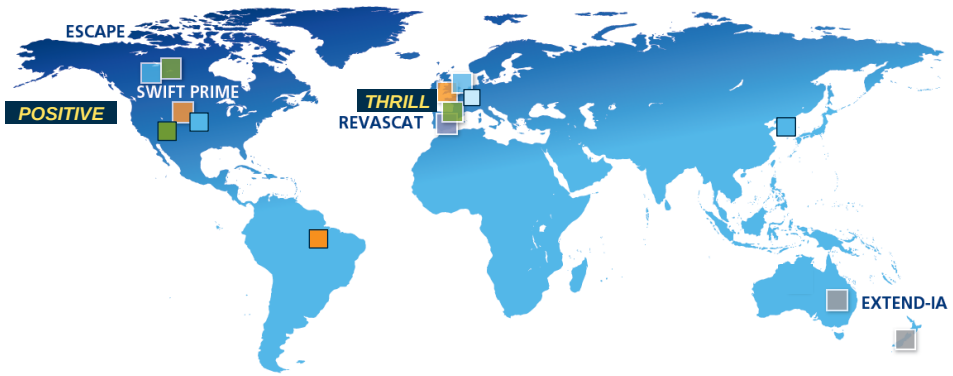
TRIALS IN THE PIPELINE

- **SWIFT PRIME**: IV tPA + Solitaire FR vs IV tPA alone – based on perfusion imaging by RAPID and confirmed large vessel occlusion
- **THERAPY**: IV trPA+ Penumbra aspiration vs IV tPA – cases with clots > 8mm length
- **POSTIVE**: Any FDA-cleared IA intervention vs medical therapy within 12 hours of stroke onset, selected by perfusion imaging

STROKE STUDIES

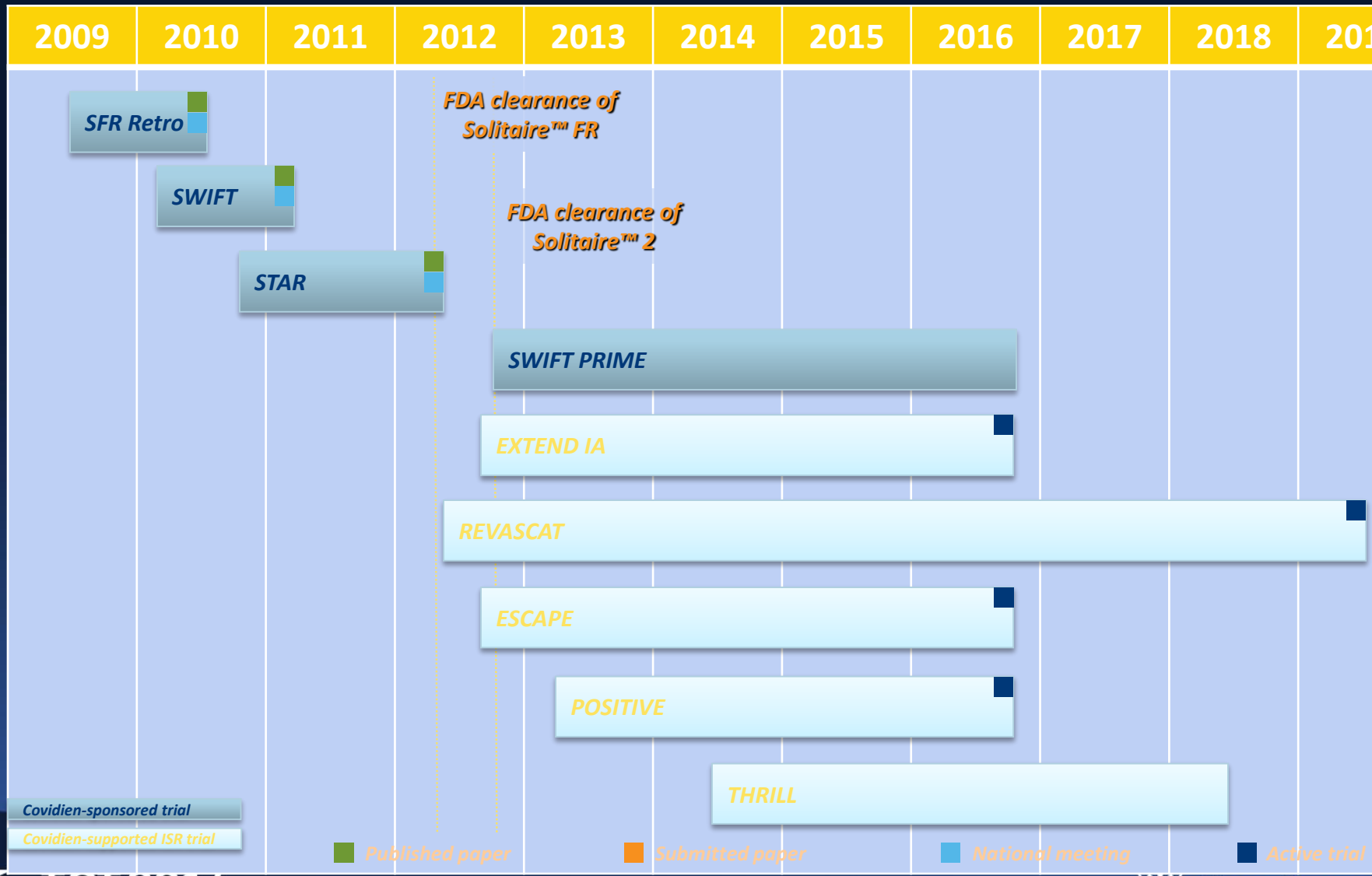
Study	SWIFT PRIME	EXTEND IA	REVASCAT	ESCAPE	POSITIVE	THRILL
Study Design	Prospective, multi-center, randomized, controlled, blinded-endpoint trial	Prospective, multi-center, randomized, controlled.	Prospective, multi-center, randomized, controlled, blinded-endpoint trial	Prospective, multi-center, randomized, controlled.	Prospective, multi-center, randomized, controlled	Prospective, bi-national, randomized, controlled, blinded endpoint trial
Tx Window	6 hrs	4.5 hrs	8 hrs	12 hrs	Wake up or 12 hrs	8 hrs
Study Arm	SFR + tPA	SFR + tPA	SFR with or without tPA	Mechanical Thrombectomy	Stent retriever or aspiration	Stent retriever
Control Arm	tPA	IV t-PA	Medical Mgt (which may include tPA or PA or ASA)	Medical Mgt	Best Medical Therapy	Best medical care alone
Sample Size/ Sizes	833 pts, 60 sites	150 pts, 15 sites	690 pts, 6 sites	250 pts, 10 sites	750 pts, 20 sites	600 pts, 20 sites
Location	US, EU	Australia and New Zealand	Spain	Canada, US, EU, Asia	US, Canada, EU	Austria and Germany
Primary Endpoints	mRS at 90 days Rankin Shift	Reperfusion at 24 hrs without sICH <72 hours	mRS at 90 days Rankin Shift	NIHSS 0-2 or mRS 0-2 at 90 days	mRS at 90 days Rankin Shift and mRS 0-2	mRS at 90 days Rankin Shift
Secondary Endpoint(s)	Mortality at 90 days, Good Neuro Outcome, Change in NIHSS @ 27hrs, Cost Effectiveness	Recanalization and infarct volume at 24 Hrs, NIHSS at 24hrs, mRS dichotomized	Infarct Vol @ 5d, Cost effect, Analysis of interventional therapy vs. medical therapy alone	NIHSS, mRS, mRS shift, Mortality, QOL, Cost effectiveness	mRS, TICI 2b-3	mRS 0-1, mRS 0-2 or NIHSS improvement ≥10, Core infarct volume, QOL
Safety Endpoint(s)	SAE, sICH @ 27 hours	sICH at 72 hrs	Mortality at 90 days, Clinically significant ICH at 24hrs, QOL at 3m and 12m	All SAE	Mortality, ICH, Procedure-related SAEs,	mRS 4-6, sICH, PH-2, NIHSS increase ≥4, SAEs, ADE, SADE, UADE, space-occupying infarction, new ischemic stroke

Changing Paradigms
Through Clinical Evidence



SWIFT PRIME Randomized study of IV therapy vs. IV therapy + mechanical thrombectomy with the Solitaire™ FR Device	US, Europe	60 centers; Up to 833 patients
REVASCAT Randomized study of IV therapy vs. mechanical thrombectomy with the Solitaire™ FR Device	Spain	5 centers; Up to 690 patients
EXTEND-IA Randomized study of IV therapy vs. IV therapy + mechanical thrombectomy with the Solitaire™ FR Device	Australia, New Zealand	10 centers; Up to 150 patients
ESCAPE Randomized study of IV therapy vs. mechanical thrombectomy with the Solitaire™ FR Device. Mechanical intervention can occur up to 12 hours after symptom onset	Canada, Europe, US, Asia	10 centers; Up to 250 patients
POSITIVE Randomized study of medical therapy vs. mechanical thrombectomy in patients ineligible for IV t-PA. Mechanical intervention can occur up to 12 hours after symptom onset	US, Canada, Europe	20 centers; Up to 750 patients
THRILL Randomized study of medical therapy vs. mechanical thrombectomy in patients ineligible for IV t-PA. Mechanical intervention can occur up to 8 hours after symptom onset	Germany, Austria	20 centers Up to 600 patients

NV Stroke Clinical Trial Timeline



Stroke Trials - MT

Study	THERAPY	DAWN
Company	Penumbra	stryker Neurovascular
Study Title	The THERAPY Trial: The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention
Study Design	Prospective, randomized, concurrent controlled safety/efficacy study	Prospective, randomized (1:1), multi-center, Phase II/III (feasibility/pivotal), adaptive, population enrichment, blinded endpoint, controlled trial
Study Objective	To assess the safety and effectiveness of the Penumbra System as an adjunctive treatment to intravenous (IV) recombinant human tissue plasminogen activator (rtPA) in patients with acute ischemic stroke from large vessel occlusion in the brain.	To demonstrate superior clinical outcomes at 90 days with Trevo XP plus medical management compared to medical management alone in appropriately selected patients treated 6-24 hours after last seen well.
Tx Window	5 hrs	24 hrs
Study Arm	IV t-PA + Penumbra System	IV t-PA + Trevo XP
Control Arm	IV t-PA	IV t-PA
Sample Size/Sites	692 pts, 40 sites	500 pts, 50 sites
Location	US, EU	US, EU
Primary Endpoint	mRS at 90 days Rankin Shift	Difference in average weighted mRS at 90 days between treatment & control in the enriched patient population
Secondary Endpoint(s)	Incidence of SAEs, Incidence of sICH and aICH at 90 days	Procedure-related complications
Follow-up	Up to 90 days	Up to 90 days
Forecasted Timelines	5/2012-12/2016	

Where Are We Now?

Stroke vs. MI in the US

Ischemic Stroke

- Prevalence: 600 000
- Endovascular treatment:
  10 000 (2%)
- Mortality: 20%

Acute Myocardial Infarction

- Prevalence 1 500 000
- Endovascular treatment:
  300 000 (20%)
- Mortality: 10%

Designing Success:

Problem	Solution
Highly effective device	Stent Retrievers or Penumbra Max System
Clots to attack	CTA/MRA
Clots poorly responsive to IVT	ICA/M1
Brain to save/Penumbra	Perfusion Imaging or Clinical Core Mismatch
Patients who will respond	Randomize ALL eligible
Minimize progression	Door to puncture optimization
Concomitant therapy	Full dose TPA if eligible
Patient Volume	Need to Collaborate!

Future of Endovascular Therapy of Stroke

- Better devices → faster recanalization
- Better identification of ischemic core and penumbra → improved patient selection
- Neuroprotection → more patients get treatment

RESULTS: Better recovery after stroke