Prehospital and Endovascular Care in the New Era of Ischemic Stroke Treatment

Jeffrey L. Saver, MD,
Director, UCLA Comprehensive Stroke Center
SA Vice-Chair and Professor of Neurology, DGSOM

JLS Disclosures

- Employee of the University of California. The University of California has patent rights in retrieval devices for stroke.
- Unpaid site investigator in multicenter trials run by Medtronic, Stryker, and Lundbeck, for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled.
- Receives funding for services as a scientific consultant regarding trial design and conduct to Medtronic/Covidien, Stryker, Neuravi, BrainsGate, Pfizer, Boehringer Ingelheim (prevention only), and St. Jude Medical.
- Serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr. Saver received any payments for this voluntary service.

Talk Outline

- Fast - Time and Intravenous Therapies
  - » IV TPA
  - » Prehospital treatment
- Furious
  - » Endovascular Therapies
  - » Systems of Care
- Future

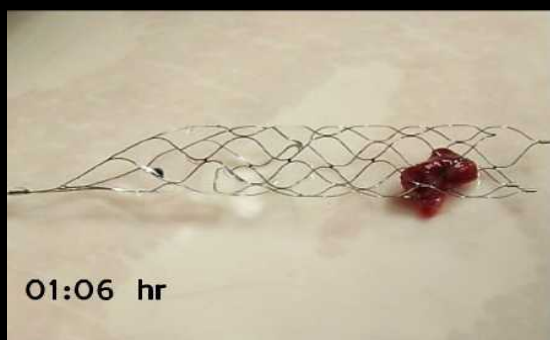
Montreal Reflections: Eleanor Young

Strategies in Acute Ischemic Stroke Therapy

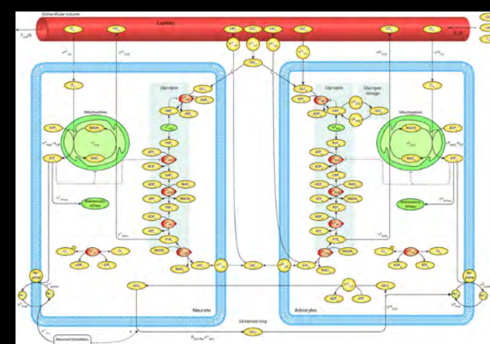
- Proven
  - » Recanalization
  - » Supportive Care
  - » Prevent Clot Propagation
- Experimental
  - » Neuroprotection
  - » Collateral Enhancement

Two Major Strategies in Acute Ischemic Stroke Treatment

Reperfusion

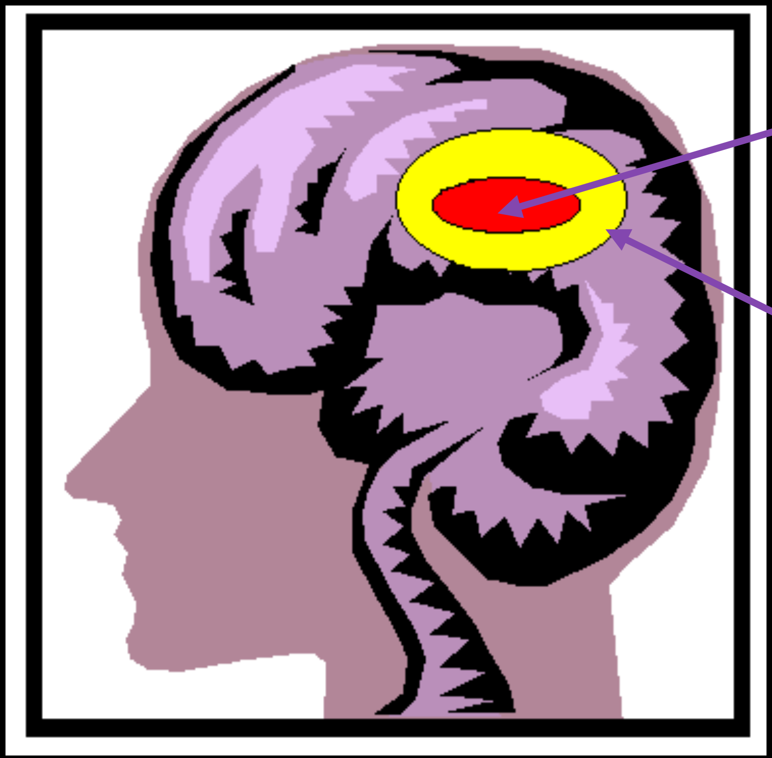


Neuroprotection



--modified from M Tymianski

The Ischemic Penumbra

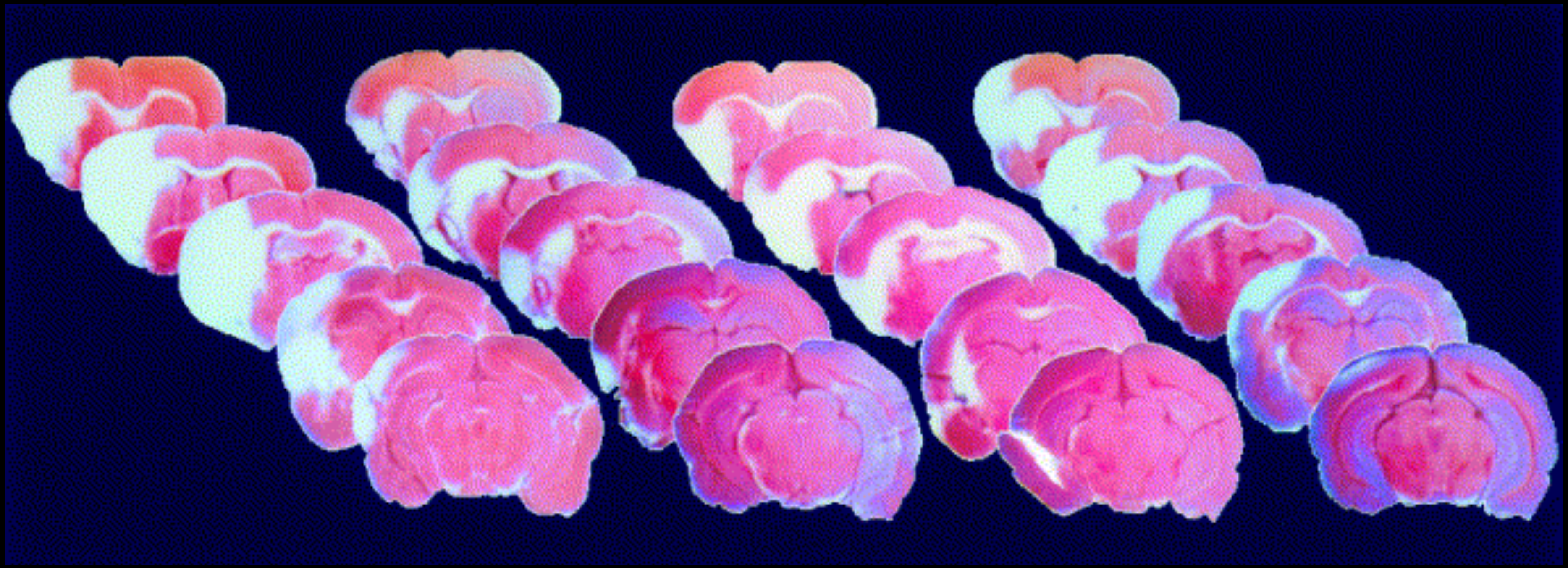


Irreversible Core Infarct

Ischemic Penumbra

zone of salvageable tissue surrounding core infarct

Brief Time Window in Animal Stroke Models



Permanent Early Medium Late

- *UCLA Stroke Center*

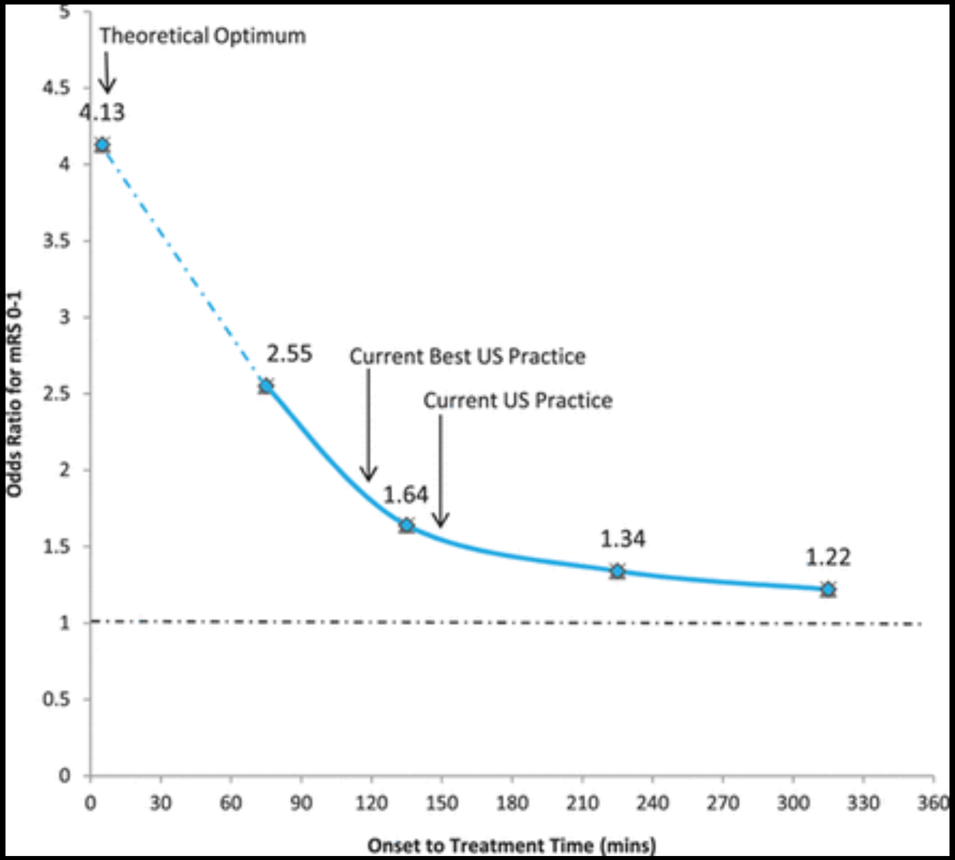
In a typical acute ischemic stroke, every minute the brain loses

- 1.9 million neurons
- 14 billion synapses
- 7.5 miles myelinated fibers

-- Saver, Stroke 2006

Onset to Treatment Time for IV TPA and Odds of Excellent Outcome

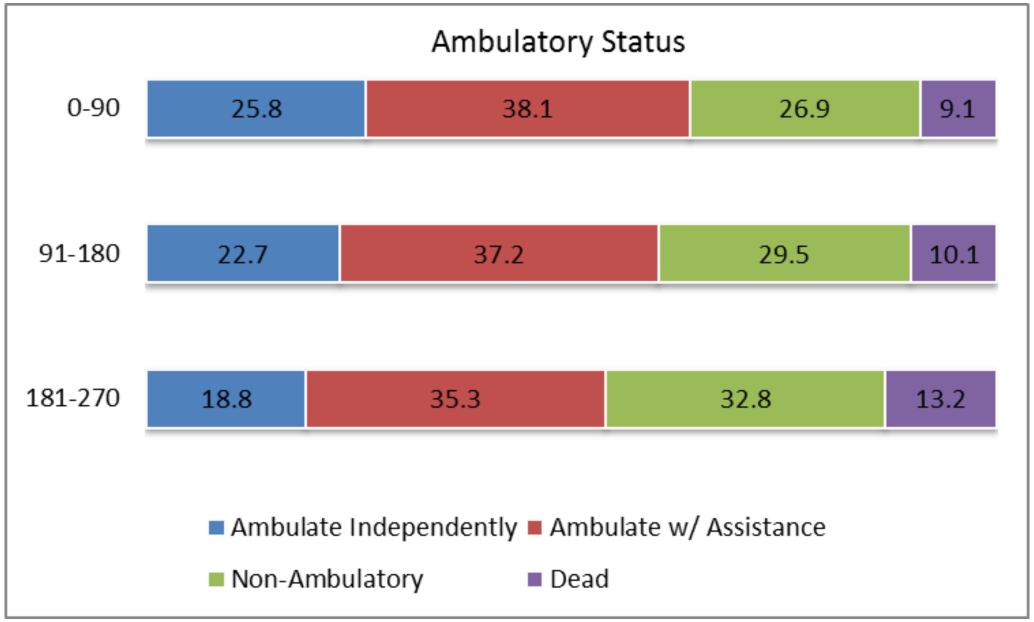
- Pooled, patient level analysis
- 8 trials
  - » NINDS 1 and 2
  - » ATLANTIS A and B
  - » ECASS 1, 2, and 3
  - » EPITHET
- 3670 patients



--Lees et al, Lancet 2010
--Saver + Levine, Lancet 2010
--Saver, Stroke 2012

TPA Treatment Time and Benefit Magnitude
58,353 Patients from 1395 GWTG-Stroke Hospitals

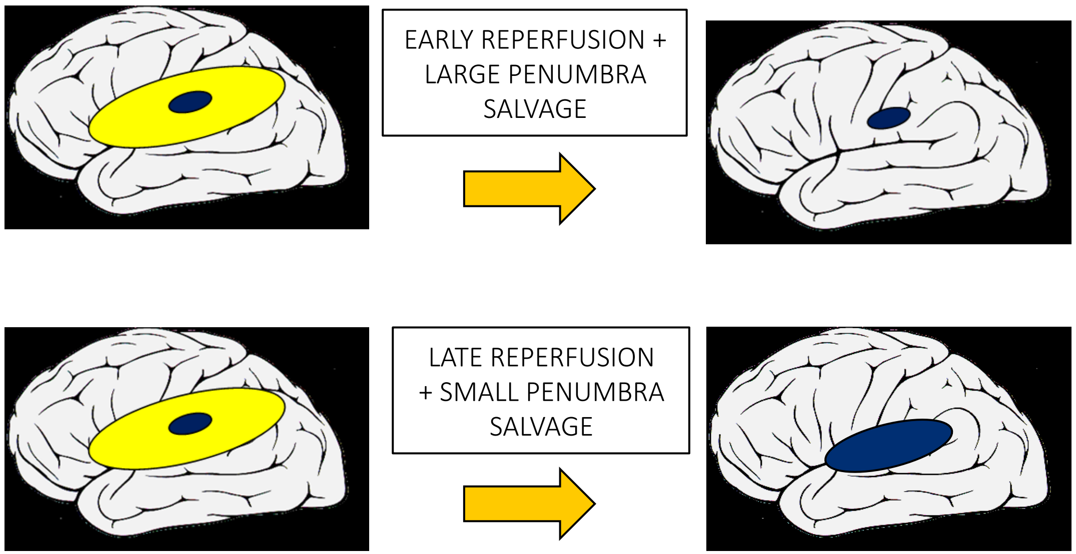
--Saver et al, JAMA 2013



Among 1000 patients, for every 15 min acceleration of tPA treatment

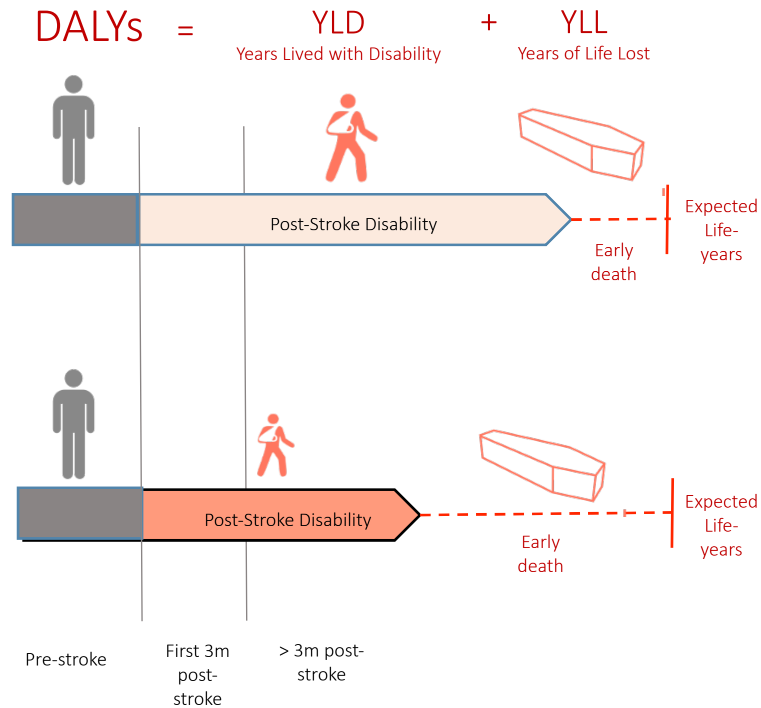
- **18 more will have improved ambulation at discharge**
  - **Including 8 more who will ambulate fully independently**
- **13 more will be discharged to a more independent environment**
  - **Including 7 more discharged to home**
- **4 fewer patients will die prior to discharge**

A Drop of Brain (1cc), A Week of Healthy Life
Quality Adjusted Life-Years (QALYs)



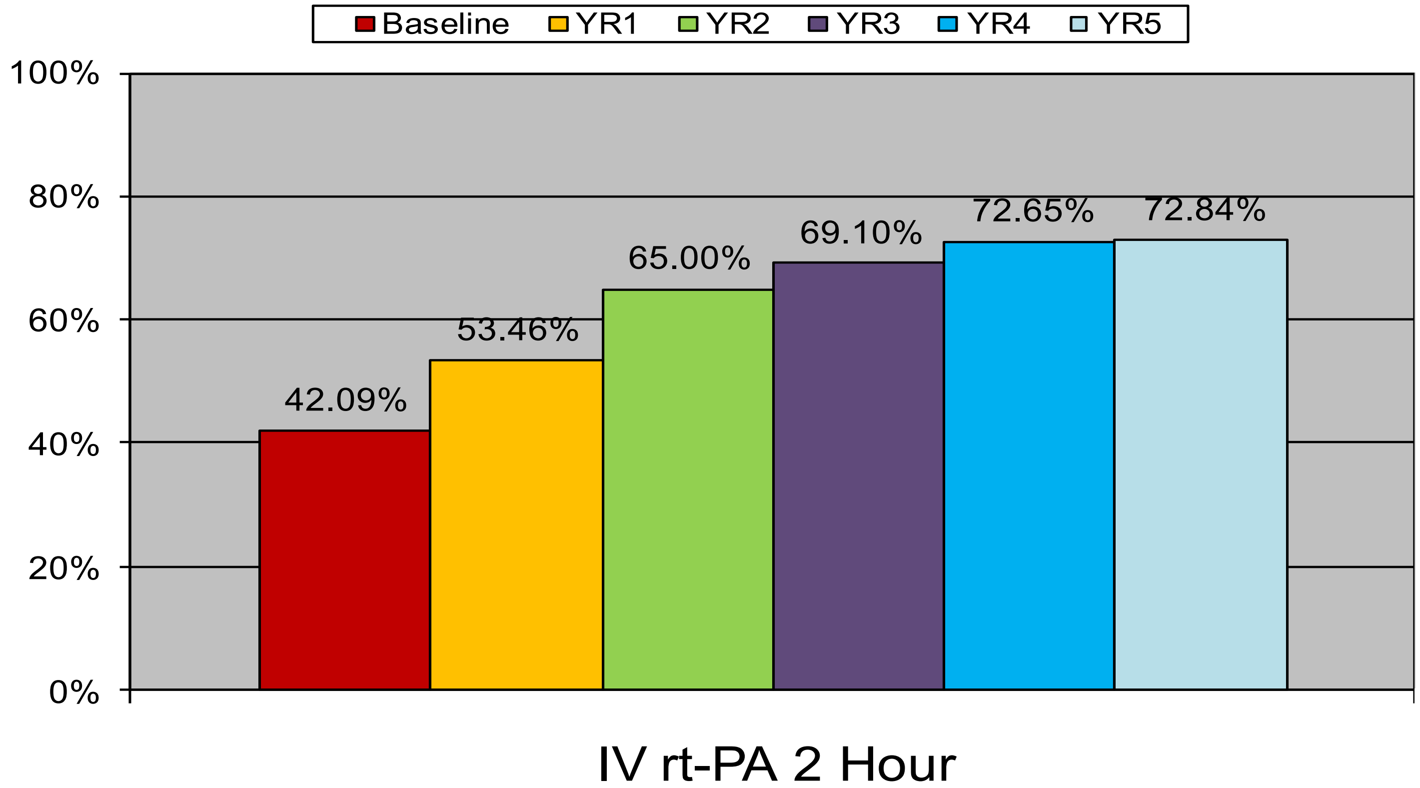
Penumbra (yellow) and core (blue) volumes on perfusion CT pre-tPA

Final infarct volume on 24h MRI



--Saver, Brain 2017
--Kawano et al, Brain 2017

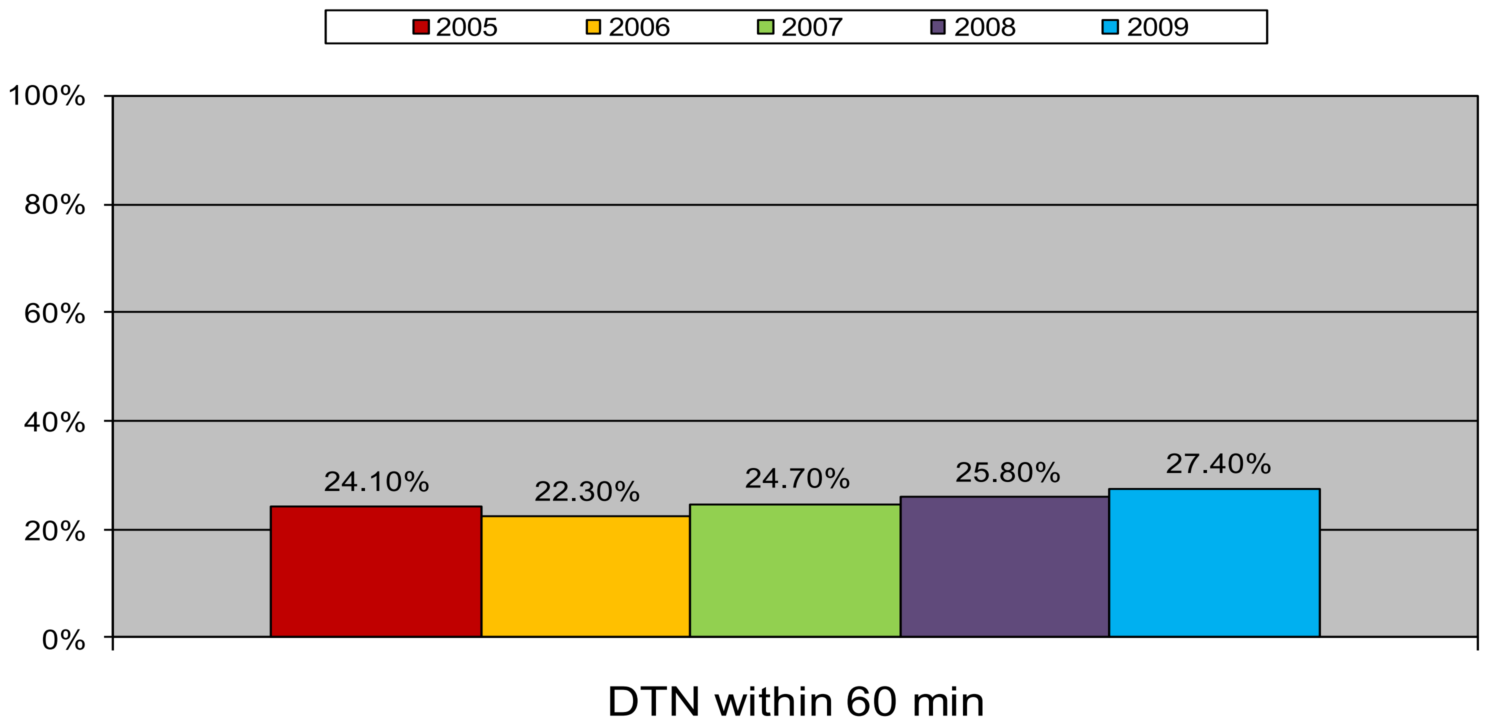
Improvement Over Time in GWTG-Stroke in the Use of IV rt-PA in Eligible Patients



- Schwamm LH et al. Circulation 2009;119:107-115

Substantial Opportunity to Improve Timeliness of IV rt-PA in Ischemic Stroke

Door-to-IV rt-PA within 60 minutes



• GWTG-Stroke Database, data on file DCRI

TARGET: STROKE℠

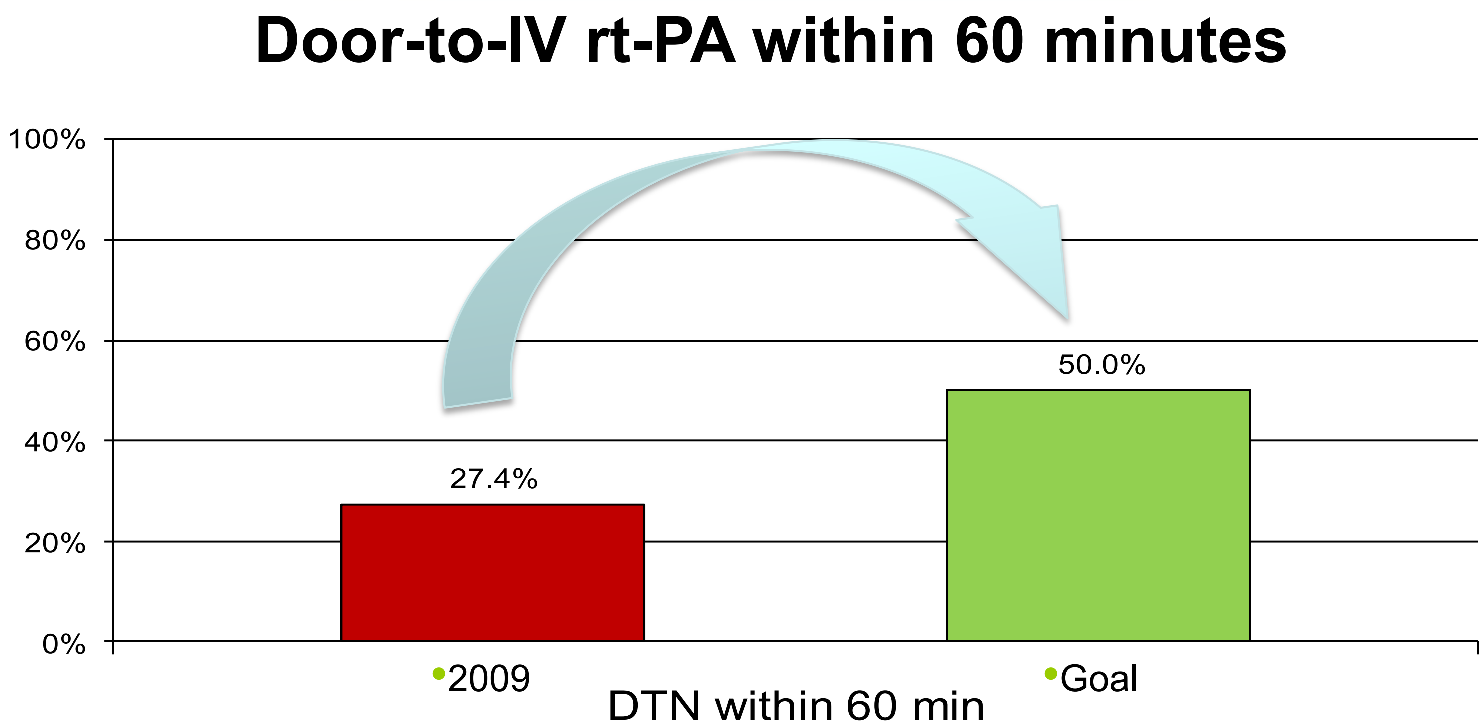
TIME LOST IS BRAIN LOST.

STROKEASSOCIATION.ORG/TARGETSTROKE

American Heart Association® | American Stroke Association®

Learn and Live.℠

Target: Stroke The Time is Now

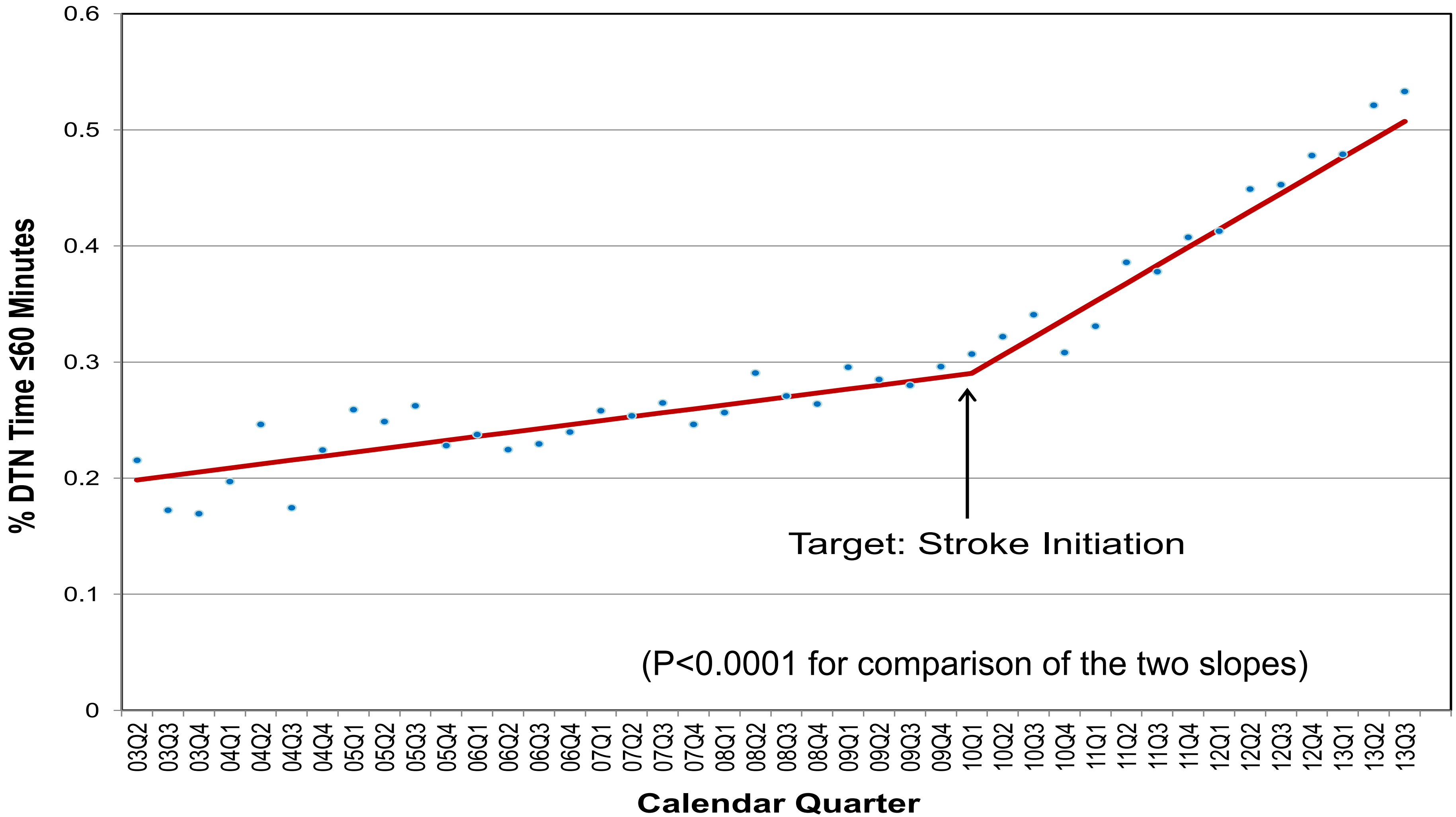


- GWTG-Stroke Database, data on file DCRI

Target: Stroke
Best Practice Strategies

1. *EMS Pre-Notification
2. Stroke Toolkit
3. Rapid Triage and Stroke Team Notification
4. *Single Call Activation System
5. *Transfer Directly to CT
6. Rapid Brain Imaging
7. *POC Laboratory Testing
8. *Premix TPA
9. *Rapid TPA Access - store TPA in ED/ radiology, start in imaging suite
10. Team approach
11. *Prompt data feedback

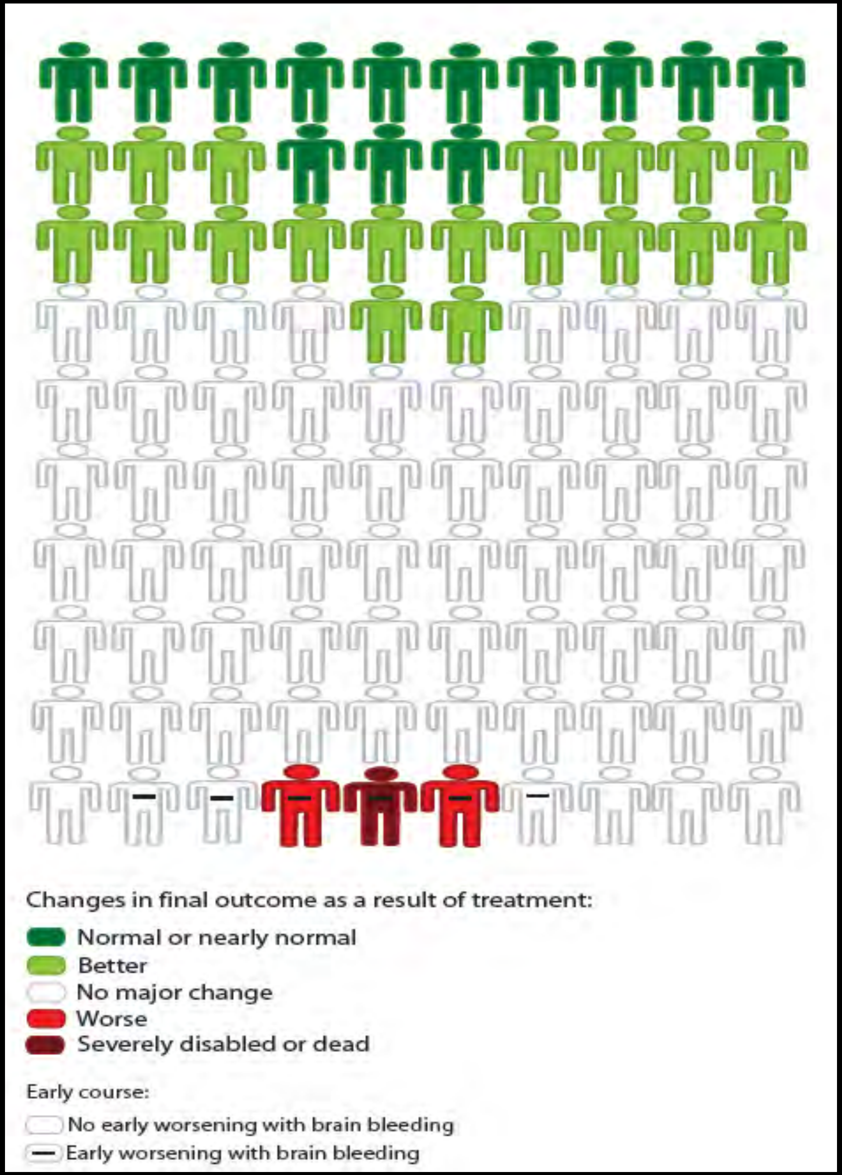
Target: Stroke Impact and Success in US: Fonarow et al, JAMA 2014



IV TPA Under 3 Hours – Patient Education

- Joint AHA-AAN-ACEP text tool to educate patients and families
- UCLA icon array tool based on AHA-AAN-ACEP

--Gadhia et al, Stroke 2010

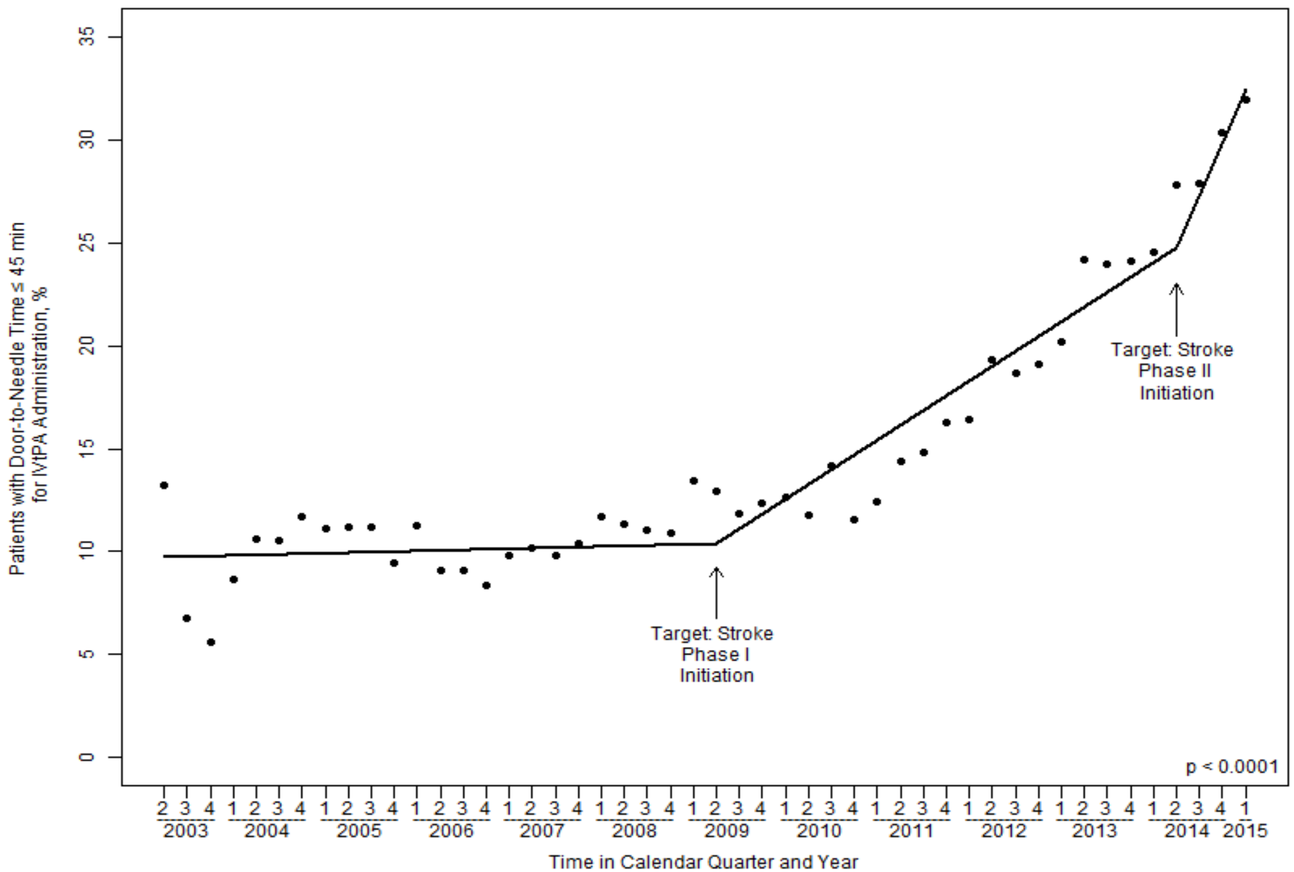


Target: Stroke Phase 2

TARGET: STROKE℠
SAVING LIVES
BY SAVING TIME

- Target: Stroke Elite
  - » DTN ≤ 60m in 75%
  - » DTN ≤ 45m in 50%

Time Trend in the Proportion of Patients with DTN Times within 45 Minutes Pre-Target: Stroke and During Target: Stroke Phase I and II



Time Period (per year)	Estimate (95% CI)	P-value
		<.0001
Pre-Target: Stroke	0.12 (-0.20, 0.43)	0.4741
Target: Stroke Phase I	2.87 (2.49, 3.25)	<.0001
Target: Stroke Phase II	10.20 (5.92, 14.48)	0.0018

Door to Needle Times with "Direct to CT" or "ED Pitstop" in Best Practice Hospitals

Stroke Center	**Median Door to Needle Times**
Helsinki, Finland	20 mins
Erlangen, Germany	25 mins
Wash U, St. Louis	39 mins

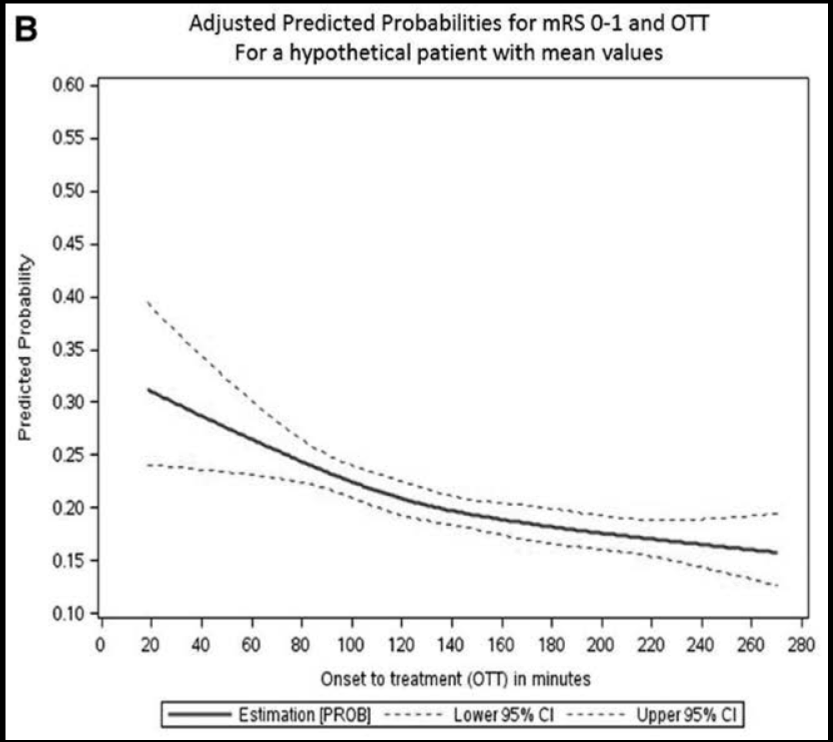
--Meretojoa et al, Neurology 2012
--Korhmann et al, Int J Stroke 2011
--Ford et al, Stroke 2012

Stroke Treatment in the Golden Hour

- GWTG-Stroke
  - 65,384 tPA patients
  - Jan 2009 – Sept 2013
  - 1456 hospitals
- Onset to treatment time ≤ 60m
  - 878 patients
  - 1.3% of under 4.5h tPA cohort
  - 15-60m vs 61-270m

Discharge to home	*OR 1.25*
Indep ambulation at d/c	*OR 1.22*
Nondisabled (mRS 0-1)	*OR 1.72*

Shape of time-benefit curve



Mildly nonlinear for mRS 0-1 and d/c home
More rapid decline first 100-170m

UCLA Stroke Center

--Kim JT et al. Circulation 2017

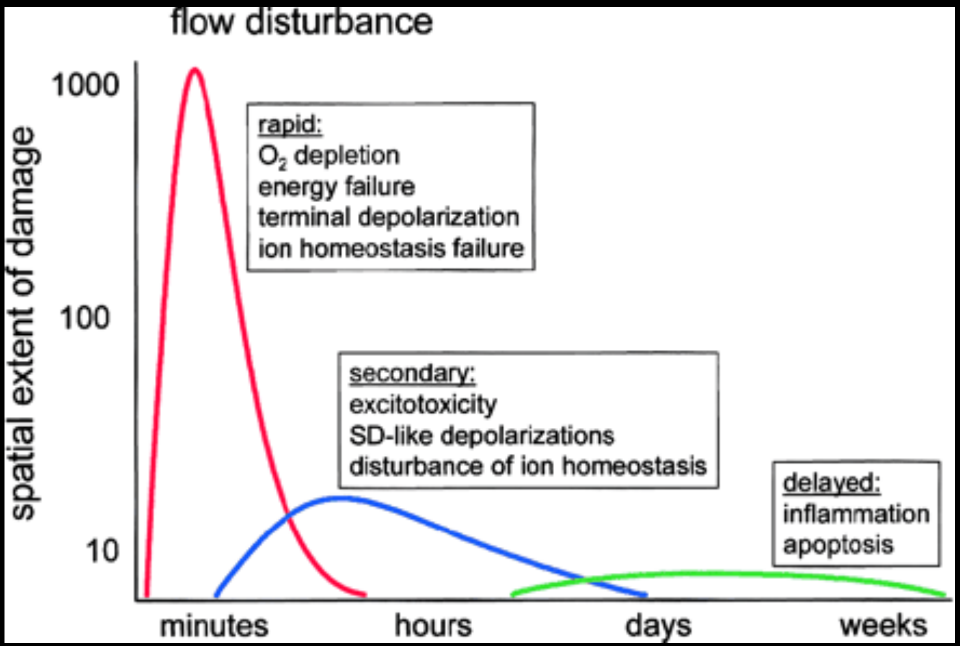
Stroke and the Golden Hour

- Narrow therapeutic time window
- Early intervention critical for stroke care
- Prehospital personnel
  - » 35-70% of stroke patients arrive by ambulance
  - » Unique position: first medical professional to come in contact with stroke patient

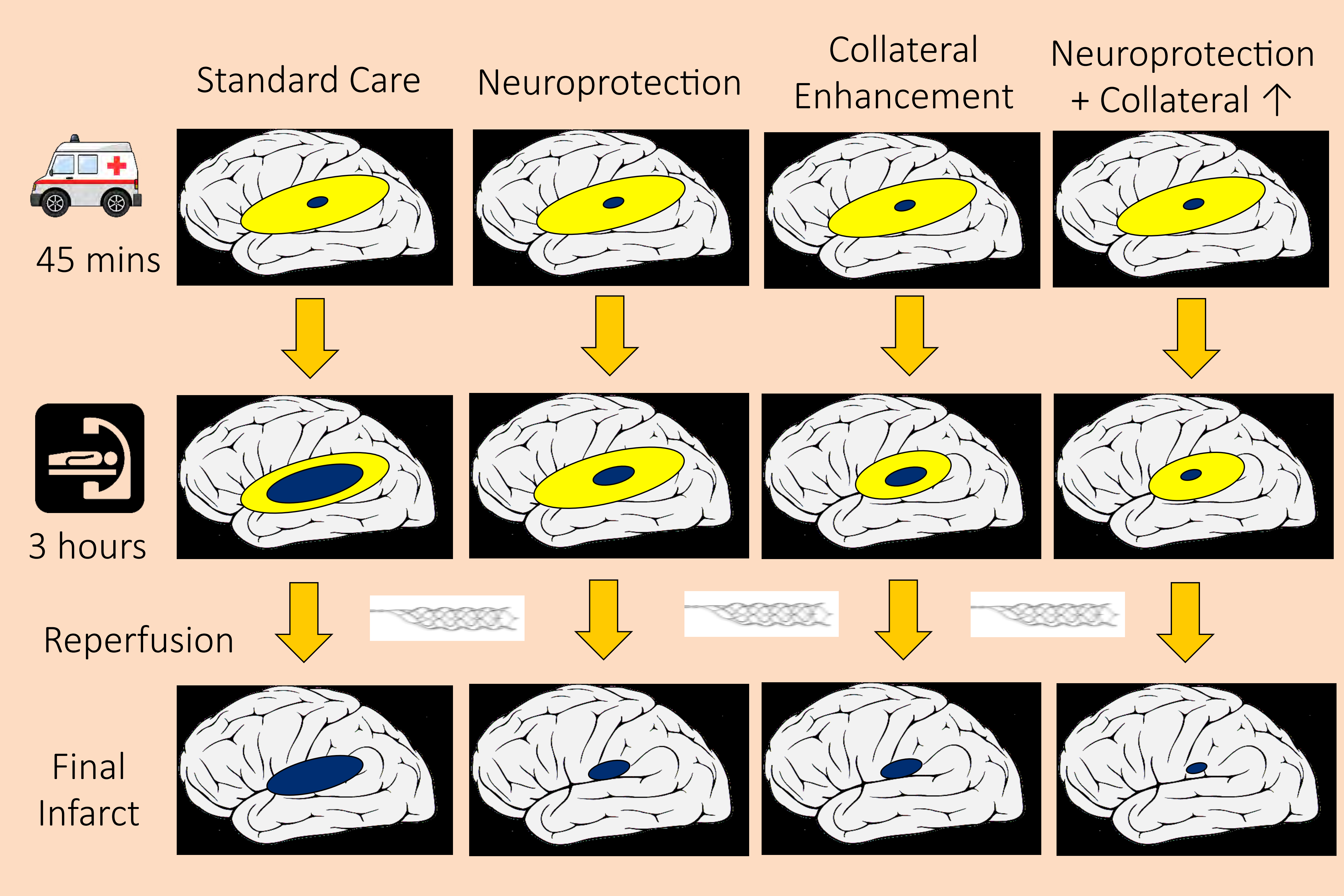
Prehospital Stroke Trials of Paramedic Delivered Therapy

Trial	Intervention	Strategy	Design	Size	Status
FAST-MAG Pilot	Magnesium	NP	Historical controls	20	2004
Helsinki EMS	IV + SQ Insulin	Homeo-Stasis	Randomized open / hist cont	23	2011
Aarhus University	Remote perconditioning	NP	Randomized open label	443	2013
RIGHT*	Glyceryl trinitrate	BP/NP	Randomized open label	41	2013
PIL-FAST*	Lisinopril	BP	Randomized open label	14	2013
FAST-MAG Pivotal	Magnesium	NP	Randomized, blinded placebo	1700	2014
FAST-BP*	Glyceryl trinitrate	NP/BP/CE	Dose escalation	45	Enrolling (California)
FRONTIER*	NA-1	NP	Randomized, 2B	500	Enrolling (Canada)
RIGHT-2*	Glyceryl trinitrate	NP/BP/CE	Randomized, sham-controlled	850	Enrolling (Great Britain)

The Ischemic Cascade and Neuroprotective Interventions



- Modulators of Excitatory Amino Acids
- Modulators of Calcium Influx
- Metabolic Activators
- Anti-edema Agents
- Inhibitors of Leukocyte Adhesion
- Free Radical Scavengers and Anti-Oxidants
- Promotors of Membrane Repair
- Unknown or Other Mechanism(s)


Standard Care
Neuroprotection
Collateral Enhancement
Neuroprotection + Collateral ↑
45 mins
3 hours
Reperfusion
Final Infarct

Trials of Neuroprotective Agents for Stroke, 1955-2000

Neuroprotective agents tested	49
RCTs performed	114
Patients enrolled	21,445
Neuroprotective agents approved	0

Time windows: 4-48 hours

-- Kidwell, Liebeskind, Starkman, Saver, Stroke 2001

Six Design Defects of Past Neuroprotective Trials

- Dose too low
  - Side effects
- Enroll patients unlikely to respond to drug action
  - White matter strokes for EAA blockade agents
- Enroll uninformative patients
  - Too mild at entry – fare well with placebo
  - Too severe at entry – fare poorly with active
- Sample sizes too small
- Outcome measures insensitive to modest but important benefits
- Late time of treatment start

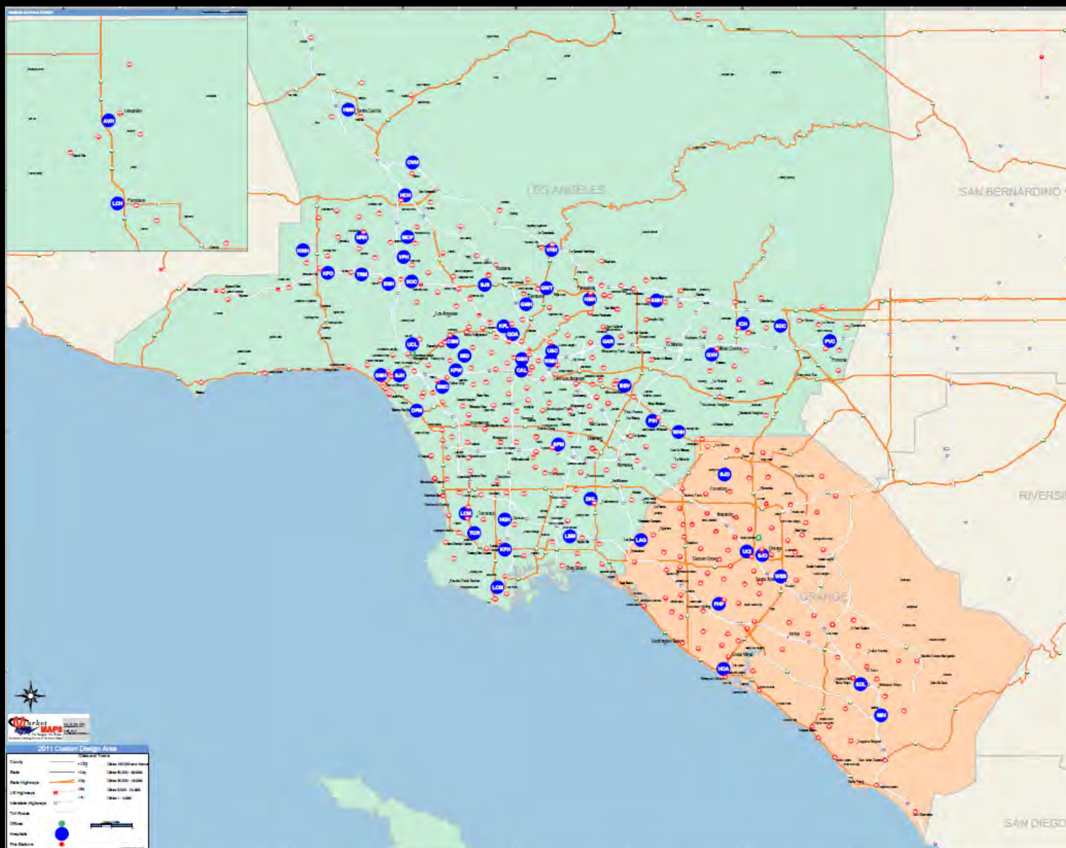
The Field Administration of Stroke Therapy – Magnesium (FAST-MAG) Phase III Trial

NIH-NINDS

Field Administration of Stroke Treatment – Magnesium (FAST-MAG) Trial

- Placebo-controlled, double-blind, randomized
- Multicenter, single region
  - » Los Angeles and Orange Counties
- 4 gm Mg field, 16 gm Mg maintenance x 24h
- 1700 patients, 1st patient Jan 2005
- Primary endpoint: Rankin Scale shift

FAST-MAG Trial Consortium



Performance Sites in Los Angeles and Orange Counties

- Los Angeles and Orange Counties
  - » Population 13.3 million
- 40 EMS Provider Agencies
  - » 315 rescue ambulances
  - » 2988 paramedics
- 60 receiving hospitals
  - » 952 physician-investigators
    - 715 Emergency Medicine (site PIs)
    - 210 Neurologist
    - 26 Nsurg/Intensiv/Hosp
- 95 CCC coordinators and research assistants

Supported by NIH-NINDS

Entry Criteria

Inclusion

- Suspected stroke identified by the Los Angeles Prehospital Stroke Screen (LAPSS)
- Age 40-95, inclusive
- Last known well time within 2h of treatment initiation
- Deficit present for ≥ 15 minutes

Exclusion

- Coma
- Rapidly improving neurologic deficit
- Pre-existing neurologic, psychiatric or advanced systemic disease that would confound outcome evaluations
- SBP<90 or>220
- Severe renal dysfunction
- Severe respiratory distress
- 2nd or 3rd degree heart block w/o pacemaker
- Major head trauma in last 24h
- Recent stroke within prior 30d,
- Patient/LAR unable to provide informed consent and EFIC not approved in catchment area

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FAST-MAG
Distinctive Methodologic Aspects

- Diagnosing stroke in the field
  - LAPSS
  - Physician cellphone review
- Rating pretreatment stroke severity
  - LAMS
- Eliciting consent
  - Physician cellphone elicitation (99%)
  - EFIC (1%)
- Prehospital treatment route
  - Fixed lumen, rate-limiting IV infusion
- Randomization
  - Pre-encounter randomization

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FAST-MAG
Explicit Informed Consent Enrollment Process*

- Paramedics
  - » Identify likely stroke patients using LAPSS
  - » Call simultaneous ring enrolling line
    - English line – 4 English speaking MDs
    - Spanish line – 4 Spanish speaking MDs
    - First MD to answer proceeds
  - » Give cellphone to patient/LAR
  - » Give consent form to patient/LAR
    - Each ambulance has 8 consent forms
      - » 4 most common hospitals (4 English, 4 Spanish)
- Cellphone Enrolling Physicians
  - » Discuss trial with patient/LAR
    - While paramedic performs usual care
  - » After patient/LAR signs form, instructs paramedic to start study infusion
  - » Co-signs consent form after ED arrival

- *99% enrolled by explicit consent; 1% by EFIC

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Neurologic Features

Characteristic	Placebo (n=843)	Magnesium (n=857)	Total (n=1700)	p value
Prestroke Function				
Residence (home)	97.6%	97.3%	97.5%	0.16
Prestroke Rankin	0 (0-0)	0 (0-0)	0 (0-0)	0.83
Final Diagnosis				
Cerebral Ischemia	72.8%	73.7%	73.3%	0.43
Intracranial Hemorrhage	22.8%	22.8%	22.8%	0.64
Mimic	4.4%	3.5%	3.9%	0.83
Presenting Severity				
LAMS (Prehospital)	3.7 (±1.3)	3.7 (±1.3)	3.7 (±1.3)	0.57
NIHSS (Hospital)	11.2 (±9.8)	11.5 (±9.0)	11.3 (±9.9)	0.41

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FAST-MAG

Time Intervals

	Placebo (n=843)	Magnesium (n=857)	Total (n=1700)	p value
Onset* to Drug (mins)	46 (36-62)	45 (35-60)	45 (35-62)	0.24

*Onset = last known well time

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FAST-MAG

Time Intervals

	Placebo (n=843)	Magnesium (n=857)	Total (n=1700)	p value
Onset* to Drug (mins)	46 (36-62)	45 (35-60)	45 (35-62)	0.24
Onset to Drug (categorical)				
0-1 hours	73.2%	75.3%	74.3%	0.61
1-2 hours	25.7%	23.7%	24.7%	
>2 hours	1.1%	0.9%	1.0%	

*Onset = last known well time

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FAST-MAG

Time Intervals

	Placebo (n=843)	Magnesium (n=857)	Total (n=1700)	p value
Onset* to Drug (mins)	46 (36-62)	45 (35-60)	45 (35-62)	0.24
Onset to Drug (categorical)				
0-1 hours	73.2%	75.3%	74.3%	0.61
1-2 hours	25.7%	23.7%	24.7%	
>2 hours	1.1%	0.9%	1.0%	
On Scene to Drug	23 (19-28)	23 (18-27)	23 (18-27)	0.58
On Scene to Door**	33 (27-39)	32 (27-39)	33 (27-39)	0.91

*Onset = last known well time
**Historical comparator, pretrial LA scene to door times = 35 minutes (Stroke 2004;35:e106-108)

Supported by NIH-NINDS

Reperfusion Treatments After Arrival in FAST-MAG Cerebral Ischemia Patients (n=1235)

	Number of Patients	Percent
IV tPA	452	36.6%
Endovascular	76	6.1%

--Nguyen P, Sanossian N, et al, Submitted

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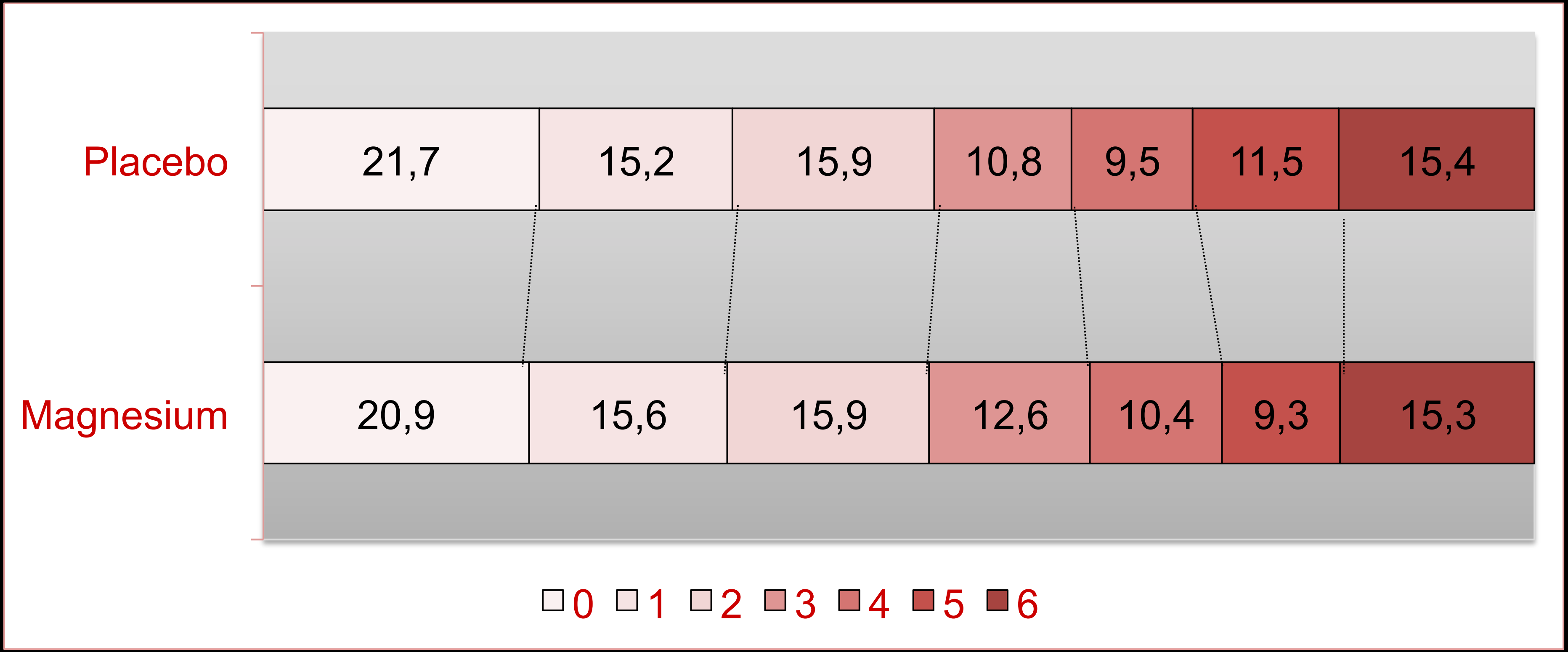
Primary Endpoint: Global Disability at 3 Months (modified Rankin Scale)



CMH test: $p = 0.28$

(Means 2.7 v 2.7)

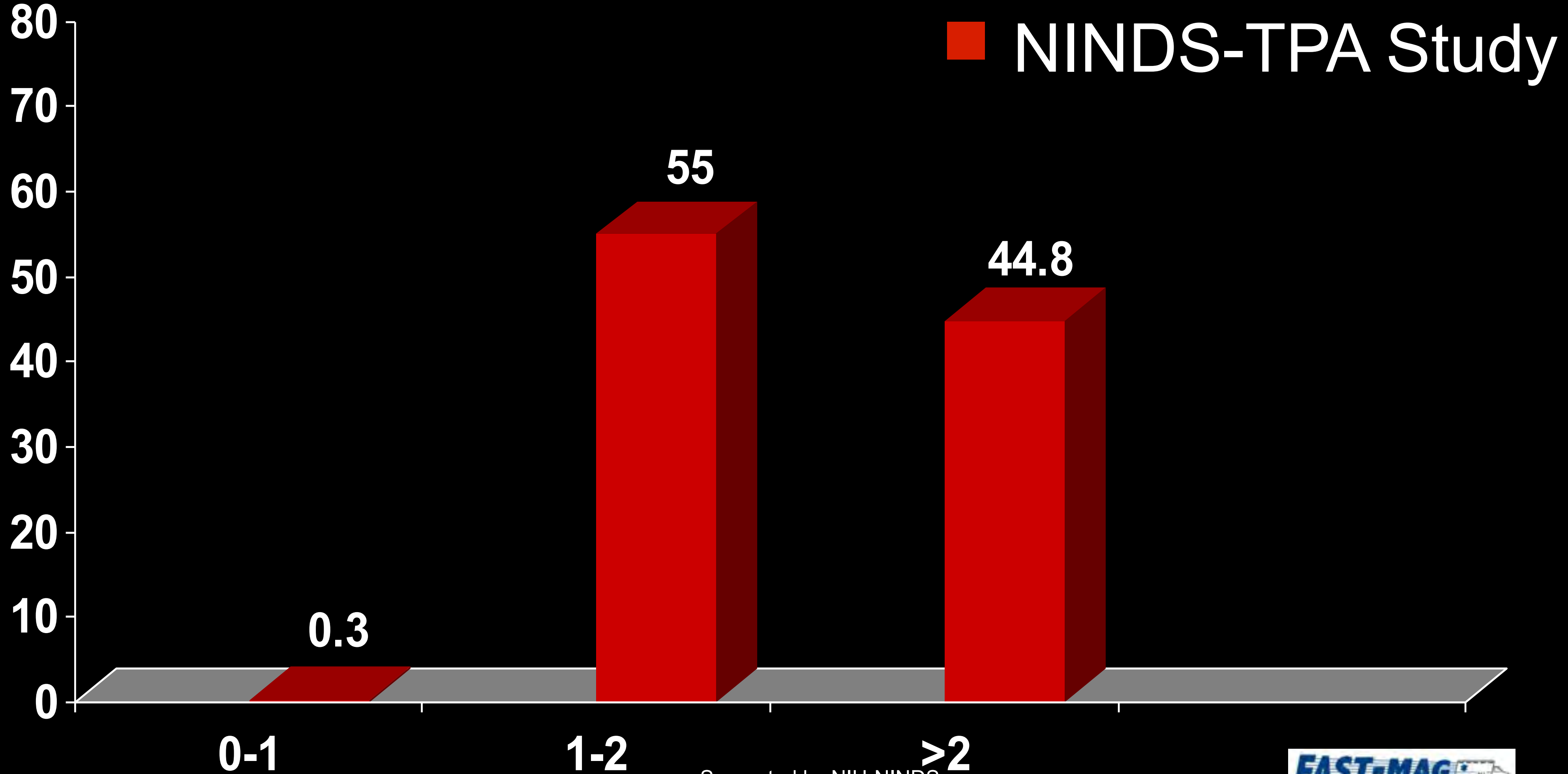
Discussion: Magnesium as a Neuroprotectant for Stroke

- FAST-MAG failed to confirm the primary hypothesis that prehospital magnesium sulfate is beneficial in likely stroke patients
- No increase in overall serious adverse events
- Potential reasons for neutral results
  - » Slow magnesium passage across blood-brain barrier despite early systemic delivery
  - » Magnesium as a single agent insufficient to suppress molecular ischemic cascade
  - » Improving standard care reduced opportunity to demonstrate benefit
    - Interim analysis point estimates favorable for magnesium
    - Better supportive care at Primary Stroke Centers
    - TPA more often and faster

Discussion: Prehospital Delivery of Phase 3 RCT Stroke Therapy

- First prehospital stroke phase 3 randomized, controlled trial
- First acute (<3 hr) neuroprotective phase 3 trial
- First stroke phase 3 trial of neuroprotection before recanalization therapy
- First prehospital RCT for any condition employing physician-elicited informed consent
- First "golden hour" (<1 hr) stroke phase 3 trial
  - Over 1250 treated within 60 mins of last known well time
- Methods and patient data available for therapies in pipeline

FAST-MAG vs NINDS-TPA Study
Time to Treatment



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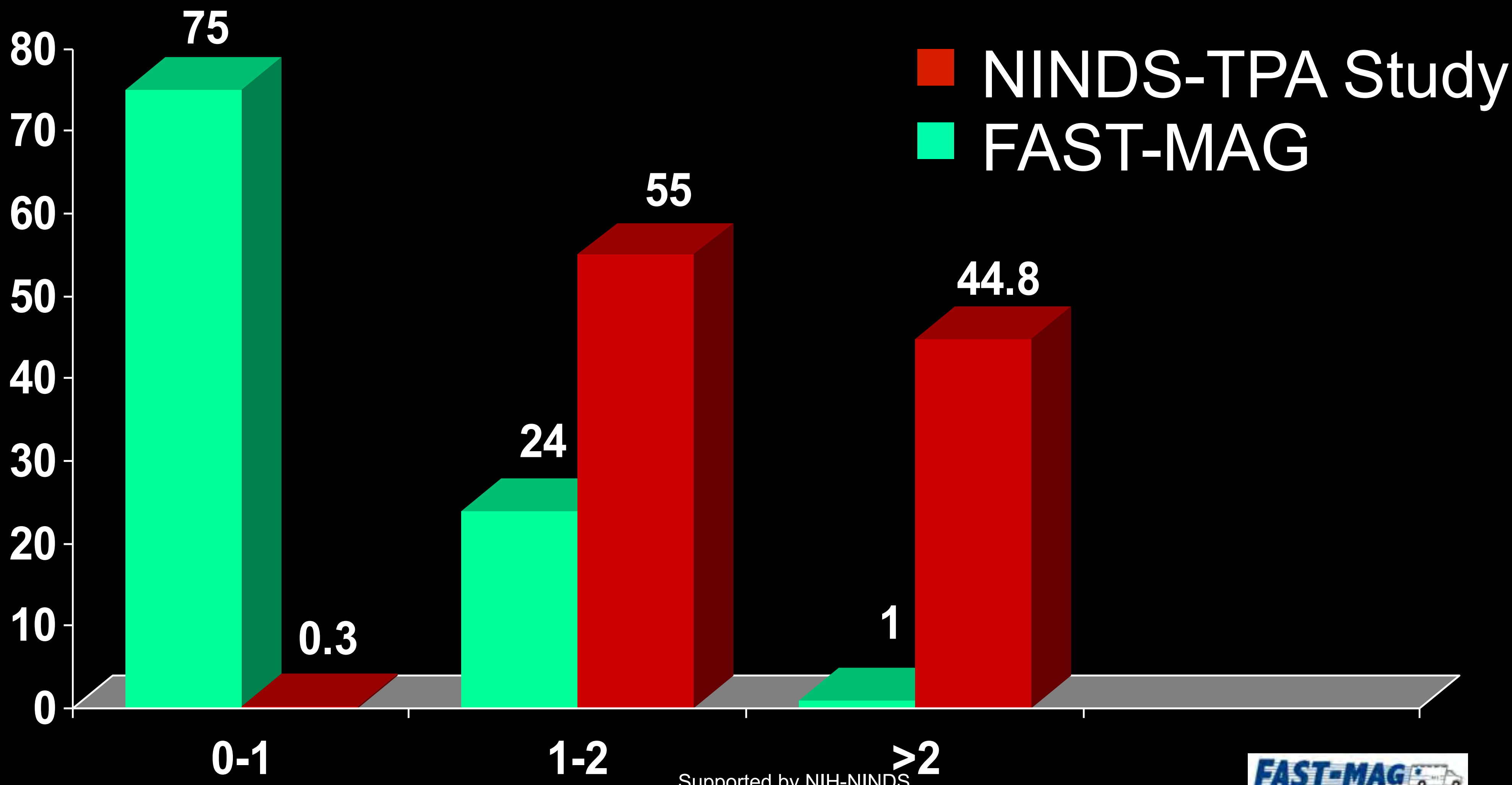
FAST-MAG vs NINDS-TPA Study
Time to Treatment



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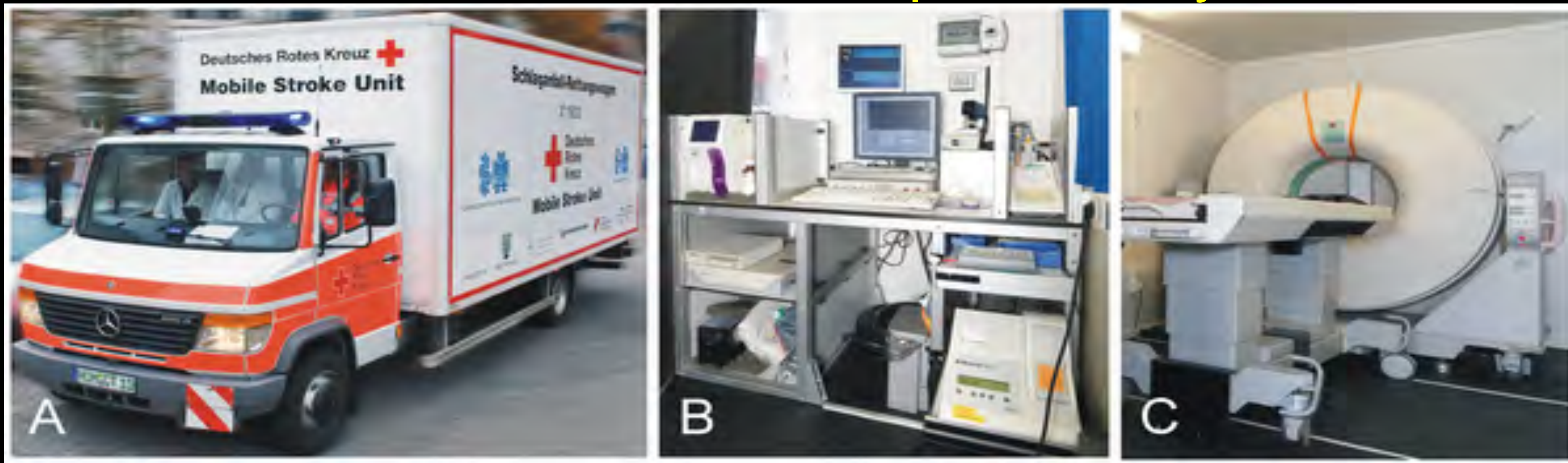
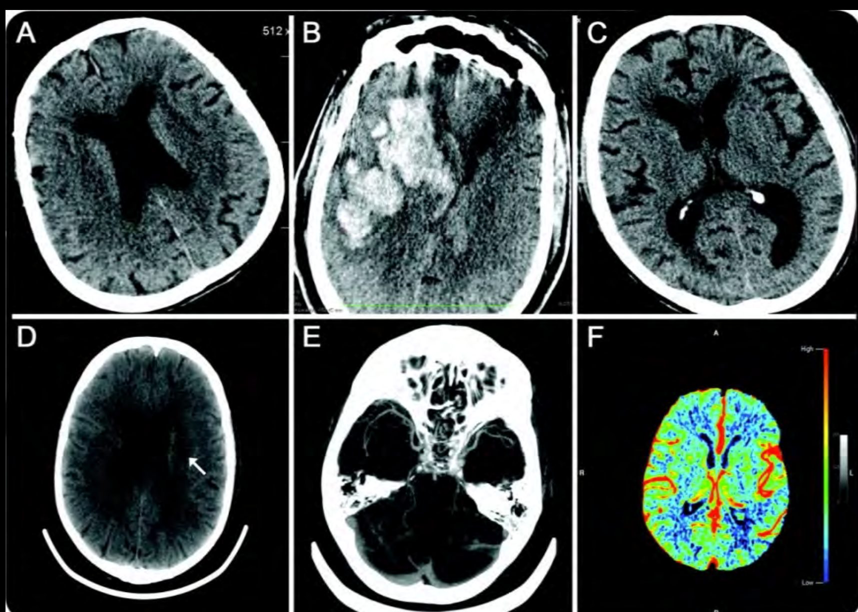
FAST-MAG

Mobile Stroke Units for Prehospital Thrombolysis





--Walter et al, PLOS One, 2010, Homburg

--Audebert et al, Berlin

In This Issue of JAMA

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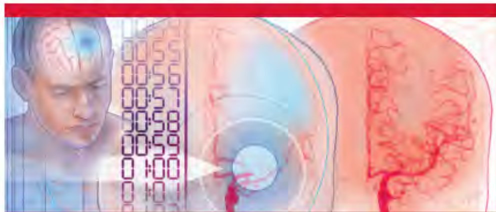


Neurology
Edited by Roger N. Rosenberg, MD, and Jeffrey L. Saver, MD

Research

Ambulance-Based Thrombolysis in Acute Ischemic Stroke 1622
Early thrombolysis with intravenous tissue plasminogen activator is associated with better outcomes in acute ischemic stroke. In a study randomized by week from May 1, 2011, to January 31, 2013, that involved 6182 German adults with suspected stroke, Ebinger and colleagues found that compared with conventional ambulance care, use of an ambulance equipped with a computed tomography scanner, laboratory capability, telemedicine connection, and trained stroke team resulted in decreased time to treatment without an increase in adverse events. In an Editorial, Grotta discusses progress in treatment of ischemic stroke.
Editorial 1615 Related Article 1632

Time to tPA Administration and Outcomes of Ischemic Stroke 1632
In an analysis of registry data from 1030 hospitals (71 169 patients) participating in Target: Stroke, a national acute ischemic stroke care quality improvement program, Fonarow and colleagues assessed door-to-needle times for tissue plasminogen activator (tPA) administration and patient outcomes before and after program initiation. The authors report the Target:Stroke initiative was associated with improved timeliness of tPA administration and lower in-hospital mortality and intracranial hemorrhage.
Editorial 1615 Related Article 1622
Author Video Interview jama.com

Effect of Acetazolamide on Vision Function in IIH 1641
Acetazolamide is commonly used to treat idiopathic intracranial hypertension (IIH) despite insufficient evidence supporting its use. In a randomized study that enrolled 165 patients with IIH and mild vision loss, Wall and colleagues found that 6 months' treatment with acetazolamide and a low-sodium weight reduction diet, compared with diet alone, resulted in modest improvement in visual field function. In an Editorial, Horton discusses beneficial effects of acetazolamide in IIH.
Editorial 1618

Lorazepam vs Diazepam for Pediatric Status Epilepticus 1652
Diazepam is approved for the treatment of status epilepticus in children. However, some data suggest lorazepam may be more effective or safer. In a randomized trial involving 273 patients aged 3 months to 18 years who presented to academic pediatric emergency departments with convulsive status epilepticus, Chamberlain and colleagues found that treatment with lorazepam did not result in improved efficacy or safety compared with diazepam.

Opinion

Instructions for Authors
jama.com/public/instructionsforauthors.aspx

Editor in Chief
Howard Bauchner, MD

130 YEARS OF CONTINUOUS PUBLICATION

Research

Original Investigation

Effect of the Use of Ambulance-Based Thrombolysis on Time to Thrombolysis in Acute Ischemic Stroke
A Randomized Clinical Trial

Martin Ebinger, MD; Benjamin Winter, MD; Matthias Wendt, MD; Joachim E. Weber, MD; Carolin Waldschmidt, MD; Michal Rozanski, MD; Alexander Kunz, MD; Peter Koch, MD; Philipp A. Kellner, MD; Daniel Gierhake, MD; Kersten Villringer, MD; Jochen B. Fiebach, MD; Ulrike Grittner, PhD; Andreas Hartmann, MD; Bruno-Marcel Mackert, MD; Matthias Endres, MD; Heinrich J. Audebert, MD; for the STEMO Consortium

--JAMA, April 2014

PHANTOM-S Trial
TPA Frequency and Speed

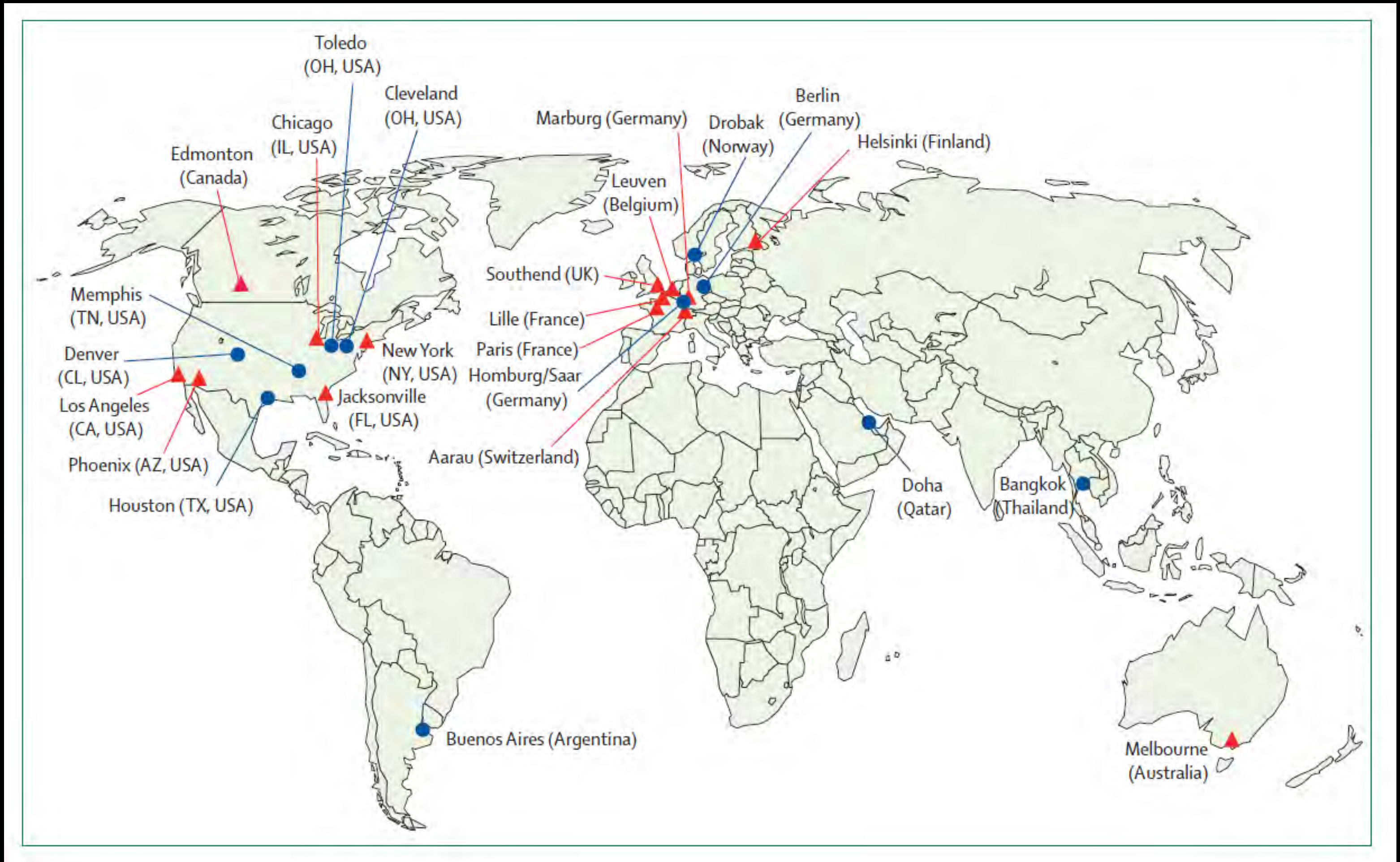
	CT Ambulance Patients	p value	CT Ambulance Weeks	p value	Control Weeks
N	1804		3213		2969
Pct of AIS	32.6%	<0.001	28.9%	<0.001	21.1%
DTN Hosp (min)					42
Alarm to Hosp (min)	85	<0.001	67	<0.001	35
Alarm to Imaging	38	<0.001	44	<0.001	52
Imaging to TPA	14	<0.001	17	<0.001	24
*Alarm to TPA	52	<0.001	61	<0.001	76
Onset to TPA	103	<0.001	110	0.003	119
Onset to TPA <90m	58%	<0.001	48%	0.02	37%

*Primary Endpoint

No differences in efficacy or safety outcomes (not powered to detect)

UCLA Stroke Center

Growing Worldwide Use of Mobile Stroke Units



UCLA Stroke Center

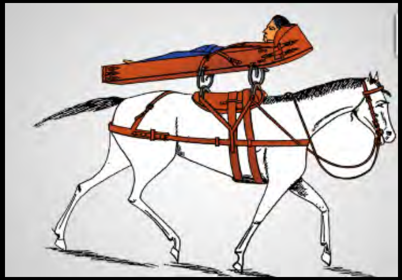
--Fassbender, Grotta, Walter, Grunwald, Ragoschke-Schumm, Saver. Lancet Neurol 2017

BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU) Trial

- Cluster-control RCT
  - 5 EMS Regions USA
  - 1 week on, 1 week off
  - Patients
    - 6000 assessed
    - 1200 enrolled
      - 700 fully tPA eligible
- Key entry criteria
  - LKW within 4.5h prior to ambulance evaluation
  - tPA eligible prior to CT/labs
- Outcome
  - Utility-weighted mRS at 90d
- Timeline
  - 2014-2021

Trials of Novel Therapies Using Mobile Stroke Unit as Platform

- Intracerebral hemorrhage
  - » Anticoag reversal
    - PRESTO-Reverse
    - B-SPATIAL
  - » Hemostatic therapy
    - Aust transexamic acid RCT
  - » BP control
    - HEME-MSU
- Acute cerebral ischemia
  - » Neuroprotection
    - TEMPO-EMS



1837 – First patented US ambulance in US

1889– Patented ambulance with built-in stretcher

1914 – First x-ray ambulance – Madame Curie

2011 – First CT ambulance - Homburg

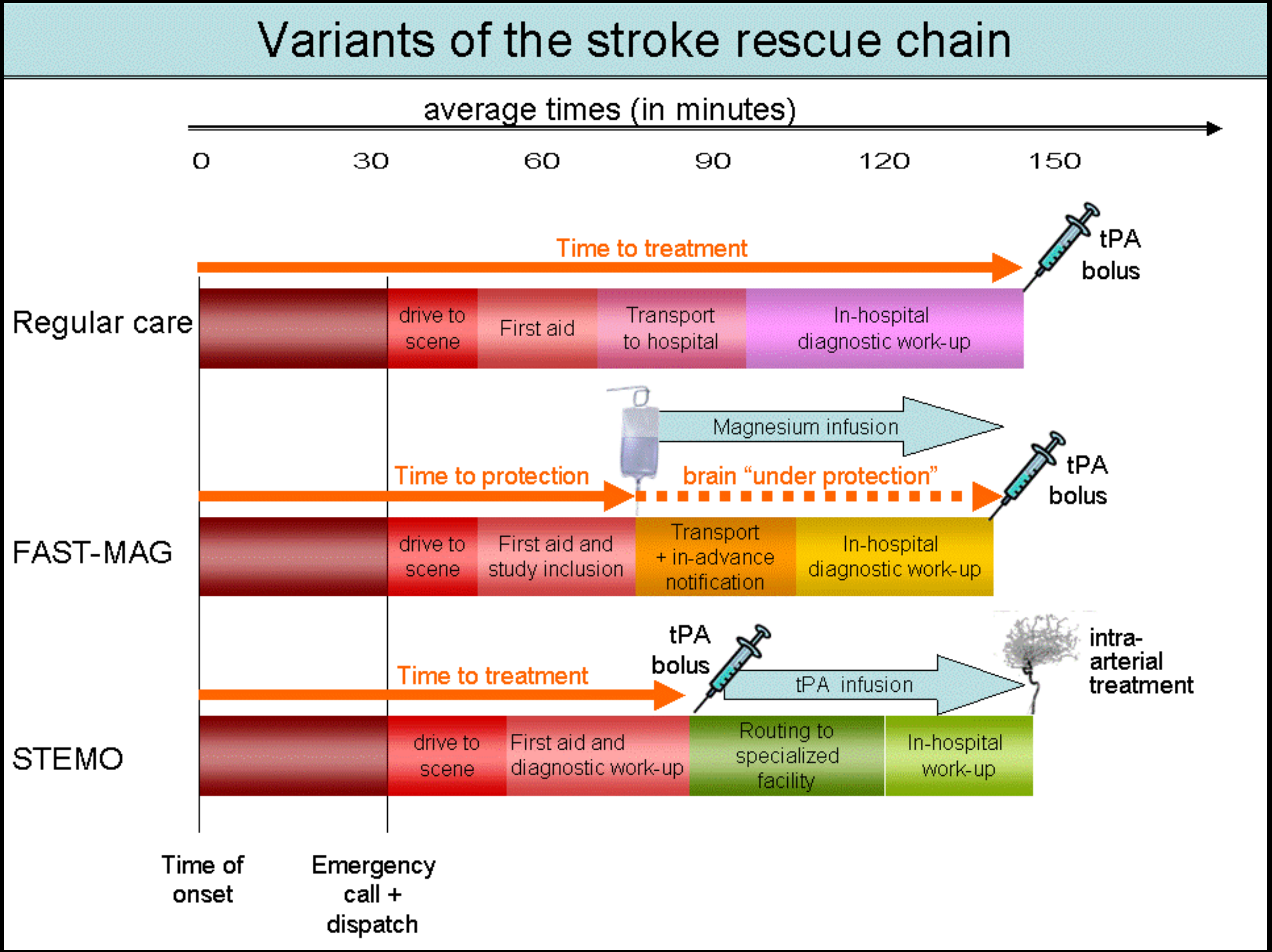
--Modifed from Nour, Brain Attack 2017

Future Technology / Trials?

Helicopter MSU

Mobile Neurointervention Suite

Varieties of Treatment Strategies



--Audebert, Lees, Starkman, Saver, Endres, Neurology 2013

Catheter-Based Reperfusion Therapies

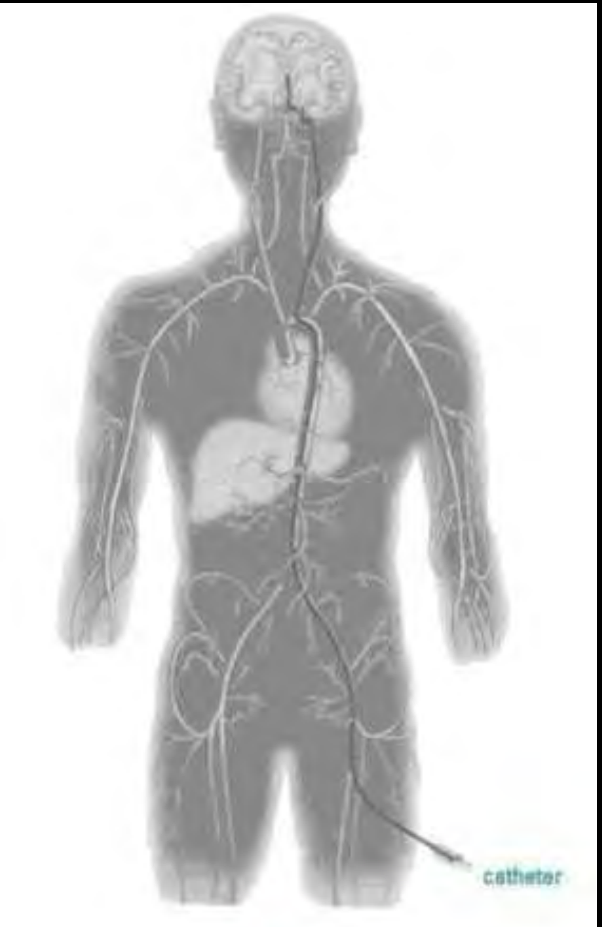


figure 4:
catheter introduced at the groin

Historical Development of Endovascular Technologies for Acute Recanalization

Technology	First Human Studies
IA microcatheter lysis	1988 (1999)
IA angioplasty	1994
IA aspiration thrombectomy	2001 (2009)
IA ultrasound sonothrombolysis	2003
IA implanted stents	2003
IA laser clot destruction	2004
IA Archimedes screw	2004
IA coil retrievers	2004 (2004)
IA basket/brush retrievers	2006
IA stent retrievers	2010 (2010)

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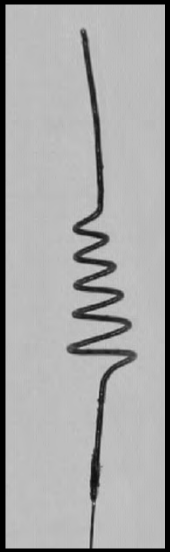
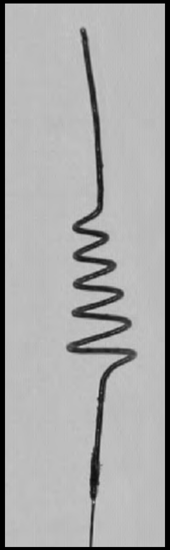
Mechanical Thrombectomy Devices



Coil
Retriever

Mechanical Thrombectomy Devices



Coil
Retriever

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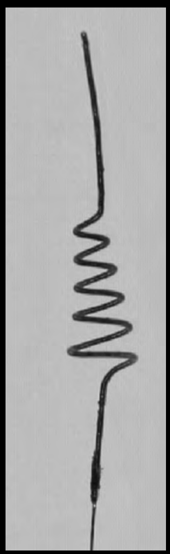
Mechanical Thrombectomy Devices



Coil
Retriever

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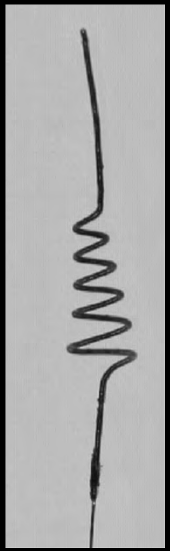
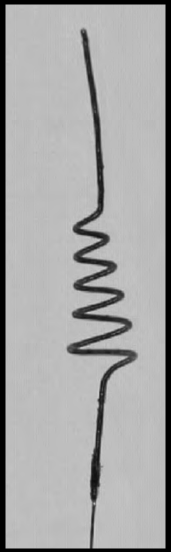
Mechanical Thrombectomy Devices



Coil Retriever

Stent Retriever

Mechanical Thrombectomy Devices



Coil
Retriever

Stent
Retriever

Covered
Stent
Retriever

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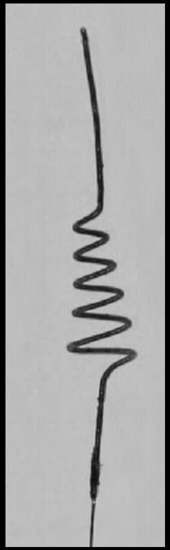
Mechanical Thrombectomy Devices



Coil Retriever

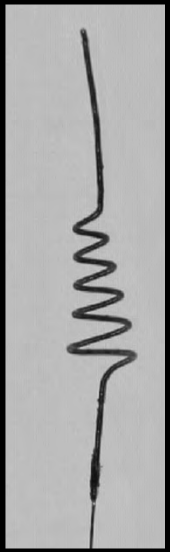
Stent Retriever

Covered Stent Retriever

Basket Retriever

UCLA Stroke Center

Mechanical Thrombectomy Devices

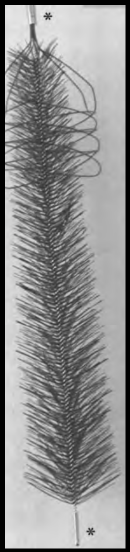


Coil Retriever

Stent Retriever

Covered Stent Retriever

Basket Retriever



Brush Retriever

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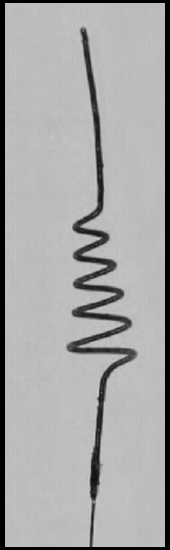
Mechanical Thrombectomy Devices

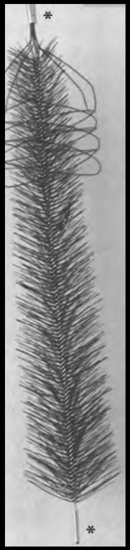


Coil
Retriever

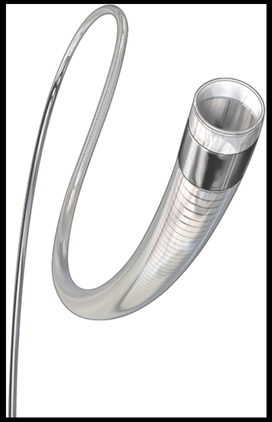
Stent
Retriever

Covered
Stent
Retriever

Basket
Retriever



Brush
Retriever



Aspiration
Catheter

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Acute Mechanical Recanalization Strategy Depends on Target Occlusion Composition

Embolus

- Relatively normal recipient artery
- Strategy: remove the thrombus
  - Retrievers
  - Aspirators
  - +/- Lytics

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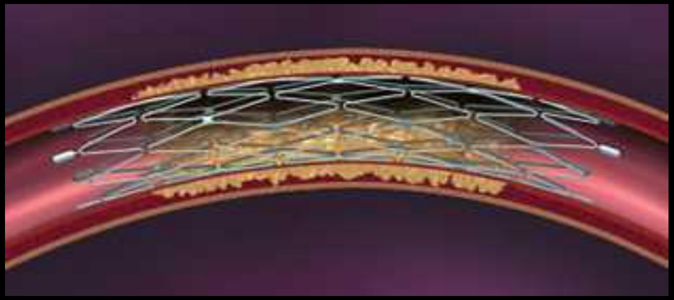
In Situ Atherothrombosis

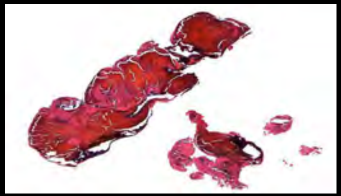
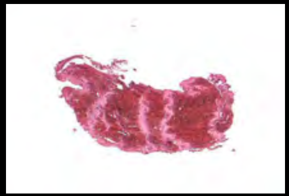
- Substantial local atherosclerotic plaque
- Strategy: Crack the plaque
  - Angioplasty
  - Stents
  - +/- Lytics

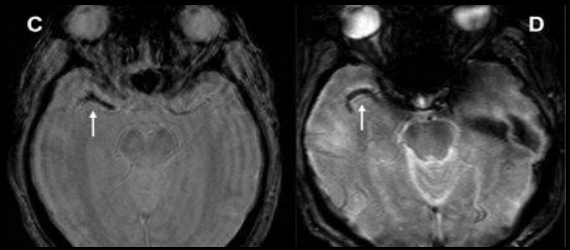


Determinants of Thrombectomy Success

- Clot burden
- Clot composition
- Clot tensile properties
- Tortuosity of feeding arteries
- Target artery size
- Recipient artery branching curvature





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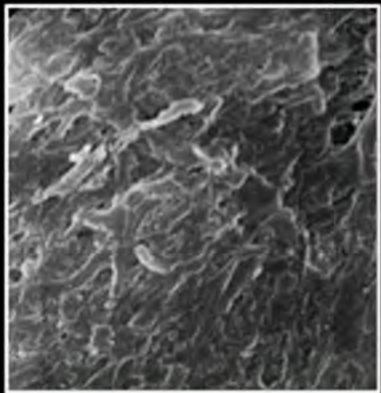


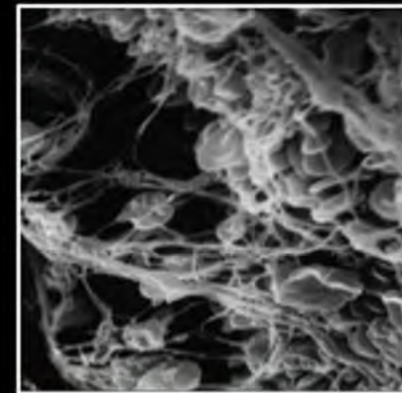
Should clot composition affect choice of endovascular therapy?

Brijesh P. Mehta, MD
Raul G. Nogueira, MD

Correspondence & reprint requests to Dr. Nogueira: raul.g.nogueira@emory.edu

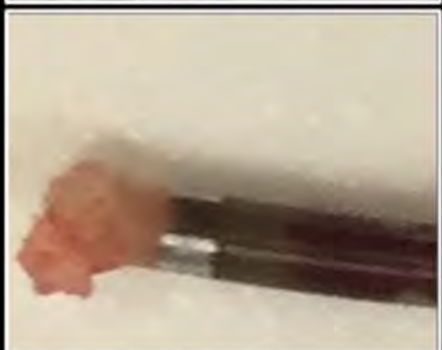
ABSTRACT

Endovascular therapy has become a promising alternative for patients who are ineligible for IV thrombolysis or for whom it has failed. Greater knowledge about the composition of thromboembolic material underlying the vascular occlusion in stroke patients may provide the means for improving existing endovascular therapies and developing new treatment strategies. The objective of this article is to provide a review of clinical and experimental animal studies on the histology, imaging correlation, and ultrastructure of thromboemboli retrieved during acute ischemic stroke. Neurology® 2012;79 (Suppl 1):S63–S67



Organized, Inelastic, Hard, Fibrin-Rich Clot

Fresh, Elastic, Soft, RBC-Rich Clot



Aspiration:

\+ Cohesive = lower risk of clot stripping/ fragmentation during aspiration

Stentriever:

\- Inelastic so harder to be incorporated into the stent cells

\+ Push+Fluff Technique and/or larger or hybrid cells

Stentriever:

\+ Elastic = easier to be incorporated into the stent cells

Aspiration:

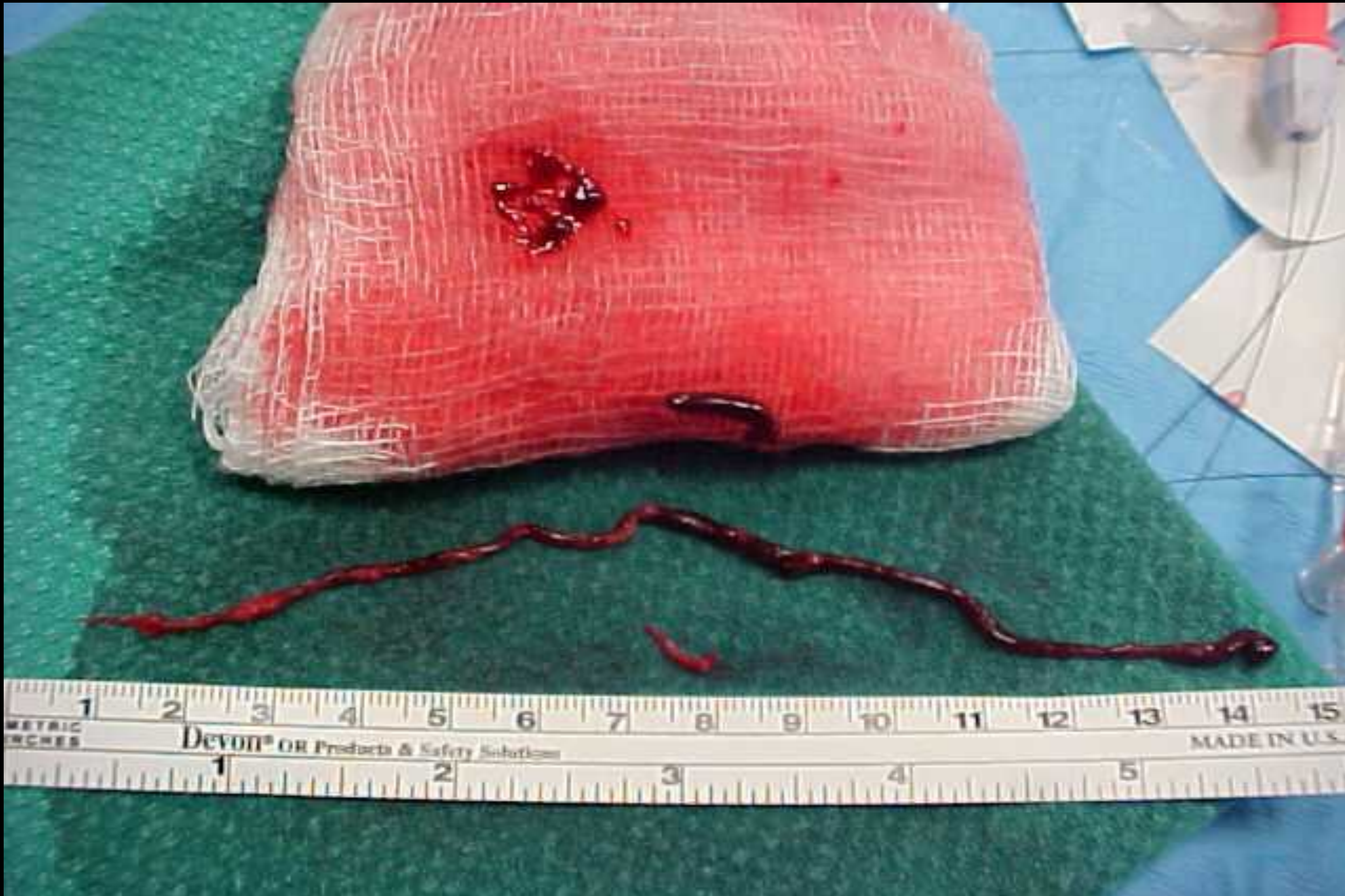
\- Friable = higher risk of clot stripping/ fragmentation during aspiration

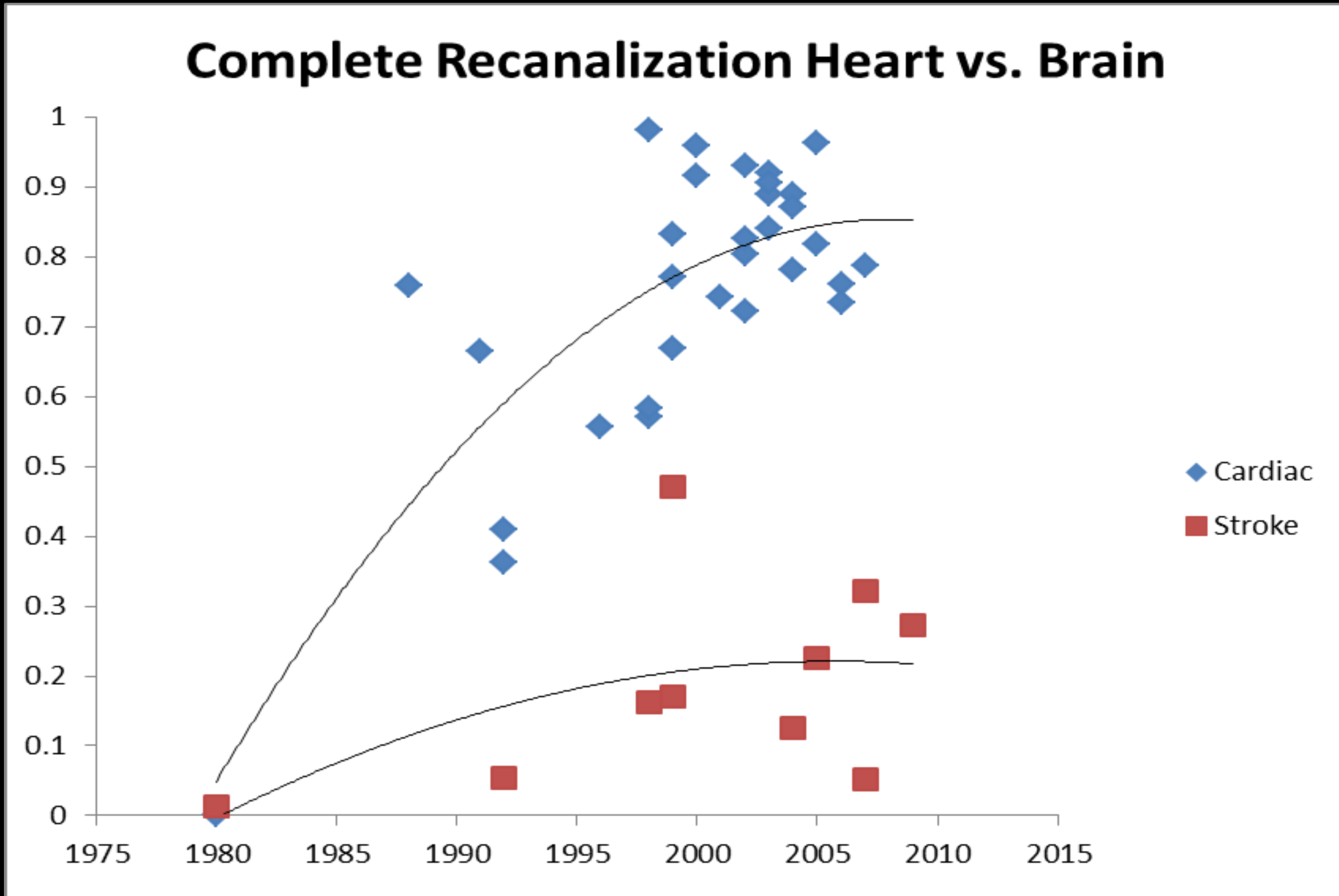
\+ Larger ID catheters closely matching vessel diameter

UCLA – MCA Occlusion

30-Year-Old Female – Baseline NIHSS 24
Symptom Onset to Final Angiogram – 5:37

NIHSS	24 hours	1	mRS	5 days post	0
	30 days post	0		90 day post	0


Devon® OR Products & Safety Solutions



--Patel + Saver, Submitted

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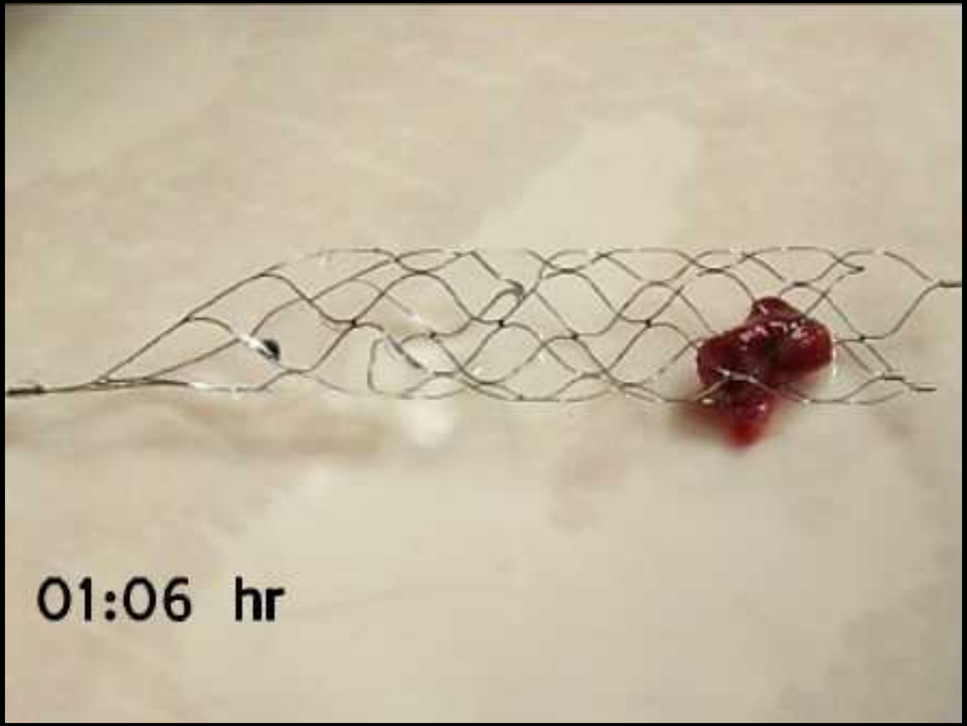
The New Wave in Endovascular Recanalization Devices: Retrievable Stents

- Advantages
  - » Immediate repefusion
  - » Potential clot retrieval
  - » Potential longterm stenting
- Devices
  - » Solitaire stent
    - Ev3
    - SWIFT Trial
  - » Mindframe stent
    - Mindframe, Inc
    - PRIISM Trial
  - » ReStore stent
    - Reverse Medical
  - » Trevo stent
    - Concentric
    - TREVO Trial



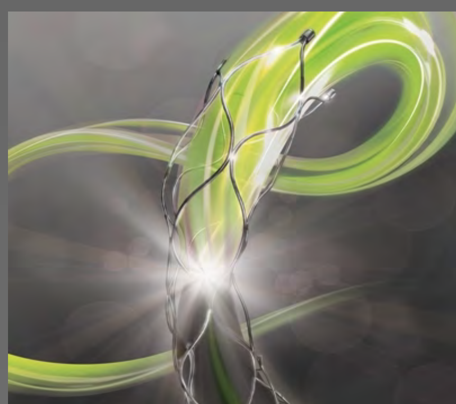
--Henkes et al, Stroke 2009, p410

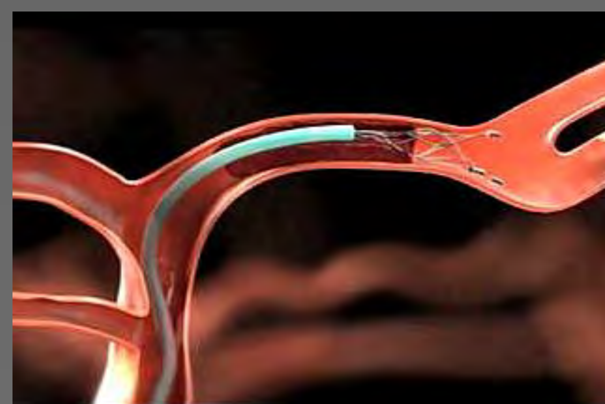
Lancet, Aug 26, 2012

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

JL Saver, R Jahan, E Levy, T G Jovin, B Baxter, R Nogueira, W Clark, R Budzik, OO Zaidat, for the SWIFT Trialists





SWIFT
IDE Clinical Trial

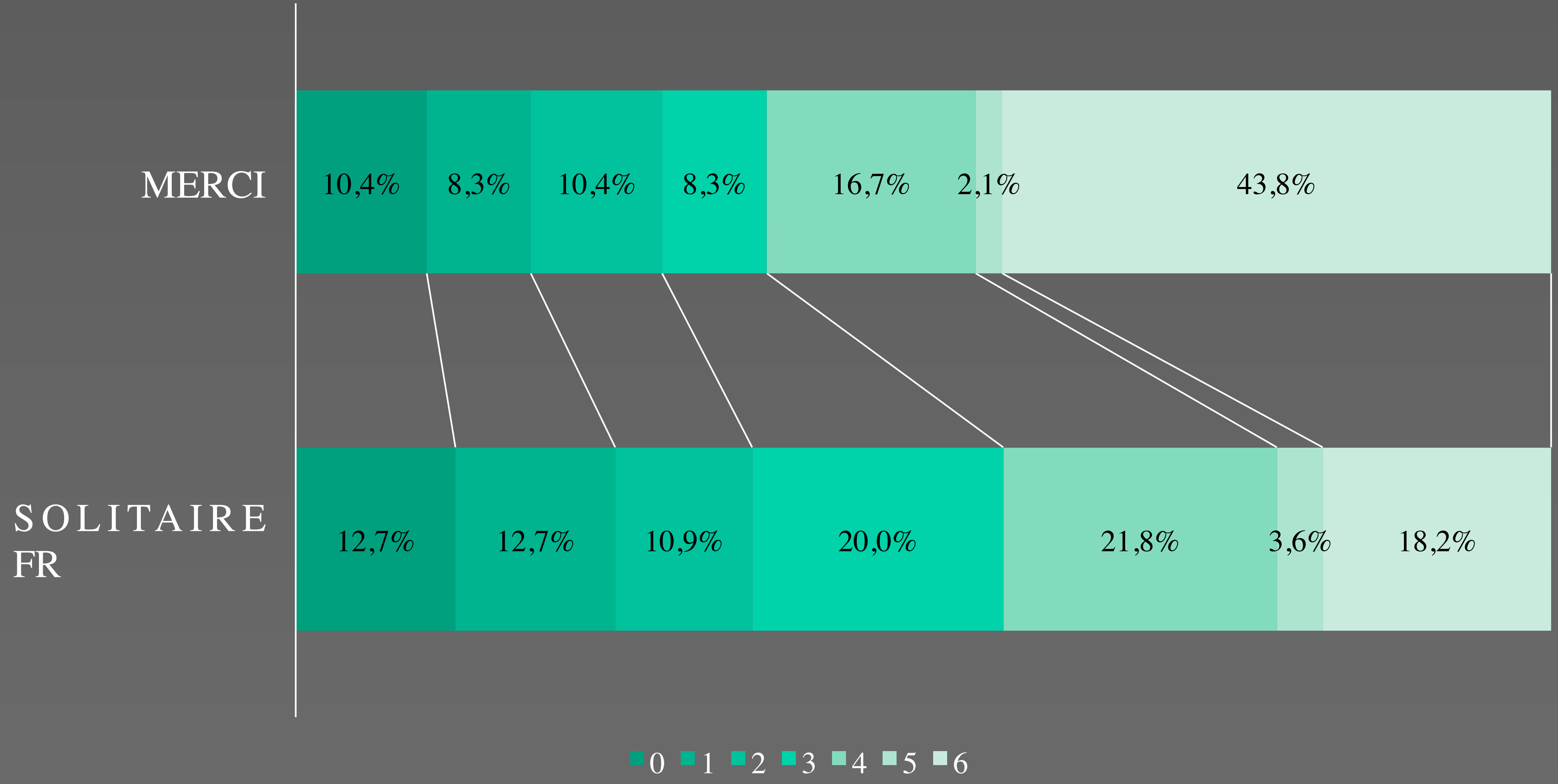
Primary Trial Endpoint

Outcomes Among Randomized Patients	Randomized Solitaire FR N=58	Randomized Merci N=55	Non-inferiority P value[1]	Superiority P value[1]
Successful recanalization without SICH[2] (Core Lab)	**60.7% (34/56)**	**24.1% (13/54)**	**<0.0001**	**0.0001**
Successful recanalization study device **(Core Lab)**	68.5% (37/54)	30.2% (16/53)	<0.0001	0.0001
Successful recanalization study device (Site Assessed)	**83.3% (45/54)**	**48.1% (26/54)**	**<0.0001**	**0.0002**
Use of rescue therapy	20.7% (12/58)	43.6% (24/55)	<0.0001	0.015
End of procedure successful recanalization **(Site)**	88.9% (48/54)	67.3% (37/55)	<0.0001	0.010
End of procedure successful recanalization **(Core Lab)**	80.4% (45/56)	57.4% (31/54)	<0.0001	0.013

1. Noninferiority by Wald's method, superiority by Fisher's Exact test
2. Symptomatic Intracranial Hemorrhage - Any PH1, PH2, RIH, SAH, or IVH associated with a decline in NIHSS ≥ 4 within 24hrs.

SWIFT IDE Clinical Trial

Global Disability at 90 Days
(Modified Rankin Score)



- CMH, p = 0.04

Hemorrhagic Transformation Outcomes

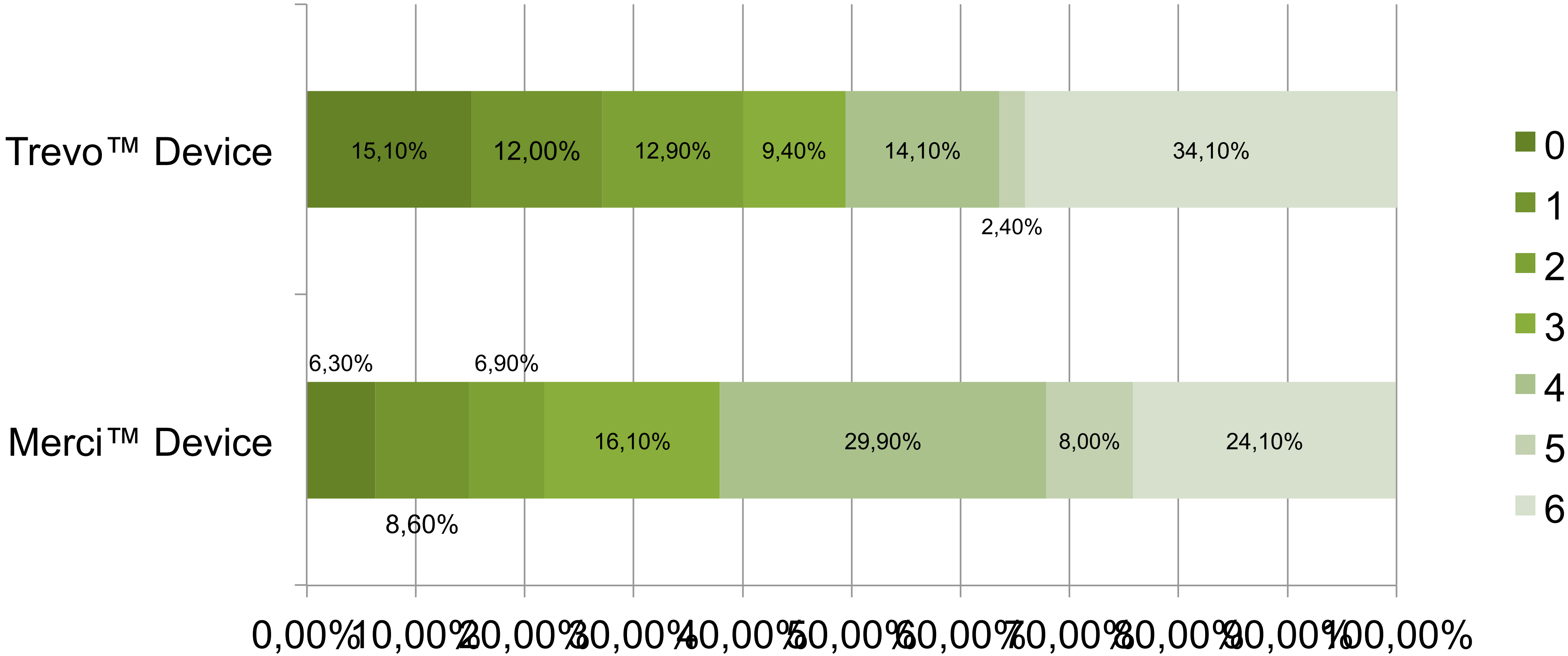
Outcomes Among Randomized Patients	Randomized Solitaire FR N=58	Randomized Merci N=55	Non-inferiority P value[1]	Superiority P value[1]
SICH	1.7% (1/58)	10.9% (6/55)	<0.0001	0.057
All ICH	17.2% (10/58)	38.2% (21/55)	0.0001	0.020

1. Fisher's Exact

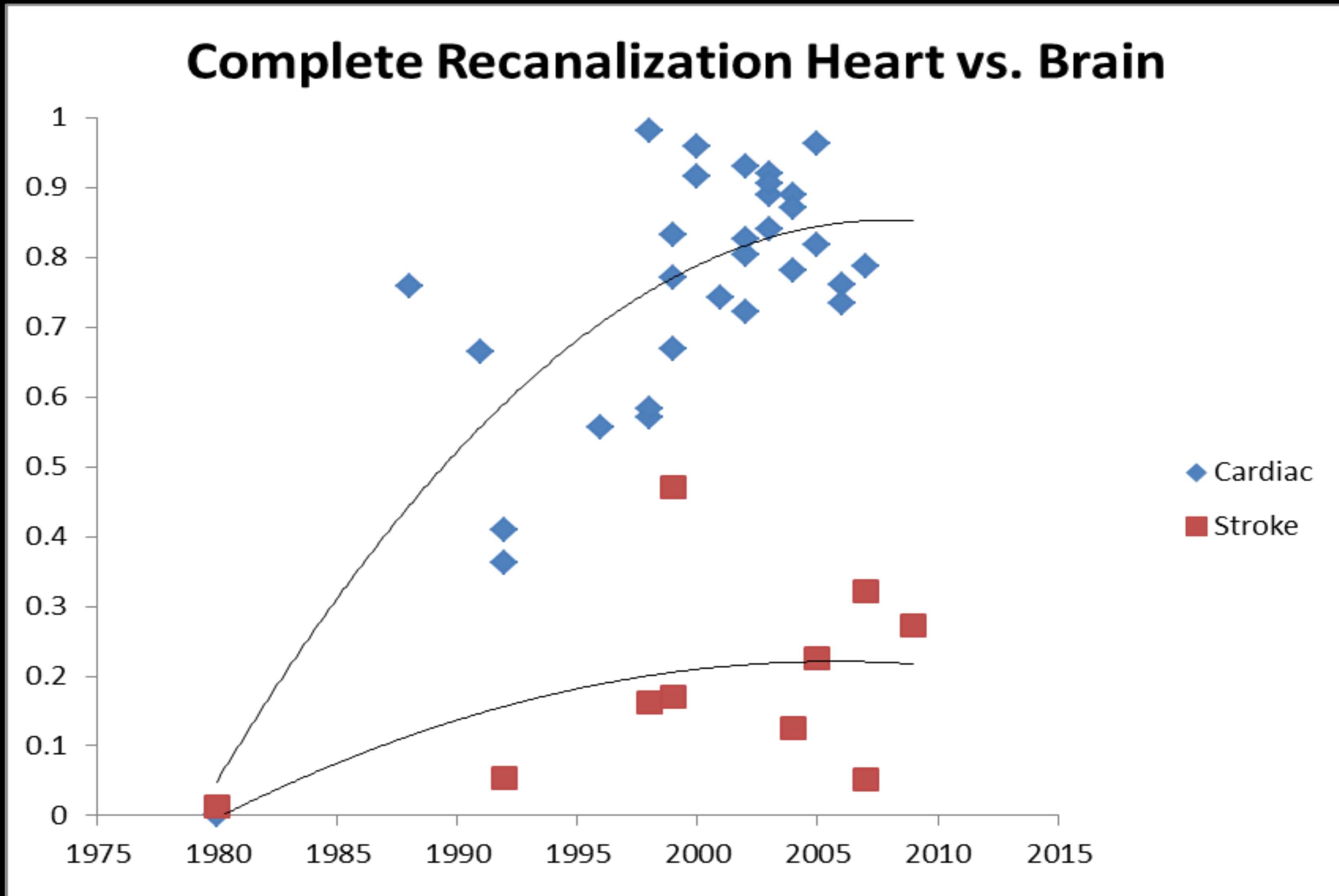
SWIFT
IDE Clinical Trial

TREVO 2 Trial

Rankin Shift



--Nogueira et al, Lancet 2012



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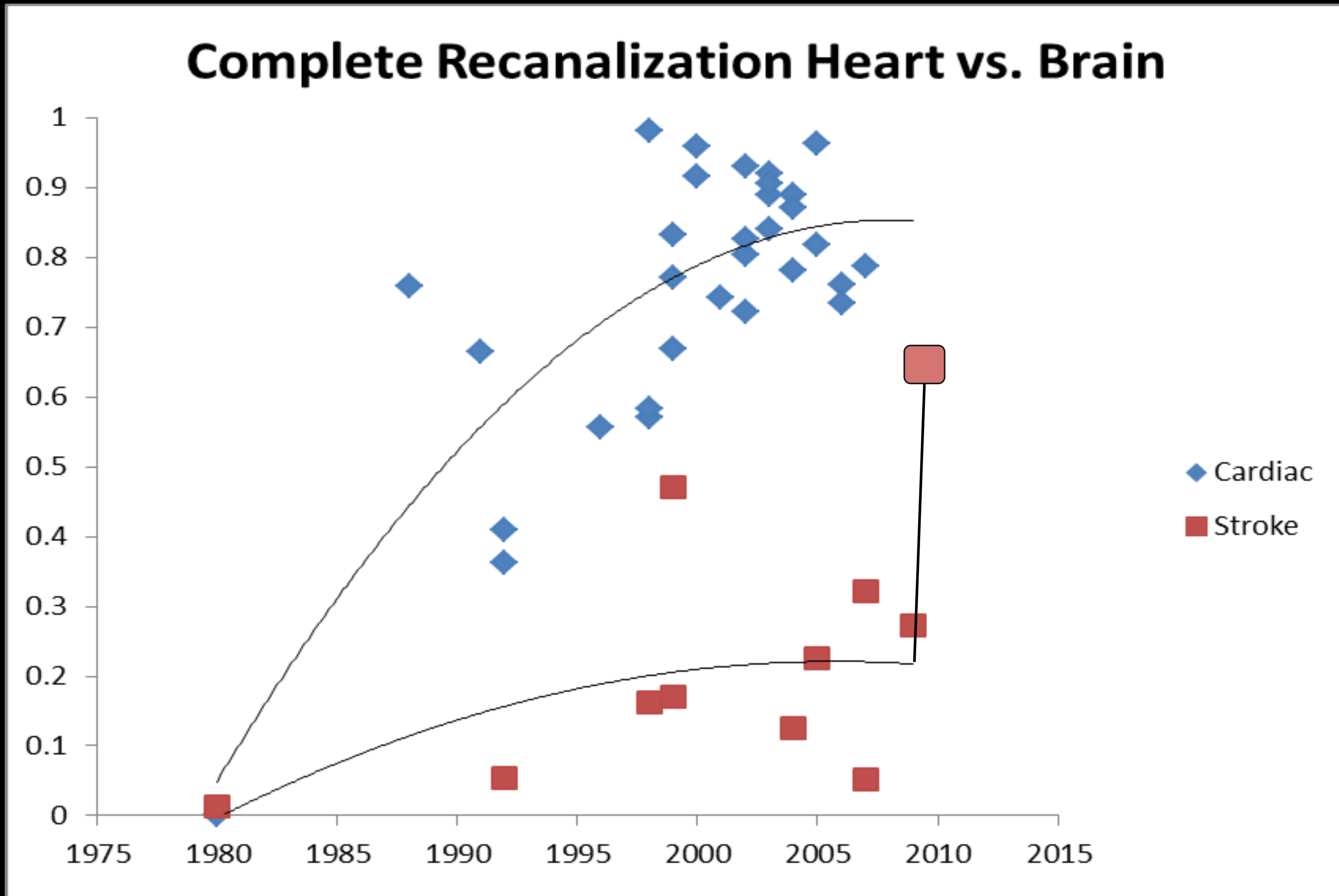

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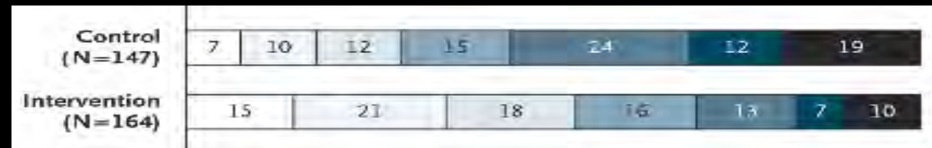
Era of Highly Effective Reperfusion Therapy

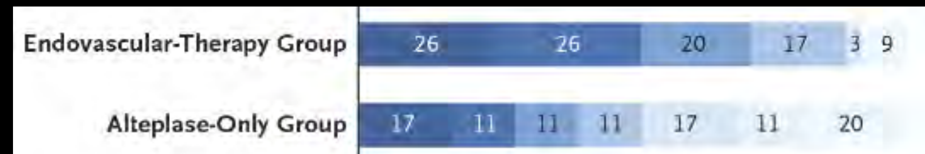
MR CLEAN

A Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

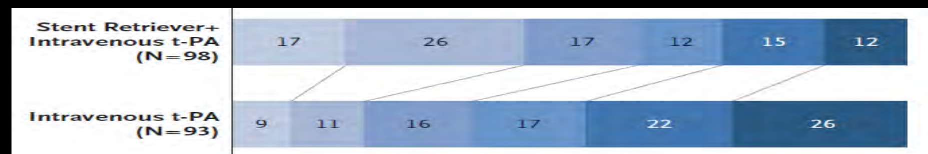
ESCAPE



EXTEND-IA



SWIFT PRIME

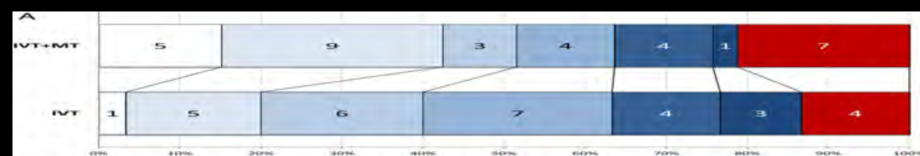


REVASCAT

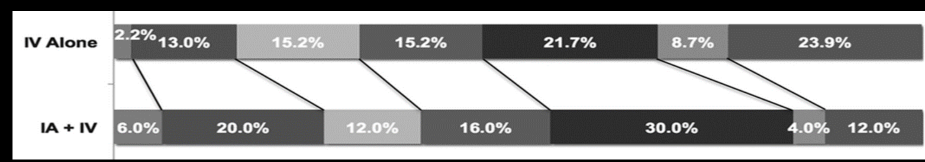
THRACE

PISTE

PRAGMATIC ISCHAEMIC STROKE THROMBECTOMY EVALUATION



THERAPY



Evidence of Benefit: Independence (mRS≤2) at 3 Months

Trial	ERT+MedRx	MedRx	OR	P value
MR CLEAN	32.6%	19.1%	2.05	0.0007
ESCAPE	53.0%	29.3%	2.73	0.00003
EXTEND-IA	71.4%	40.0%	3.75	0.009
SWIFT PRIME	60.2%	35.5%	2.75	0.0008
REVASCAT	43.7%	28.2%	1.98	0.021
All (weighted avg)	**46.1%**	**26.4%**	**2.39**	**<0.00000001**

Odds that ERT is beneficial are more than 100,000,000 to 1

Features of Second Generation Embolectomy Trials

Trial	Current N	Planned Max N	Interventio n	CTA/ MRA	Time	TPA	Imaging	Status
MR CLEAN	500	500	Variable (97% SR)	+	6 hr	Y or Inel	<1/3 MCA	Positive
ESCAPE	316	500	Variable (86% SR)	+	12 hr	Y or Inel	Collat < 50%	Positive
EXTEND IA	70	100	Solitaire	+	6 hr	Y	RAPID Mismatch	Positive
SWIFT PRIME	196	833	Solitaire	+	6 hr	Y	A ≥ 6 RAPID	Positive
REVASCAT	206	690	Solitaire	+	8 hr	Inel or Failed	A ≥ 6/7	Positive
THRACE	~450	480	Variable	+	R 4h	Y		Positive
THERAPY	108	692	Penumbra 3D	HVS≥8 mm	(6 hr)	Y	< 1/3 MCA	Trend Positive
PISTE	~75	800	Variable	+	6 hr	Y	CT hypo	Enrolling

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Features of Second Generation Embolectomy Trials

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THERAPY	108	692	Penumbra 3D	HVS≥8 mm	(6 hr)	Y	< 1/3 MCA	Trend Positive
PISTE	~75	800	Variable	+	6 hr	Y	CT hypo	Enrolling

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AHA/ASA Guideline

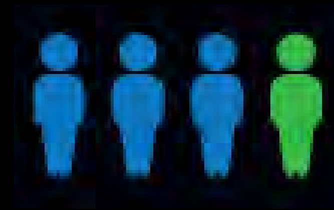
2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment

Endovascular therapy if patients meet all the following criteria

- Prestroke mRS score 0-1
- Received IV tPA (Ia) or tPA-ineligible (IIa)
- ICA or M1 MCA occlusion
- Age ≥ 18 yo
- NIHSS ≥ 6
- ASPECTS ≥ 6
- Treatment start (puncture) within 6h of onset

NNTs for Cerebral and Cardiac Ischemia Binary Outcomes

Thrombectomy
for AIS (vs Lysis)
Independence

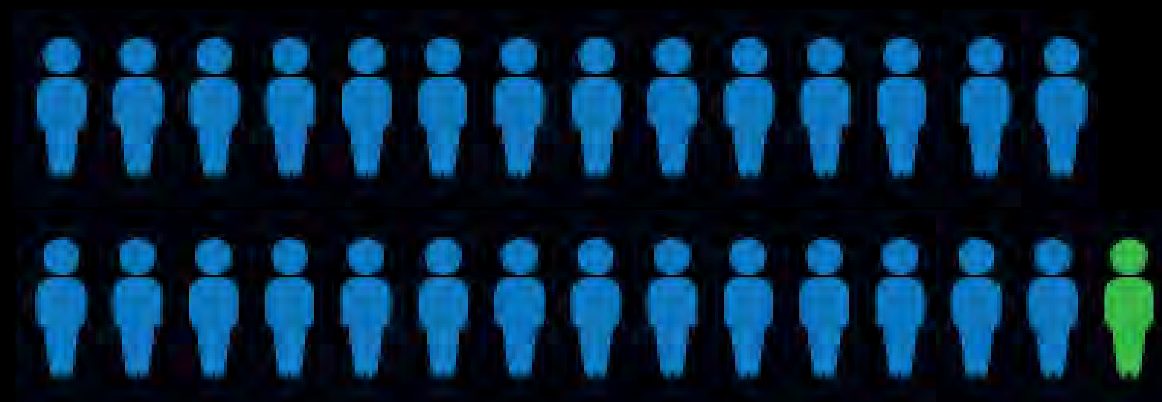


(4)

IV Lytics
for AIS (vs ASA)
Nondisability

(10)

PCI
for STEMI (vs Lysis)
Mortality



(29)

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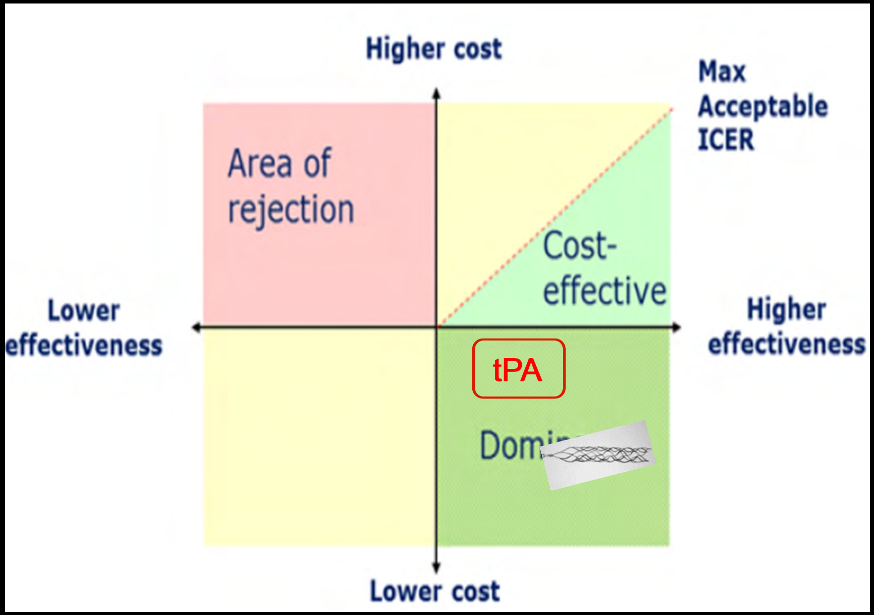
--Huyn et al, Circulation 2009 / Emberson et al, Lancet 2014 / Saver et al, NEJM 2015

Cost Effectiveness
US Payer Perspective - Lifetime

- IV tPA vs supportive
  - » QALY Gain
    - 0.39 yrs
  - » Healthcare Costs
    - Reduced $25,000
- ET+IV TPA vs IV tPA
  - » QALY Gain
    - 1.74yrs
  - » Healthcare Costs
    - Reduced $23,203



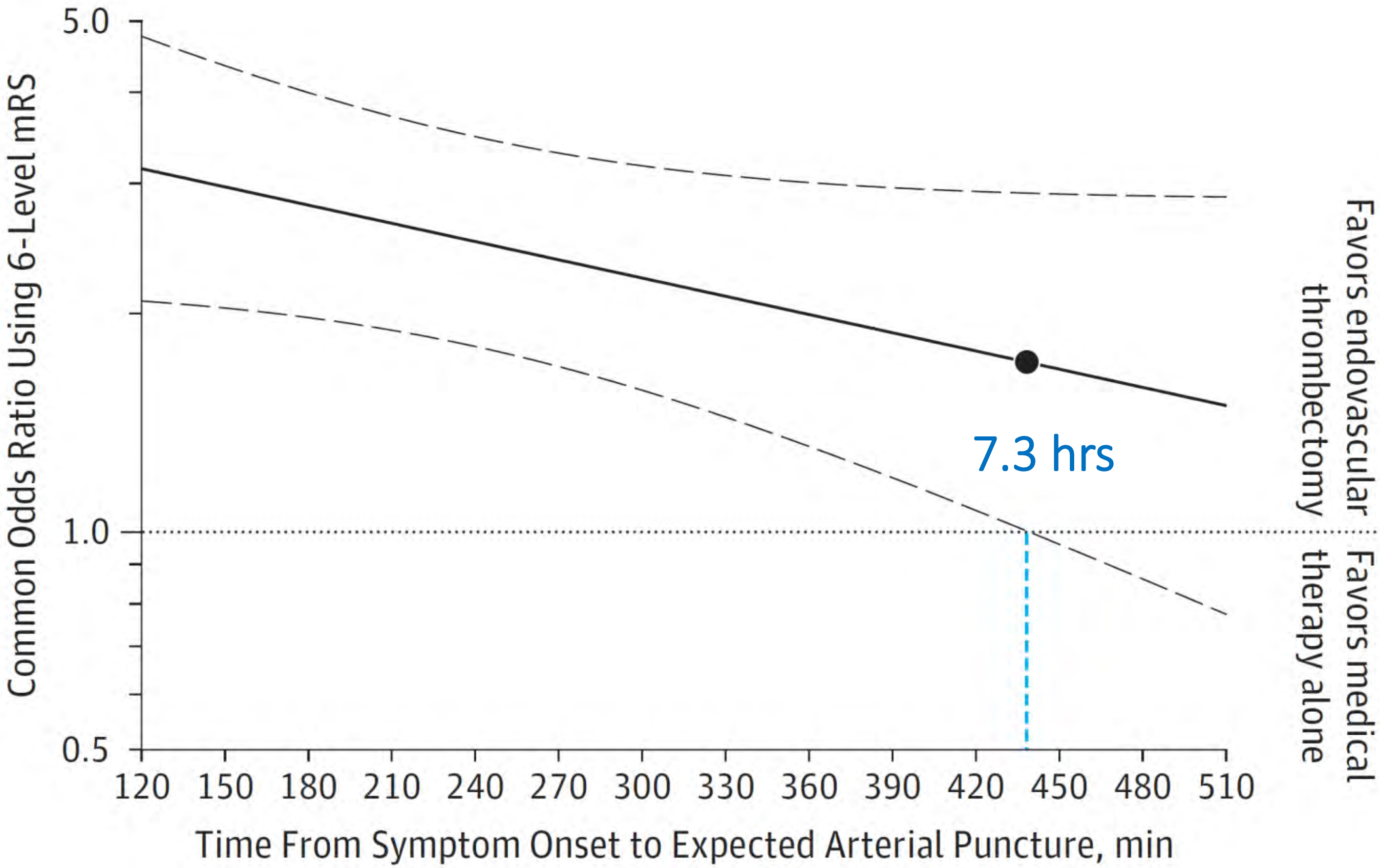
--Boudreau et al, Stroke 2014
--Shireman et al, Stroke 2017

Contribution of Intracranial Occlusions to Outcome in 643 Consecutive Ischemic Stroke and TIA Patients

--Reanalysis of Smith et al, Stroke 2009

Occlusion	Proportion of All AIS and TIA	Proportion of Dependent or Worse (mRS 3-6) AIS or TIA	Proportion of Fatal AIS or TIA
LVO	44%	62%	72%
No LVO	56%	38%	28%

Time from Onset to Expected Puncture Odds of Reduced Disability with EVT vs Medical

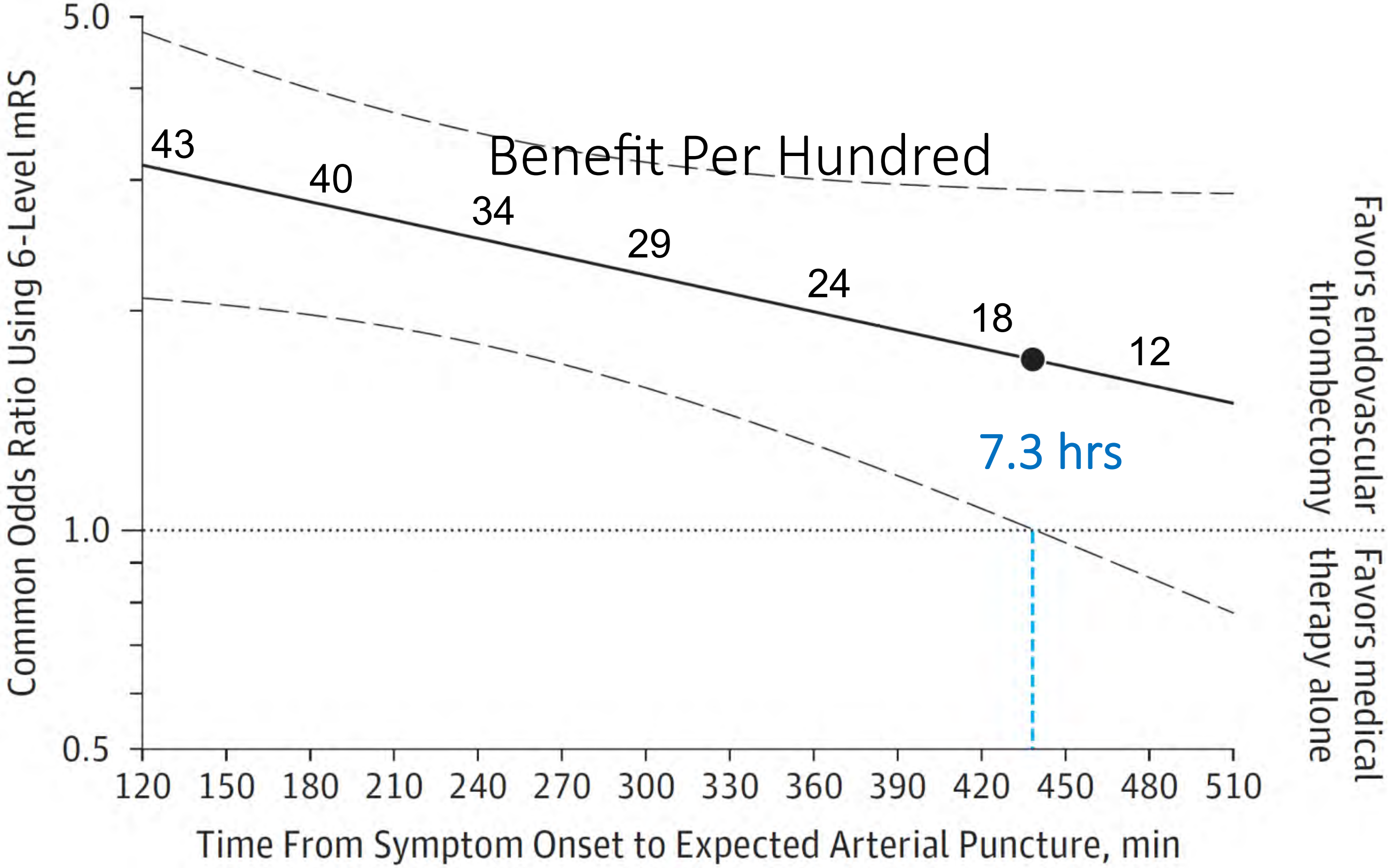


JAMA. 2016;316(12):1279-1288. doi:10.1001/jama.2016.13647

ESCAPE REVASCAT MR CLEAN EXTEND-IA SWIFT PRIME

HERMES Collaboration

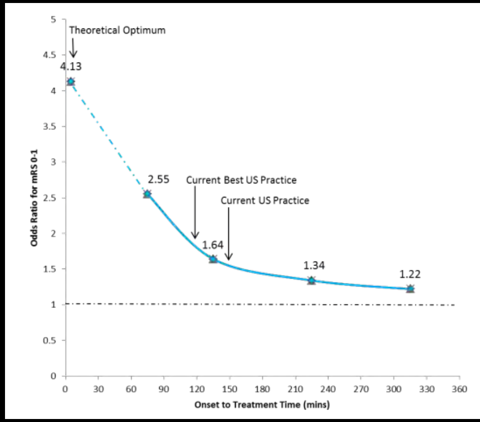
Time from Onset to Expected Puncture Odds of Reduced Disability with EVT vs Medical

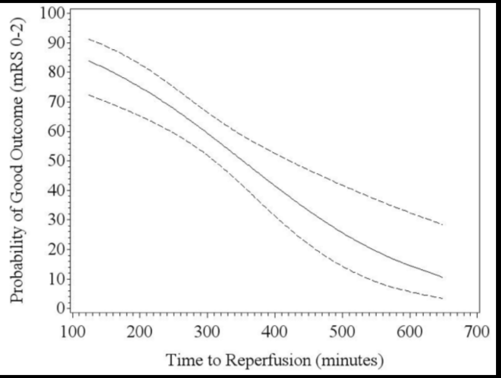


JAMA. 2016;316(12):1279-1288. doi:10.1001/jama.2016.13647

Minutes Matter

- IV TPA
  - » Every 8 minute delay causes 1 fewer of 100 treated patients to benefit in improved ambulation
- IA Neurothrombectomy
  - » Every 4 minute delay causes 1 fewer of 100 reperfused patients to benefit in reduced final disability





--Saver, Stroke 2013; Saver et al, JAMA 2013; Sheth et al, Ann Neurol 2015; Saver et al, JAMA 2016

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Minutes Matter

- IV TPA
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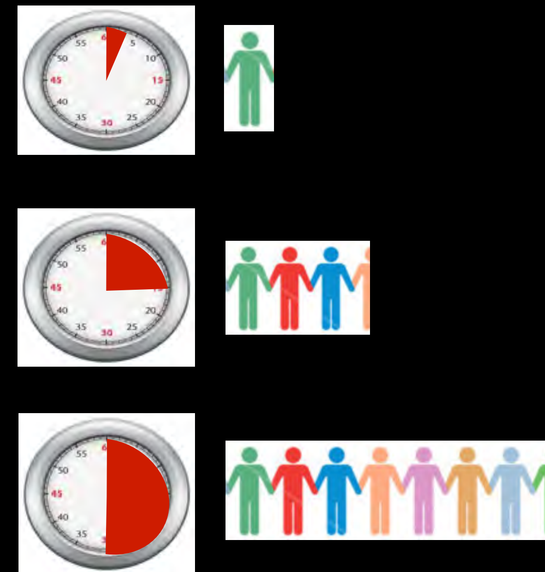

1 worse outcome every 4 minutes

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2013

STANDARDS OF PRACTICE

Multisociety Consensus Quality Improvement Guidelines for Intraarterial Catheter-directed Treatment of Acute Ischemic Stroke, from the American Society of Neuroradiology, Canadian Interventional Radiology Association, Cardiovascular and Interventional Radiological Society of Europe, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, European Society of Minimally Invasive Neurological Therapy, and Society of Vascular and Interventional Neurology

David Sacks, MD, Carl M. Black, MD, Christophe Cognard, MD, John J. Connors III, MD, Donald Frei, MD, Rishi Gupta, MD, Tudor G. Jovin, MD, Bryan Kluck, MD, Philip M. Meyers, MD, Kieran J. Murphy, MD, Stephen Ramee, MD, Daniel A. Rüfenacht, MD, M.J. Bernadette Stallmeyer, MD, PhD, and Dierk Vorwerk, MD

Endovascular Time Targets

Time Metric	Multi-Society Guideline 2013
Door to Puncture	120 min
Picture to Puncture	95 min
Puncture to 1st pass	45 min
Door to Revasc	210 min (3h 30m)

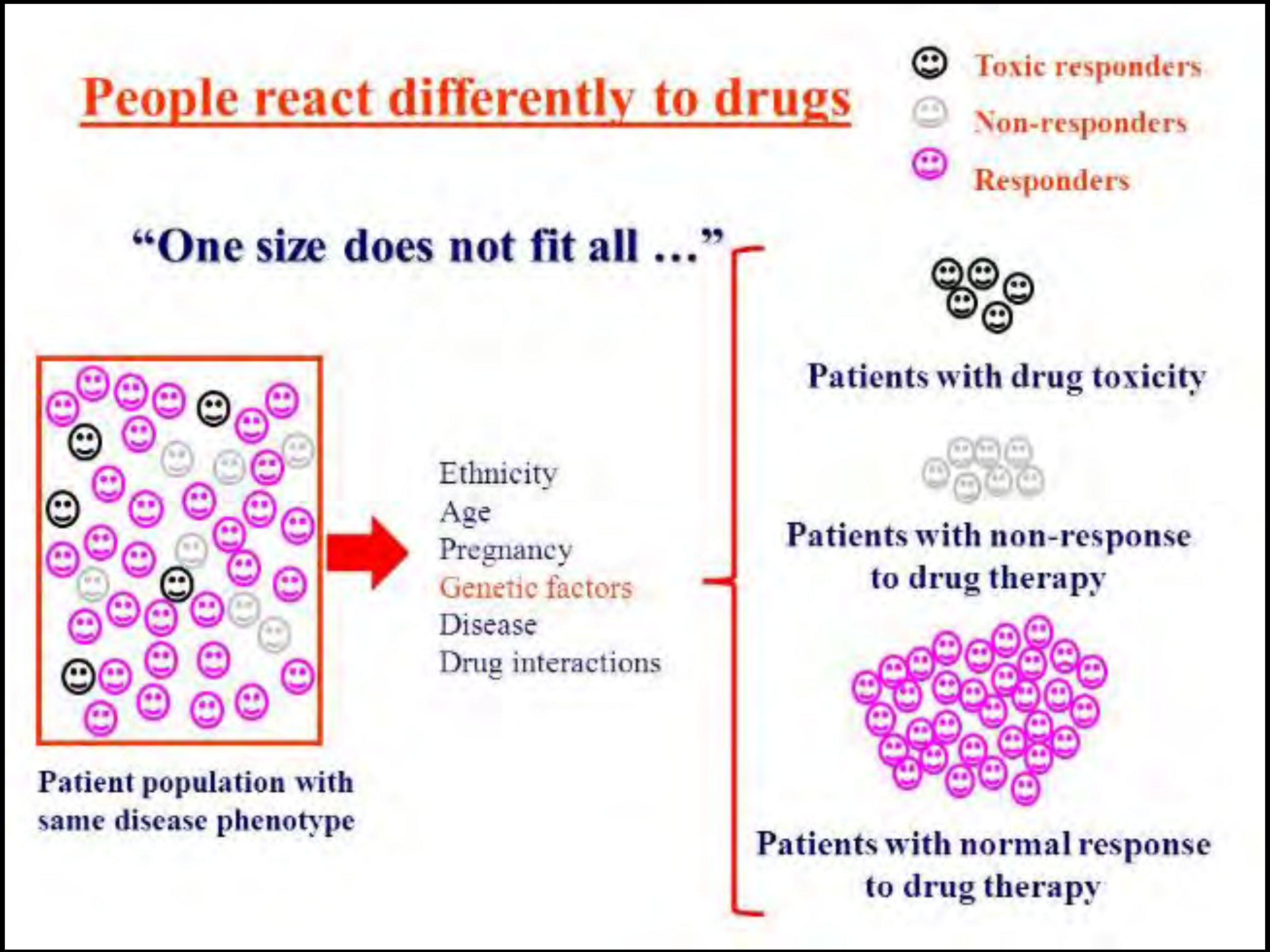
Endovascular Time Targets

Time Metric	Multi-Society Guideline 2013	SWIFT PRIME
Door to Puncture	120 min	90 min
Picture to Puncture	95 min	57 min
Puncture to 1st pass	45 min	24 min
Door to Revasc	210 min (3h 30m)	139 min (2h 19m)

Endovascular Time Targets

Time Metric	Multi-Society Guideline 2013	SWIFT PRIME	SNIS Guideline 2015 “Ideal”
Door to Puncture	120 min	90 min	60 min
Picture to Puncture	95 min	57 min	30 min
Puncture to 1st pass	45 min	24 min	--
Door to Revasc	210 min (3h 30m)	139 min (2h 19m)	90 min (1h 30m)

Mapping the Responder Population



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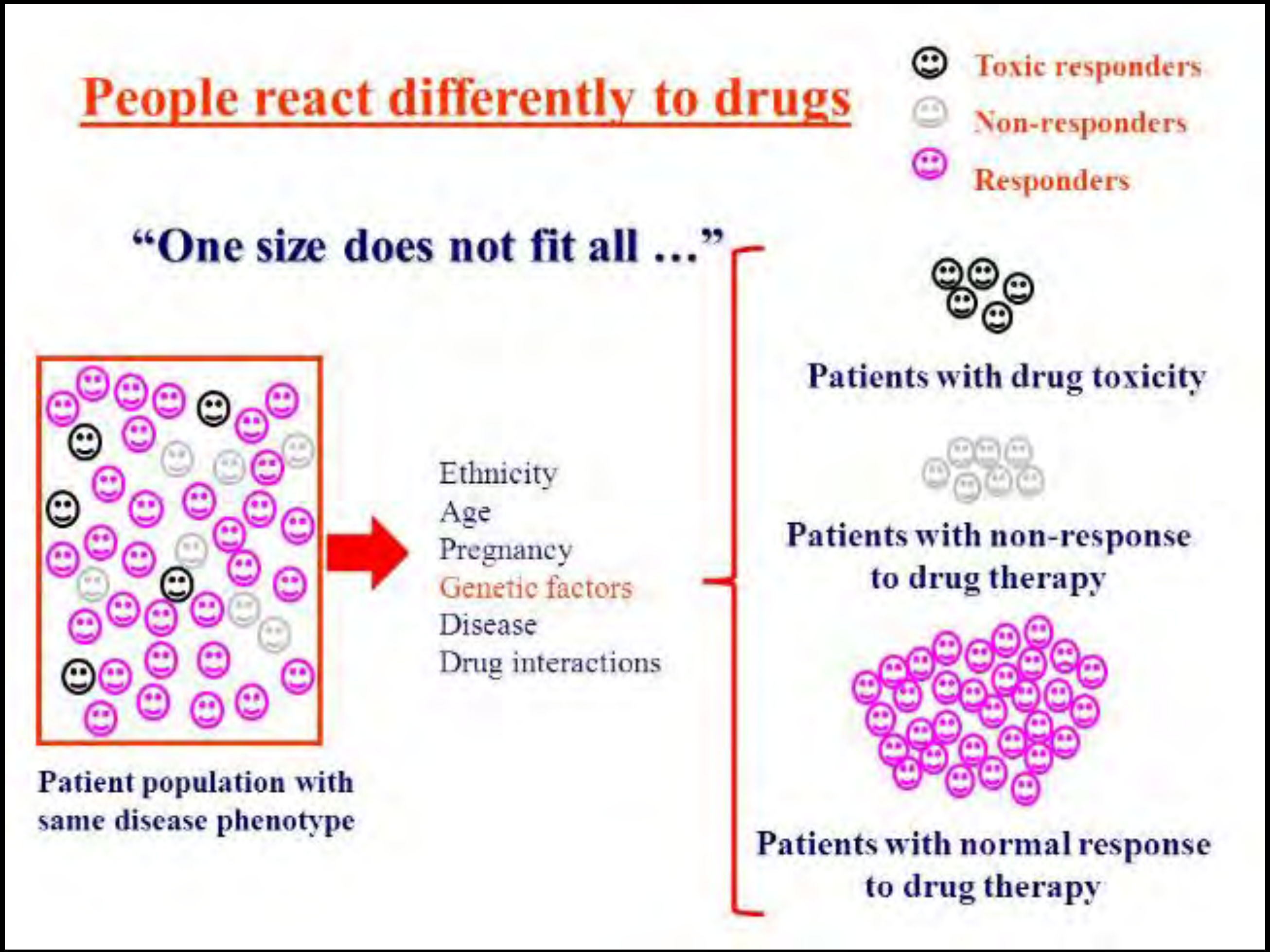
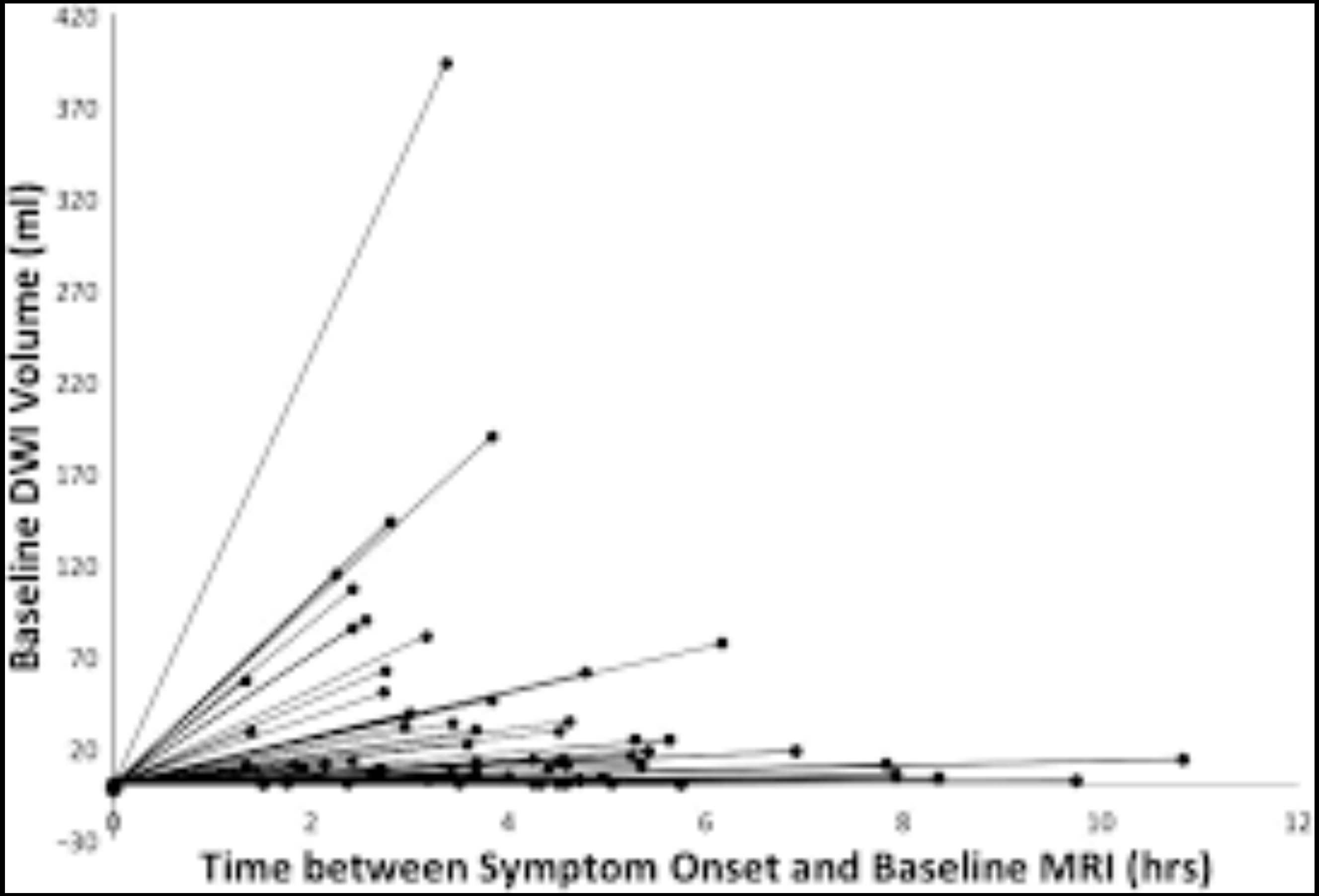
Mapping the Responder Population



- More arteries
  - MVOs (M2, etc)
  - BA/VA
- Mild deficits
- Large cores
- Late-presenters

Fast and Slow Progressors
Collateral Variability



--Wheeler et al, Int J Stroke 2015

Tissue Status

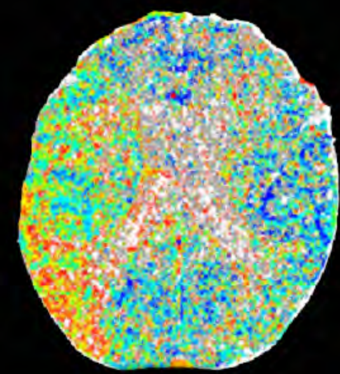
Perfusion Status

Vessel Status

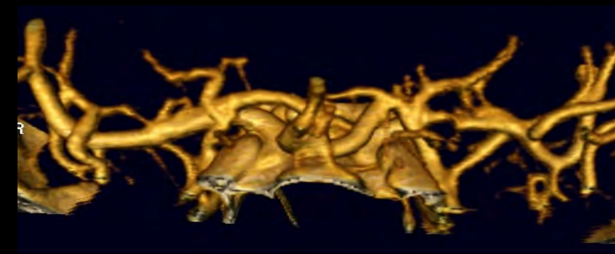
Multimodal CT

CBV CT

PCT

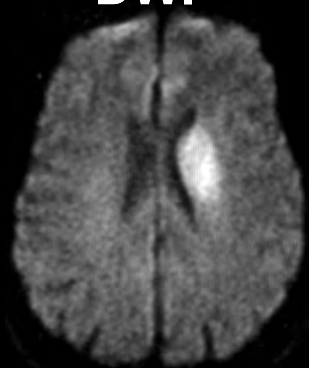


CTA

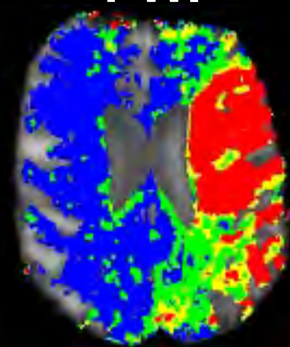


Multimodal MRI

DWI



PWI



MRA

Bioenergetic Compromise

Hemodynamic Compromise

Occlusions or Stenoses

Strategies to Identify LVO Patients with Salvageable Ischemic Penumbra

< 6 Hrs

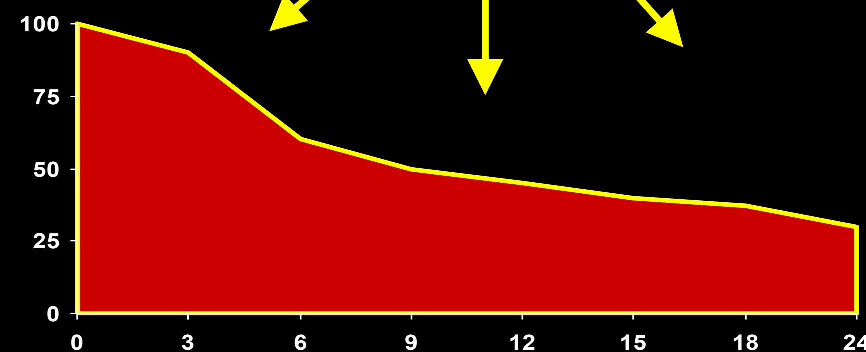
=

Hyperacute therapy when nearly all patients have penumbra

> 6 Hrs

Imaging required to assess pathophysiology

% Patients with Penumbra



Time From Onset (Hours)

Strategies to Identify LVO Patients with Salvageable Ischemic Penumbra

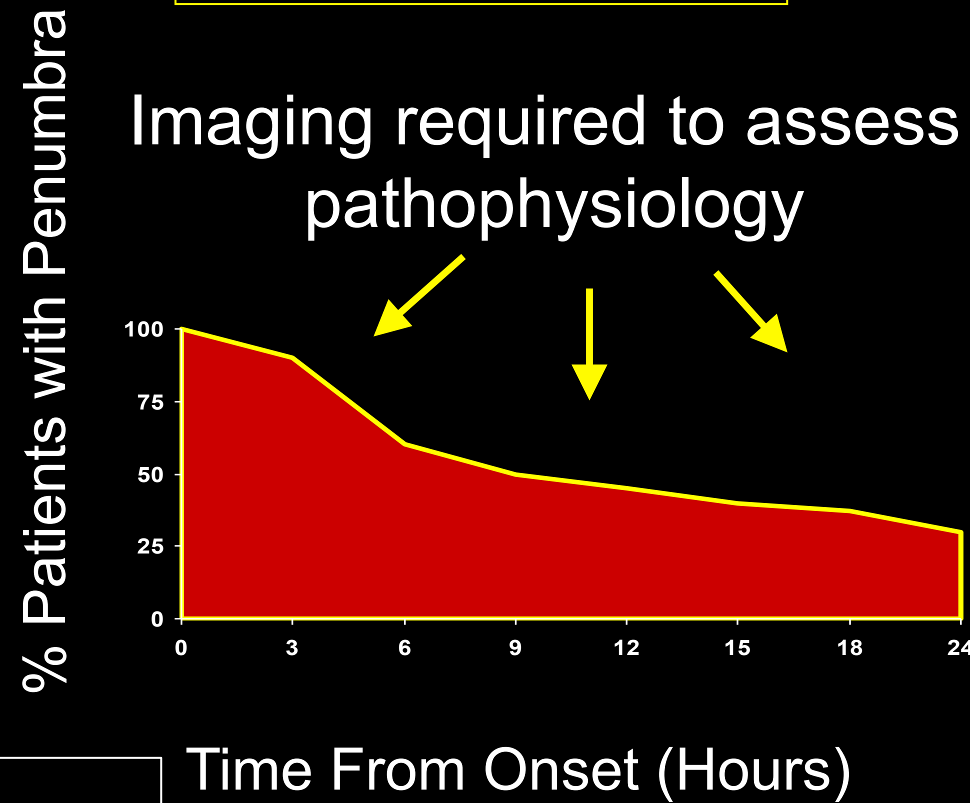
< 6 Hrs

=

Hyperacute therapy when nearly all patients have penumbra

> 6 Hrs

Imaging required to assess pathophysiology



Trials

DAWN / DEFUSE 3

Potential Populations for Thrombectomy: Example of Time

Mismatch	0-3h	3-6h	6-7h	7-8h	8-12h	12-16h	16-20h	20-24h	>24h
Not performed									

Potential Populations for Thrombectomy: Examples of Time and Penumbra

Mismatch	0-3h	3-6h	6-7h	7-8h	8-12h	12-16h	16-20h	20-24h	>24h
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Not performed									
>200%									
150-199%									
100-149%									
50-99%									
20-49%									

Trial Design Options for Expanding Eligible Patients

- Older approaches
  - » Incremental expansion
    - From "sweet spot" out
    - Series of trials or adaptive expansion
  - » Mega-trial
    - Wide entry criteria with enroll all or uncertainty principle
    - Sort it out in subgroup analysis
- Newer approach
  - » Adaptive exploration

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

- Entry criteria
  - 6-24h after onset
  - Clinical-imaging mismatch on DWI MRI or CTP-rCBF
    - Age < 80 yo
      - NIHSS≥10, 0-30 cc core
      - NIHSS≥20, 31-50 cc core
    - Age ≥ 80 yo
      - NIHSS≥10, 0-20 cc core
- Sample size
  - Adaptive Bayesian design
    - Up to 500 patients
    - Interim analyses at 150 and every 50 thereafter

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Feb 28, 2017

DAWN Trial: Breaking News

Dear DAWN Investigators:

Today, the DAWN DSMB has performed an interim analysis of the first 200 enrolled subjects in DAWN. It is with great excitement that we announce that based on crossing of pre-specified probability thresholds for efficacy, **the DSMB recommended trial enrollment to be stopped.**

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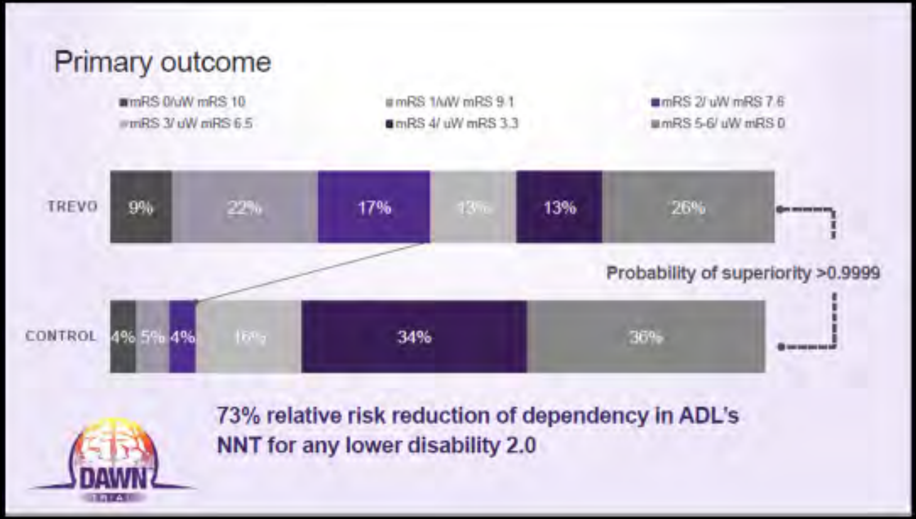


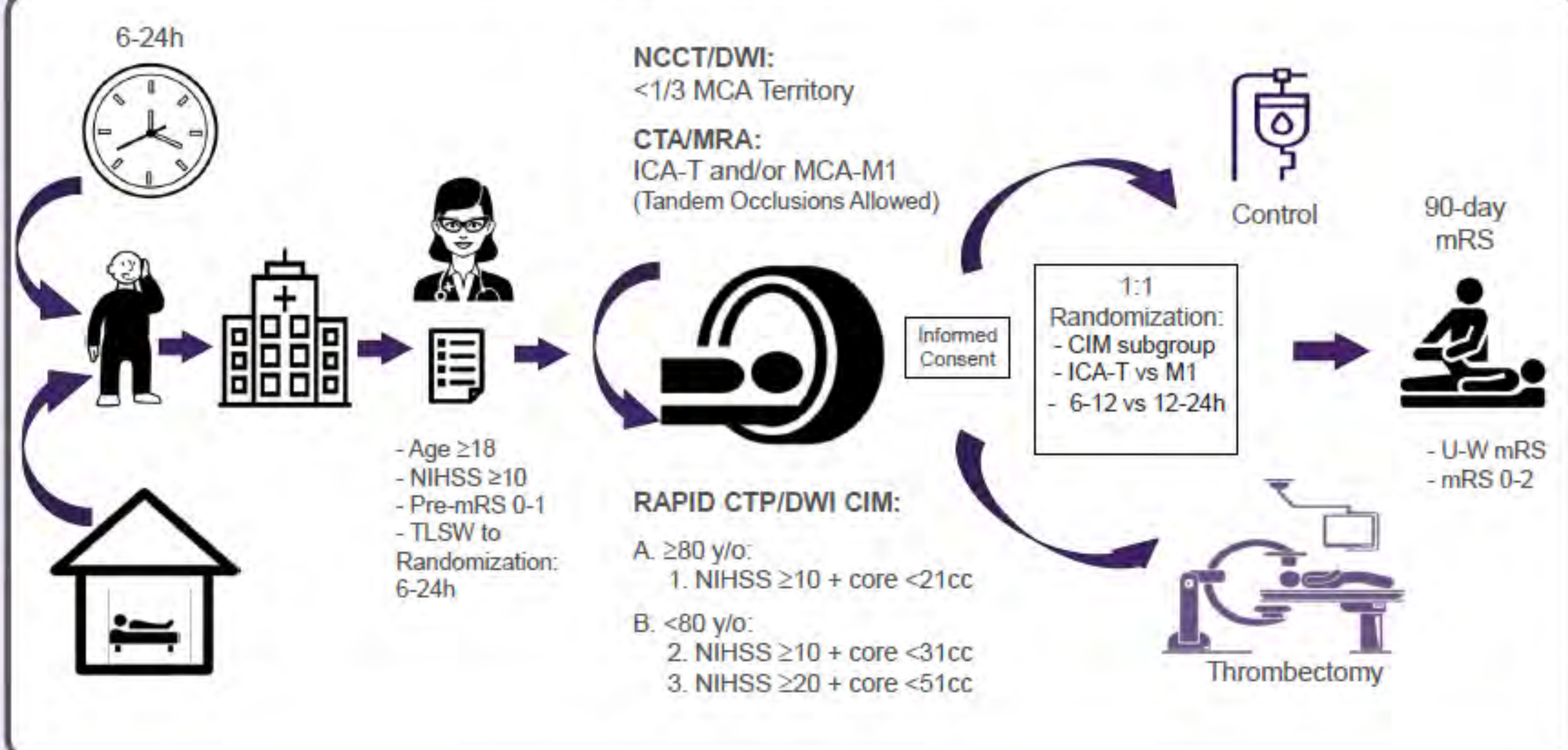
DAWN TRIAL

DAWN in Full Daylight

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

Tudor G. Jovin MD & Raul G. Nogueira MD
on behalf of the DAWN investigators

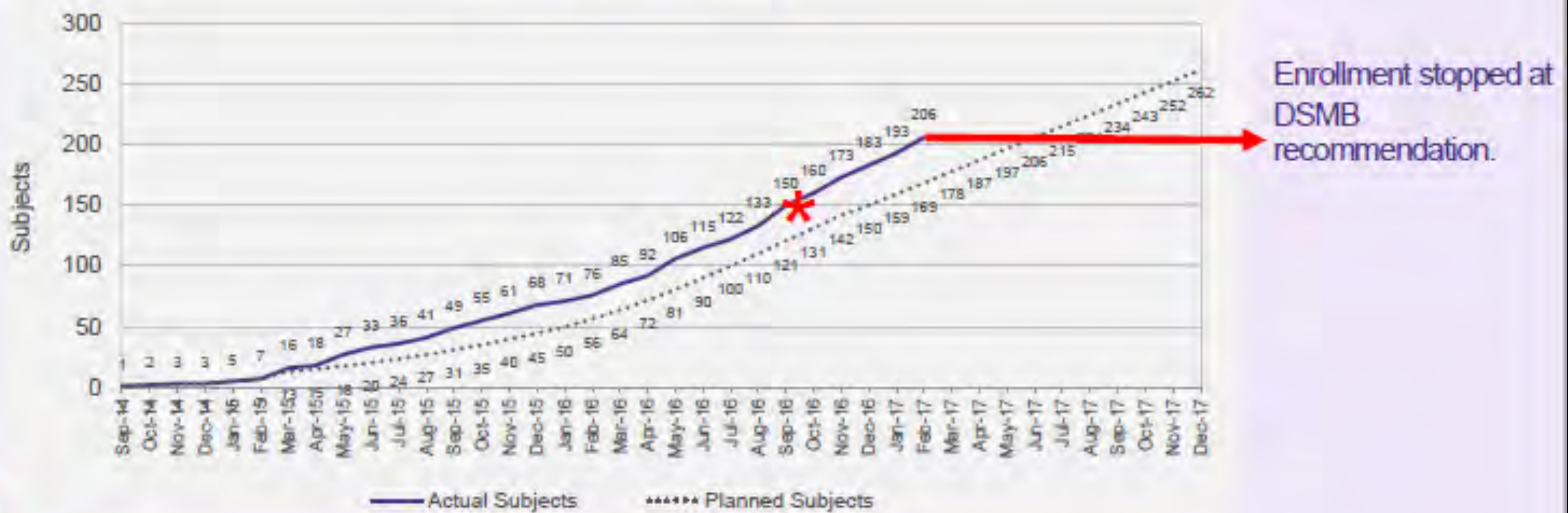
Study Methods: Workflow



TRIAL ENROLLMENT RATE AND TERMINATION

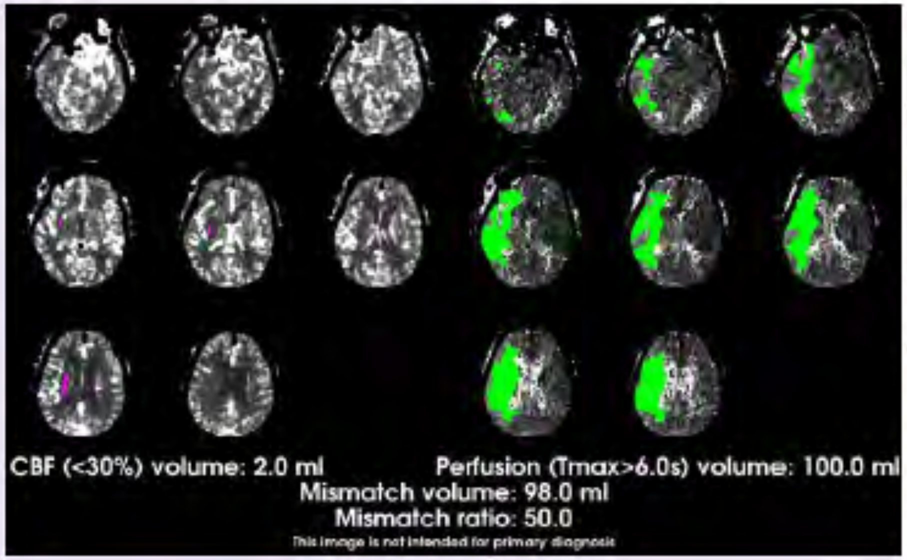
Site Status			
Sites Qualified	36	Contracts Executed	31
Sites Initiated	30	Sites Activated to Enroll	30
IRB/EC Approvals	31	Subjects Enrolled	206

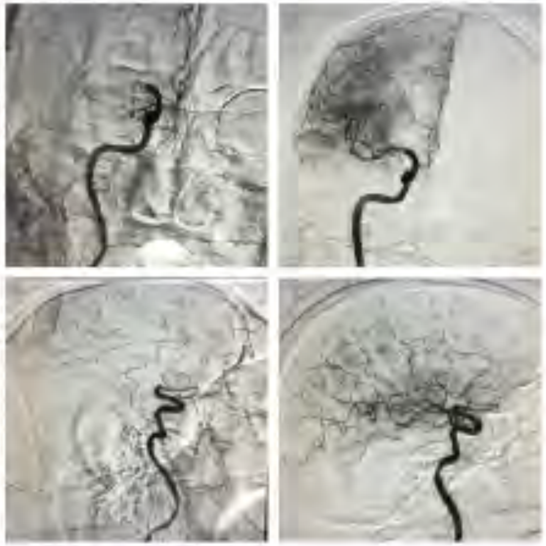
Actual / Projected Enrollment



*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
This image is not intended for primary diagnosis



Patient presentation

	Treatment arm N=107	Control arm N=99	P- value
Time since time last seen well to randomization (hrs)			
Mean ± SD Median (Q1, Q3) Range (min, max)	13.4 ± 4.1 12.2 (10.2, 16.0) (6.1, 23.5)	13.0 ± 4.5 13.2 (9.4, 15.8) (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

DAWN TRIAL

Co-primary endpoints

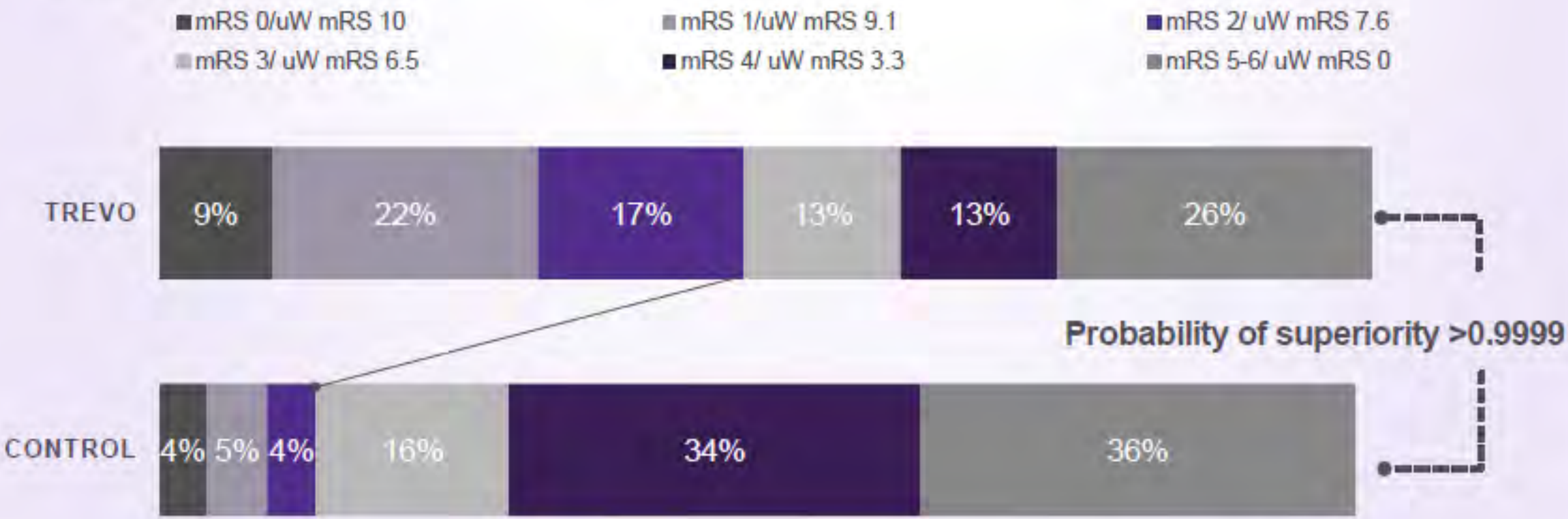
	Trevo	MM	Treatment benefit (95% CI)	Bayesian probability of superiority
Day 90 weighted mRS	5.5 ± 3.8	3.4 ± 3.1	2.1 (1.20, 3.12)	>0.9999*
Day 90 mRS (0-2)	48.6%	13.1%	35.5% (23.9%, 47.0%)	>0.9999*

NNT for 90-day functional independence = 2.8

*Similar to p<0.0001

DAWN TRIAL

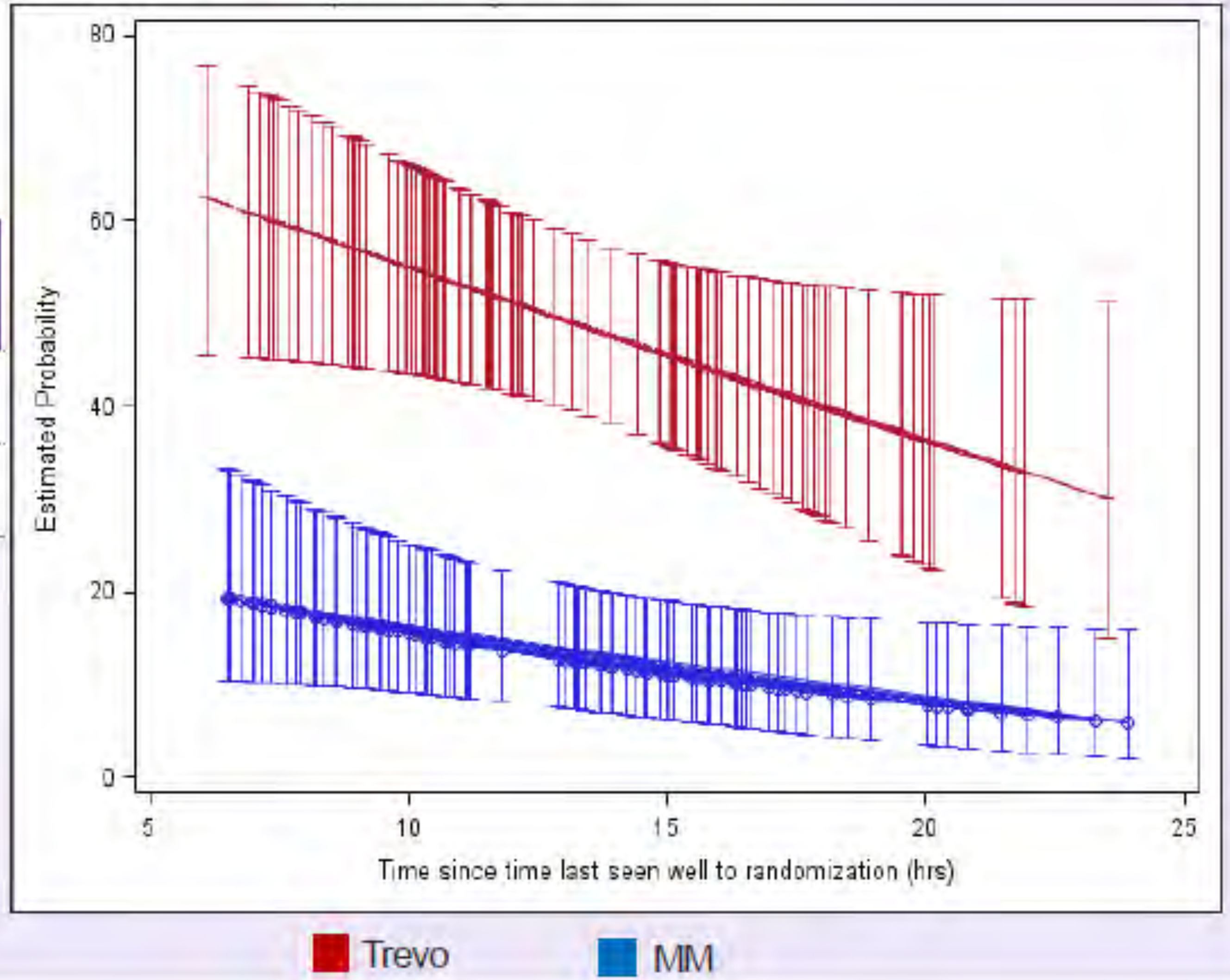
Primary outcome



73% relative risk reduction of dependency in ADL's
NNT for any lower disability 2.0

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



Populations for Thrombectomy: Time and Penumbra

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Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3

defuse · 3

- Entry criteria
  - » 6-16h after onset
  - » Target mismatch profile on DWI/PWI MRI or CTP
    - Ischemic core < 70 cc
    - Mismatch ratio ≥ 1.8
    - Penumbra (mismatch) volume ≥ 15 cc
- Sample size
  - » Adaptive design
    - Up to 476 patients
    - First interim efficacy analysis planned at 200
    - (Stopped for efficacy at 182)

Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3

defuse 3

- Entry criteria
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July 26, 2017

DEFUSE 3 – **DSMB has halted the trial permanently because of a high likelihood of efficacy in the endovascular treatment group.** The Study is currently under continuing review.

Data cleaning is underway. Please complete the 90 day visits as soon as possible so they can get the database cleaned and locked.

Populations for Thrombectomy: Time and Penumbra

Mismatch	0-3h	3-6h	6-7h	7-8h	8-12h	12-16h	16-20h	20-24h	>24h
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Population Impact of Imaging Selection for Additional Patients Who Benefit from Thrombectomy

Acute (<24h) Ischemic Stroke Subtypes	Percent	Number per Year
All	100%	600,000
LVO	40%	240,000
LVO < 6h (70%)	28%	168,000

--Smith et al, Stroke 2009; van Seeters et al, Cerebrovasc Dis 2015; Tong et al, Stroke 2012; Malhotra and Saver, Stroke 2017 (abstract); Darby et al, Stroke 1999

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LVO	40%	240,000
LVO < 6h (70%)	28%	168,000
LVO 6-24h (30%)	12%	72,000
LVO 6-24h DAWN eligible (15%)	2%	12,240
LVO 6-24h DEFUSE 3 eligible (30%)	4%	24,480

--Smith et al, Stroke 2009; van Seeters et al, Cerebrovasc Dis 2015; Tong et al, Stroke 2012; Malhotra and Saver, Stroke 2017 (abstract); Darby et al, Stroke 1999

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LVO 6-24h DEFUSE 3 eligible (30%)	4%	24,480
LVO 6-24h all who benefit (50%?)	6%?	36,720?

UCLA Stroke Center

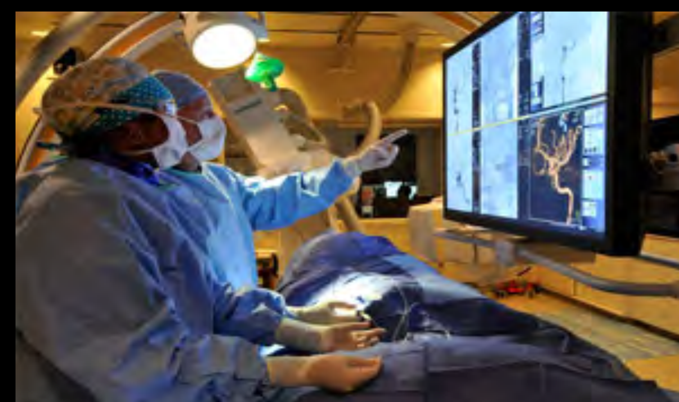
--Smith et al, Stroke 2009; van Seeters et al, Cerebrovasc Dis 2015; Tong et al, Stroke 2012; Malhotra and Saver, Stroke 2017 (abstract); Darby et al, Stroke 1999

Stroke Systems: ~~Two~~ Four Tier US Model

- <u>EMS</u>
  --Trained dispatchers, high priority triage
  --Paramedics trained in stroke recognition (e.g. LAPSS)
  --Deliver patients to nearest stroke capable hospital
  --Pre-arrival notification

- <u>Spokes</u>
  - Stroke Ready Hospitals (SRHs)
    --Able to provide initial, ED care, often via telemedicine
    --Able to use rt-PA and other acute therapies safely and efficiently
  - Primary Stroke Centers (PSCs)
    --Able to provide initial, ED care
    --Able to use rt-PA and other acute therapies in a safe and efficient manner
    --Have Stroke Units and can admit patients

- <u>Hubs</u>
  - Thrombectomy Stroke Centers (TSCs)
    -- Able to provide endovascular thrombectomy but not other advanced care
  - Comprehensive Stroke Centers (CSCs)
    --Able to care for all complex patients
    --Advanced treatments (i.e. coils, clips, stents, endovascular recanalization, etc)
    --Trained specialists in key areas (Vascular neurology, Neurointerventional procedures, Neurocritical Care, Vascular Neurosurgery)



Warning Signs and Activation of EMS System

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Ubiquitous Computing and Ambient Intelligence
Accelerated Stroke Onset Detection

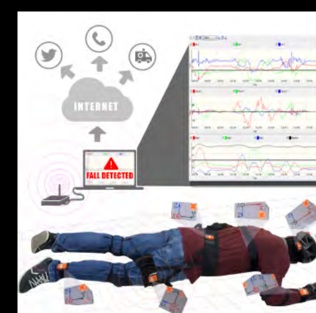
Las Vegas Casinos

Home Cameras

Home Health Robots

Computer Vision and Acclerometer Fall Detection

(also wearable pajamas)



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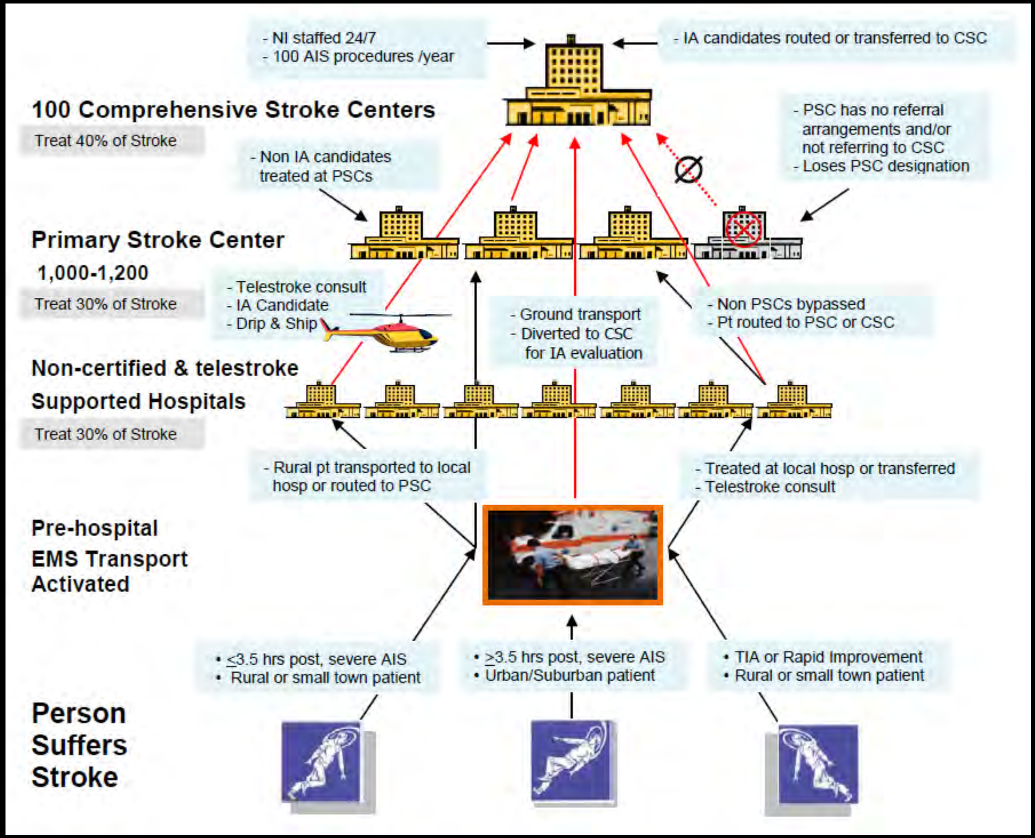
--Example: Leone et al. Detecting falls with 3d range camera in ambient assisted living applications. Medical Engineering & Physics 2011

Advanced Stroke Center Buildout

- Comprehensive Stroke Centers
  - » 2011
    - AHA CSC metrics paper
    - TJC technical advisory panel
  - » 2012
    - TJC pilot testing
  - » 2012-2013
    - National CSC certification
  - » 2014
    - CSC Performance Measures
- Thrombectomy Stroke Centers
  - » 2018
    - National TSC certification



--Saver et al, Stroke Interventionalist 2013

Identifying Likely Large Vessel Occlusion Patients in Field

- Medium (distal) vessel and small (penetrator) occlusions
  - IV tPA - works well, want asap
  - Thrombectomy – not an option
  - Primary Stroke Center or Acute Stroke Ready Hospital
- Large vessel occlusions
  - IV tPA - works poorly
  - Thrombectomy – works well
  - Comprehensive Stroke Center

Routing Protocols in Tiered Systems: ASRHs, PSCs, CSCs

- Tiered routing options
  - » None
  - » Time (e.g. 3.5-6h)
  - » Severity (e.g. LAMS 4-5)
  - » Type (H/A, ICH)
- Considerations
  - » Urban v rural
  - » Geography
  - » Traffic
  - » Resources
  - » Minimize time out of service area

AHA/ASA Policy Statement

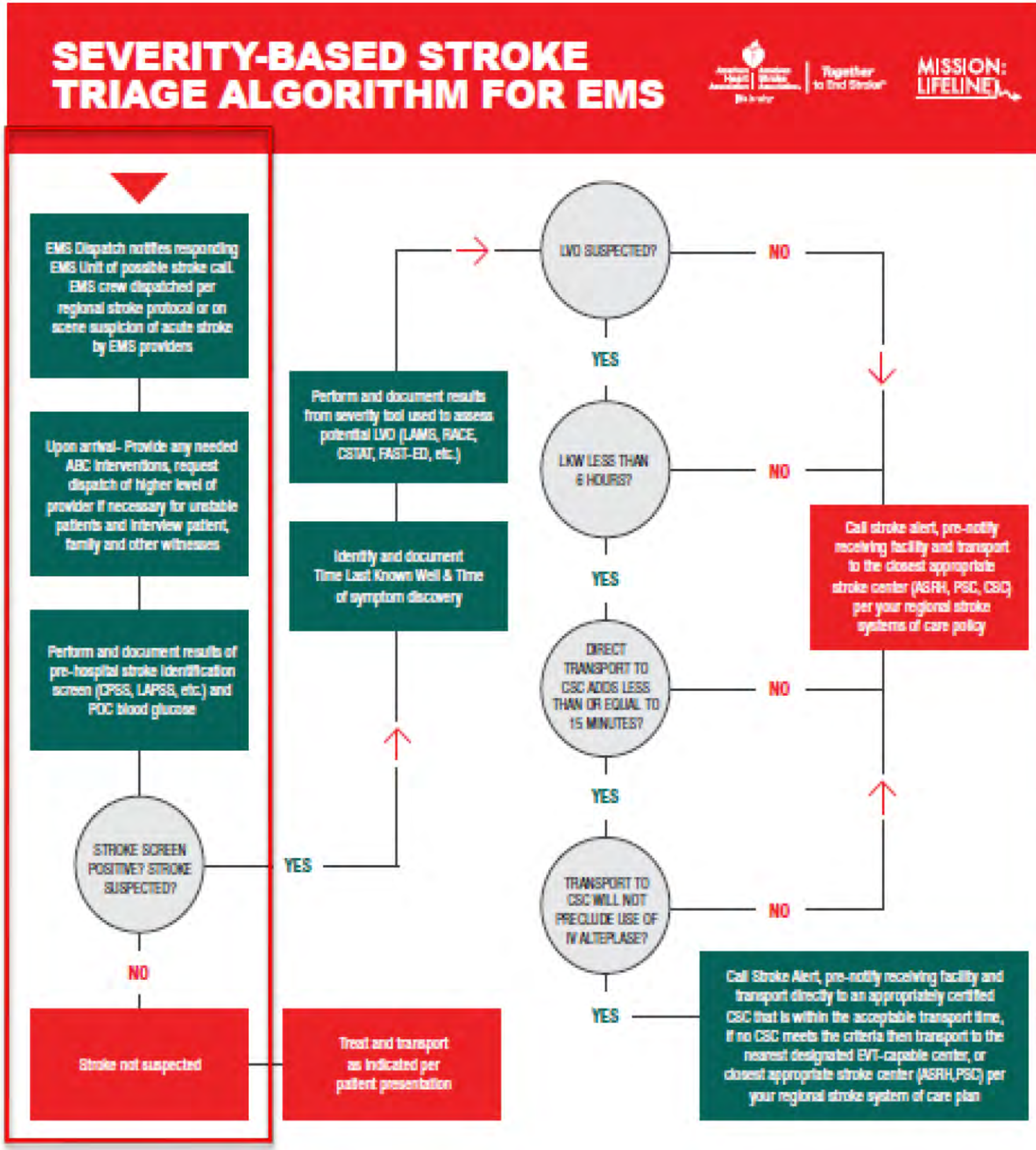
Interactions Within Stroke Systems of Care

A Policy Statement From the American Heart Association/American Stroke Association

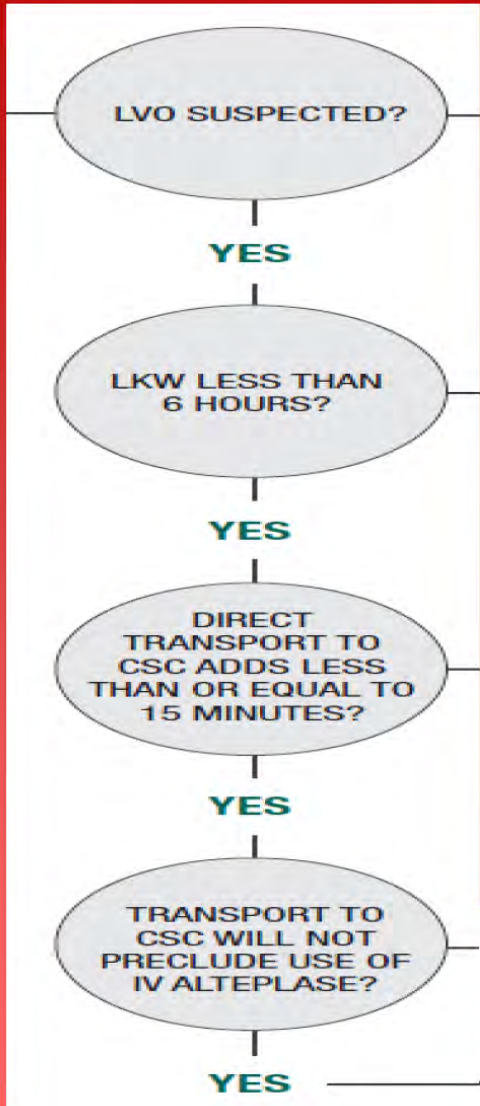
Randall Higashida, MD, FAHA, Chair*; Mark J. Alberts, MD, FAHA, Co-Chair*;
David N. Alexander, MD; Todd J. Crocco, MD; Bart M. Demaerschalk, MD;
Colin P. Derdeyn, MD, FAHA; Larry B. Goldstein, MD, FAHA;
Edward C. Jauch, MD, MS, FAHA; Stephan A. Mayer, MD, FAHA; Neil M. Meltzer, MPH;
Eric D. Peterson, MD, FAHA; Robert H. Rosenwasser, MD, FAHA; Jeffrey L. Saver, MD, FAHA;
Lee Schwamm, MD, FAHA; Debbie Summers, RN, MSN, ACNS-BC, FAHA;
Lawrence Wechsler, MD, FAHA; Joseph P. Wood, MD, JD;
on behalf of the American Heart Association Advocacy Coordinating Committee

Comprehensive Stroke Center Routing Within Regional Systems of Care

- IV TPA ineligible
  - » Direct to CSC
  - » 3.5-7 hours after onset
- IV TPA eligible
  - » Drip and ship
    - Faster IV TPA, slower cath
  - » Mothership
    - Slower IV TPA, faster cath
    - Large vessel occlusion
      - » LAMS 4-5
    - Likely hemorrhage
  - » BATmobile trip (mobile CT)
    - Fastest IV TPA, fast cath



Mission: Lifeline Stroke has developed this algorithm to help ensure the RIGHT patient is brought to the RIGHT stroke center RIGHT on time.



Go Directly to CSC IF:

Severity Screen (++)
+
LKW < 6 Hours
+
Transport to CSC Add< 15 min
+
Transport to CSC Does Not
Place Patient Outside
Thrombolysis Window

Any 'NO' then Go to Nearest/Closest Appropriate Facility Per Regional Plan

Call Stroke Alert, pre-notify receiving facility and transport directly to an appropriately certified CSC that is within the acceptable transport time, if no CSC meets the criteria then transport to the nearest designated EVT-capable center, or closest appropriate stroke center (ASRH,PSC) per your regional stroke system of care plan

Examples of Prehospital Stroke Scales to Identify LVO

- Los Angeles Motor Scale (LAMS)
  - 3 elements
  - Facial droop, arm drift, grip weakness
- 3 Item Stroke Scale (3I-SS)
  - 6 elements
  - Level of consciousness, gaze deviation, facial droop, arm drift, R/L leg weakness
- Rapid Arterial OcClusion Evaluation Score (RACE)
  - 7 elements
  - Facial droop, arm drift, R/L leg weakness, gaze deviation, aphasia, denial of hemiparesis
- Cincinnati Prehospital Stroke Severity Scale (CPSSS)
  - 4 elements
  - Gaze deviation, arm drift, LOC command, LOC questions
- Field Assessment Stroke Triage for Emergency Destination (Fast-ED)
  - 5 elements
  - Face, Arm weakness, speech, eye deviation, Denial/Neglect
- VAN
  - 3 elements
  - Vision, Aphasia, Neglect

Supported by NIH-NINDS

FAST-MAG

KISS Principle in Prehospital Care

LAMS	
Facial Droop	
Absent	0
Present	1
Arm Drift	
Absent	0
Drifts Down	1
Falls Rapidly	2
Grip Strength	
Normal	0
Weak Grip	1
No Grip	2

RACE	
Facial Palsy	
Absent	0
Mild	1
Mod-severe	2
Arm Motor Fxn	
Normal to mild	0
Moderate	1
Severe	2
Leg Motor Fxn	
Normal to mild	0
Moderate	1
Severe	2
Head + Gaze Dev	
Absent	0
Present	1
Aphasia (if right HP)	1
Normal to mild	0
Moderate	1
Severe	2
Agnosia (if left HP)	1
Normal to mild	0
Moderate	1
Severe	2

LAMS Comparable to or Better than 6 Other Proposed Prehospital LVO Scales and the Full NIHSS

LVO among All Acute Cerebral Ischemia Transports

	Sensitivity	Specificity	PPV	NPV	Accuracy
Prehospital					
LAMS	0.74	0.63	0.79	0.56	0.70
ED					
LAMS	0.63	0.79	0.85	0.53	0.69
CPSSS	0.54	0.88	0.89	0.50	0.66
FAST-ED	0.54	0.83	0.86	0.49	0.64
PASS	0.57	0.83	0.87	0.50	0.66
RACE	0.54	0.79	0.83	0.48	0.63
VAN	0.57	0.71	0.79	0.46	0.61
3i-SS	0.41	0.96	0.95	0.46	0.60
NIHSS ≥ 7	0.65	0.67	0.79	0.50	0.66
NIHSS ≥ 10	0.54	0.83	0.86	0.49	0.64

CSC-Appropriate (LVO+ICH) among All Suspected Stroke Transports

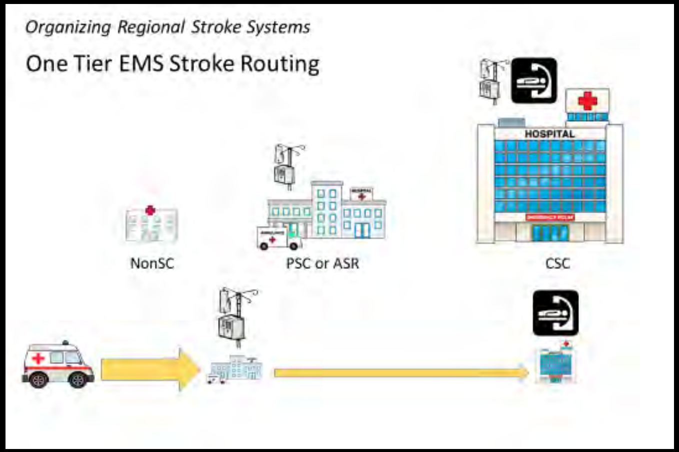
	Sensitivity	Specificity	PPV	NPV	Accuracy
Prehospital					
LAMS	0.70	0.68	0.84	0.49	0.69
ED					
LAMS	0.67	0.79	0.88	0.50	0.70
CPSSS	0.48	0.86	0.89	0.41	0.60
FAST-ED	0.53	0.82	0.88	0.43	0.62
PASS	0.55	0.82	0.88	0.43	0.63
RACE	0.56	0.79	0.86	0.43	0.63
VAN	0.59	0.71	0.83	0.43	0.63
3i-SS	0.38	0.93	0.93	0.39	0.54
NIHSS ≥7	0.71	0.68	0.84	0.50	0.70
NIHSS ≥ 10	0.56	0.82	0.88	0.44	0.64

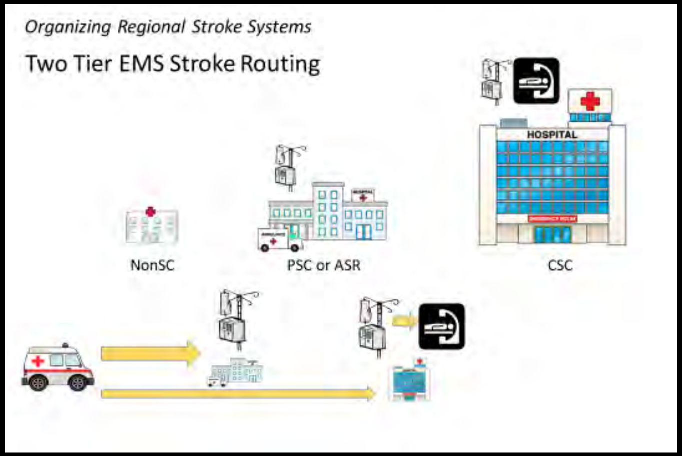
Supported by NIH-NINDS

FAST-MAG

RACECAT Trial

- Cluster-control RCT Spain
  - 12 hospitals, 1754 patients
- Key entry criteria
  - LVO by RACE and teleneurology
  - Can reach an EVT-SC within 7h of onset
- Randomized strata
  - Daytime vs evening
  - Weekday vs weekend
  - Urban vs rural
- Outcome: mRS 0-2
- Timeline: 2017-2020





Stroke physician prehospital real-time telestroke assessment of the National Institutes of Health Stroke Scale in the moving ambulance

Liman T G et al. Stroke 2012;43:2086-2090

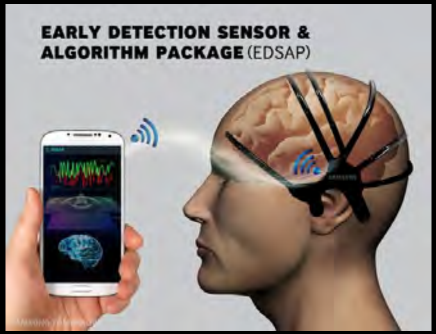
Figure 1 iTREAT ambulance setup with cradled iPad and suction mounting

American Heart Association
Learn and Live

Mobile Technologies

(other than CT)

- Ultrasound
  - » Burl – Sonas
  - » Neural Analytics
- EEG
  - » Samsung – EDSAP
- Near infra-red
  - » B+W Tek – i-Spec
- Microwave
  - » Australia - Strokefinder helmet



Acute Ischemic Stroke Treatment 1.0:
IV TPA and Moderately Effective Endovascular Therapy


Symptoms


911


EMS

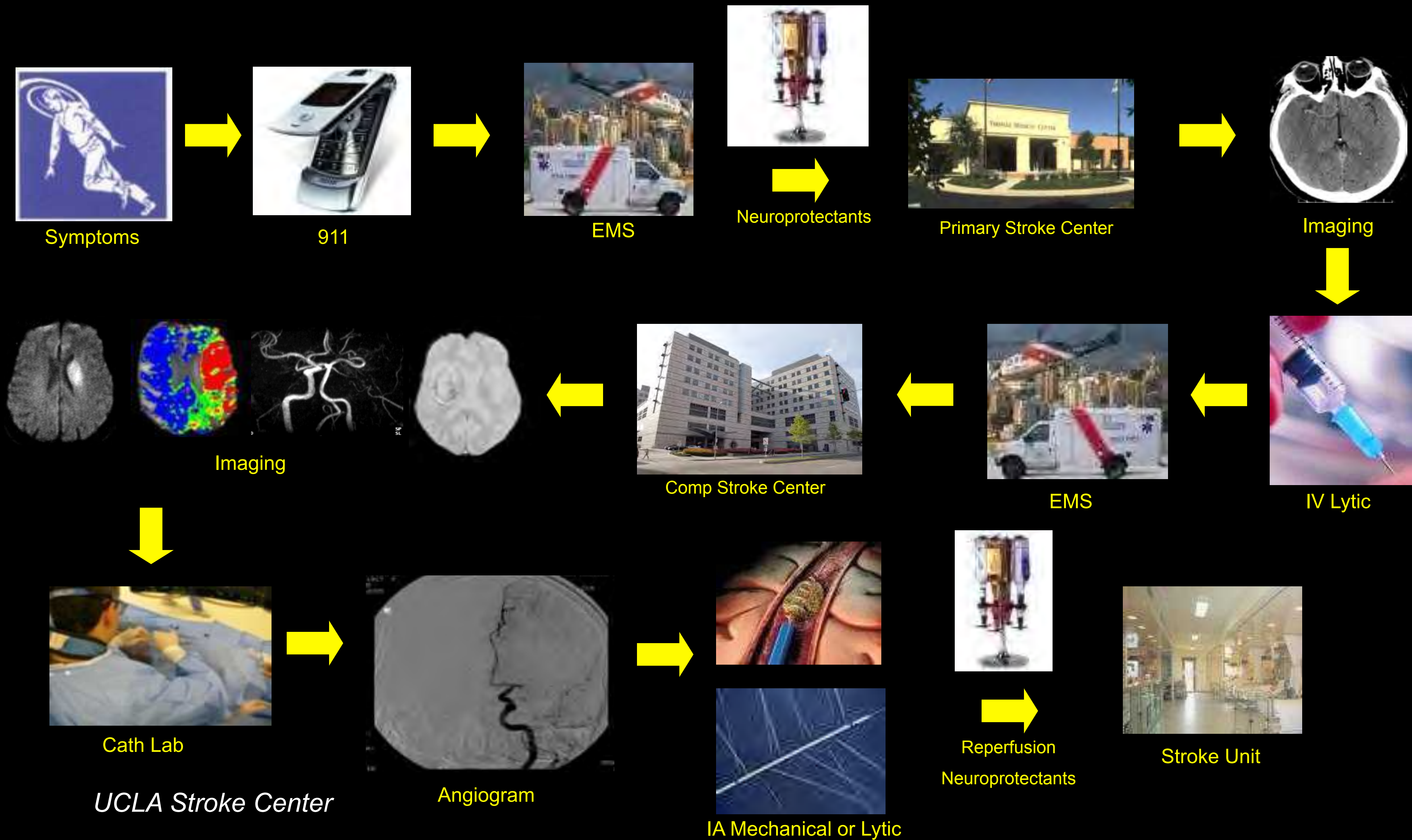

Primary Stroke Center


Imaging

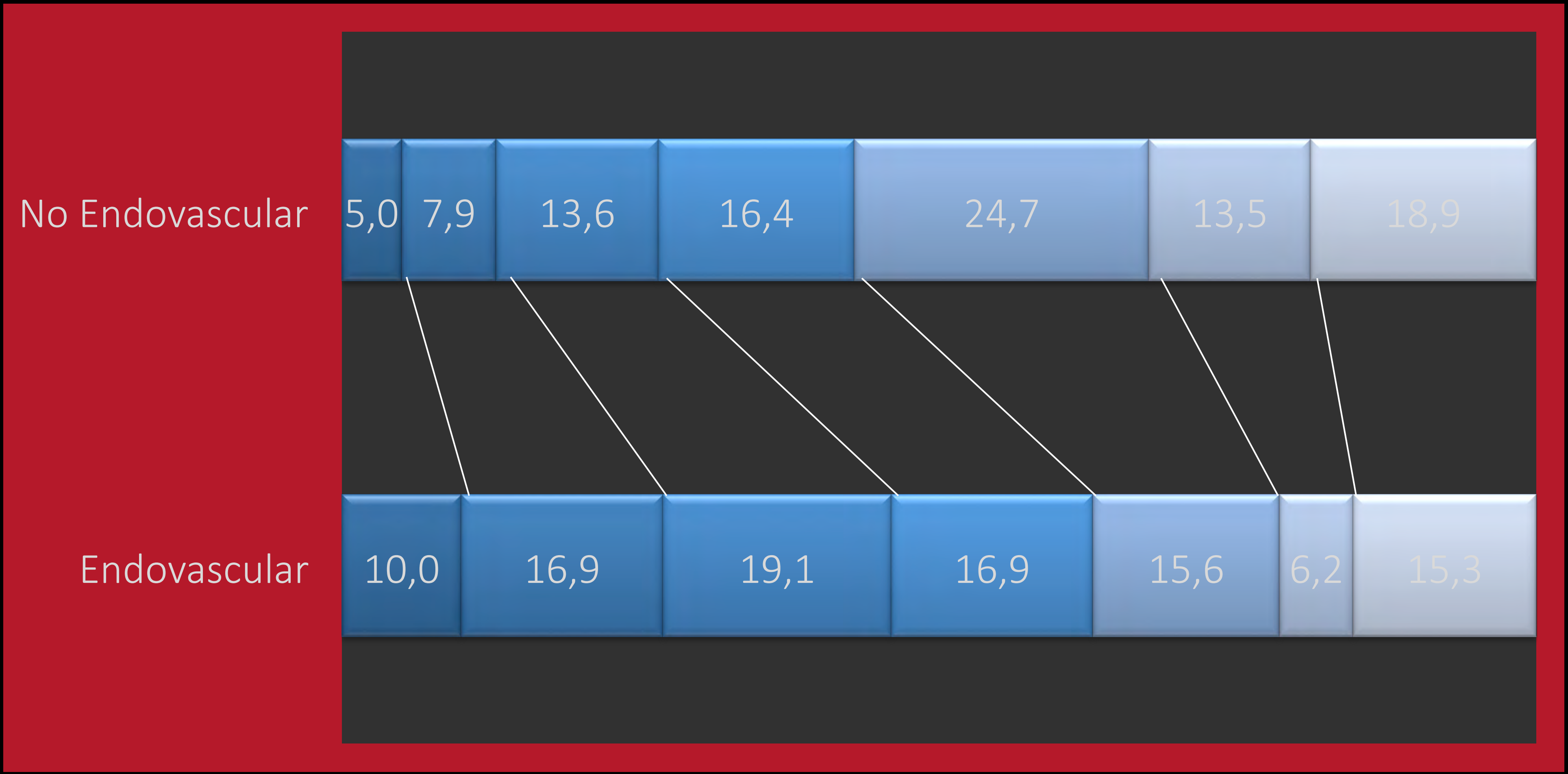

IV Lytic

UCLA Stroke Center

Acute Ischemic Stroke Treatment 2.0:
Highly Effective Recanalization - Fast and Furious



Are We Done Yet?
Second Generation Neurothrombectomy Therapy
Outcome Across All Disability Levels (5 Trials – HERMES)



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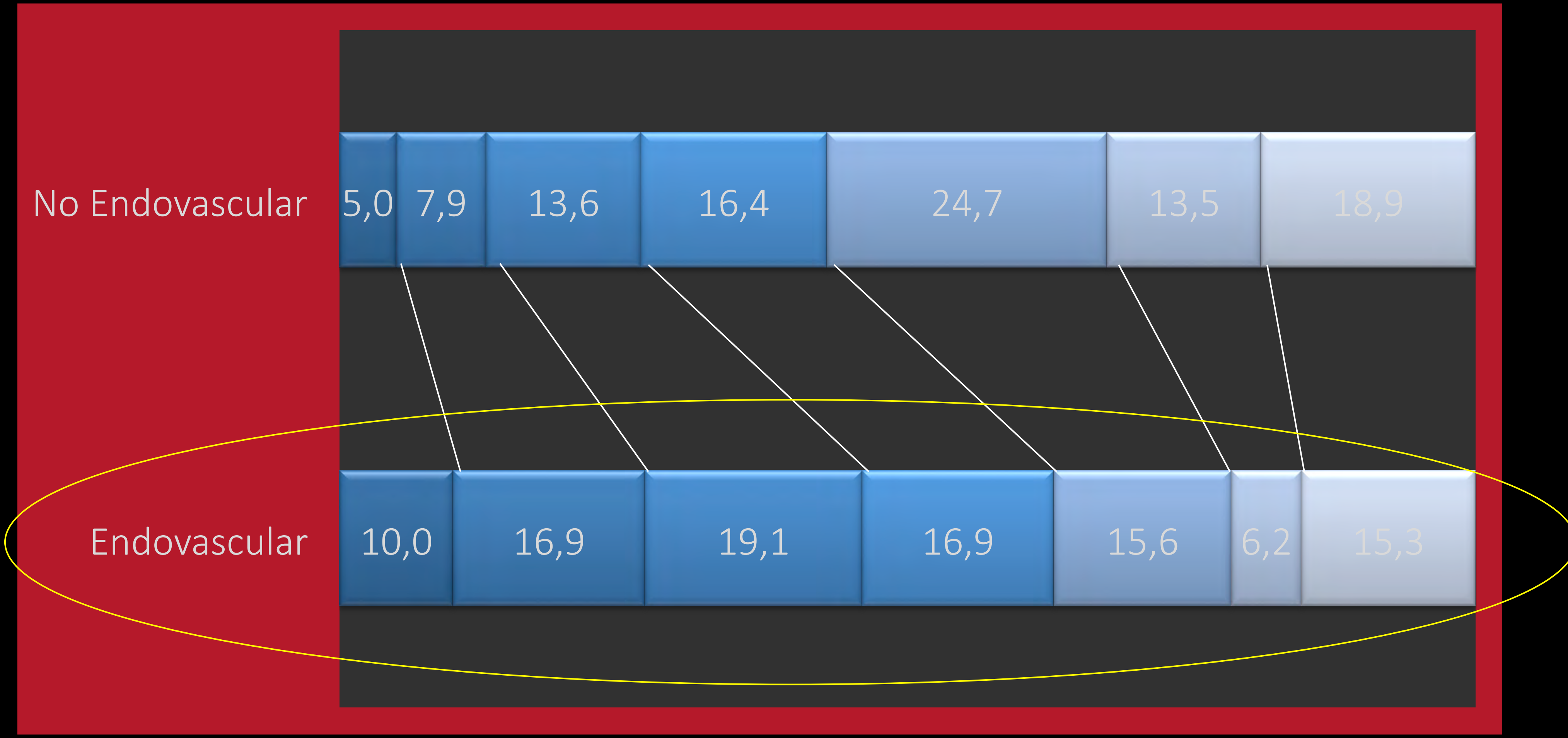

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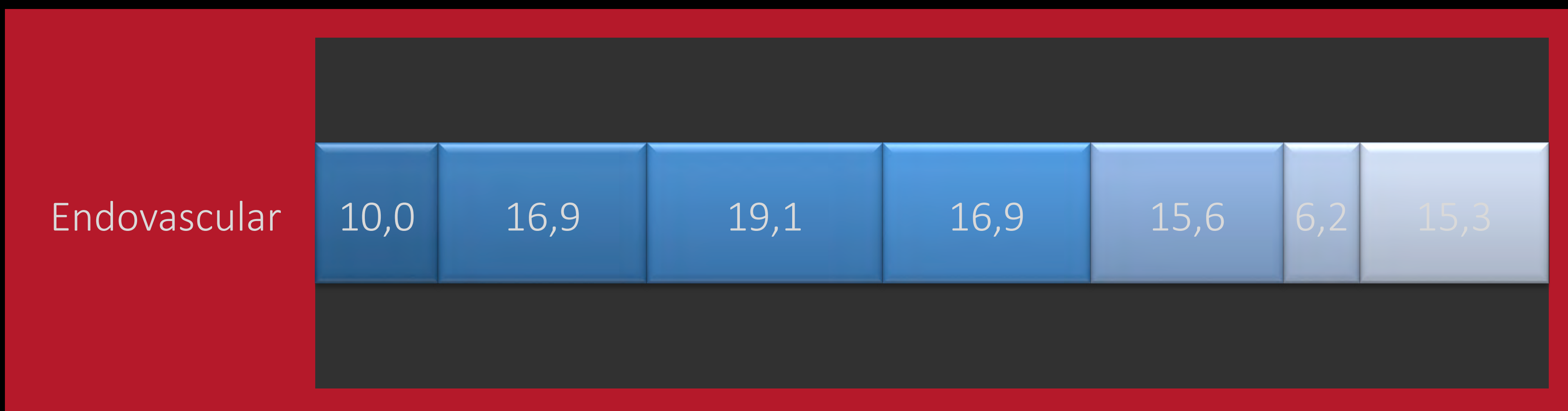

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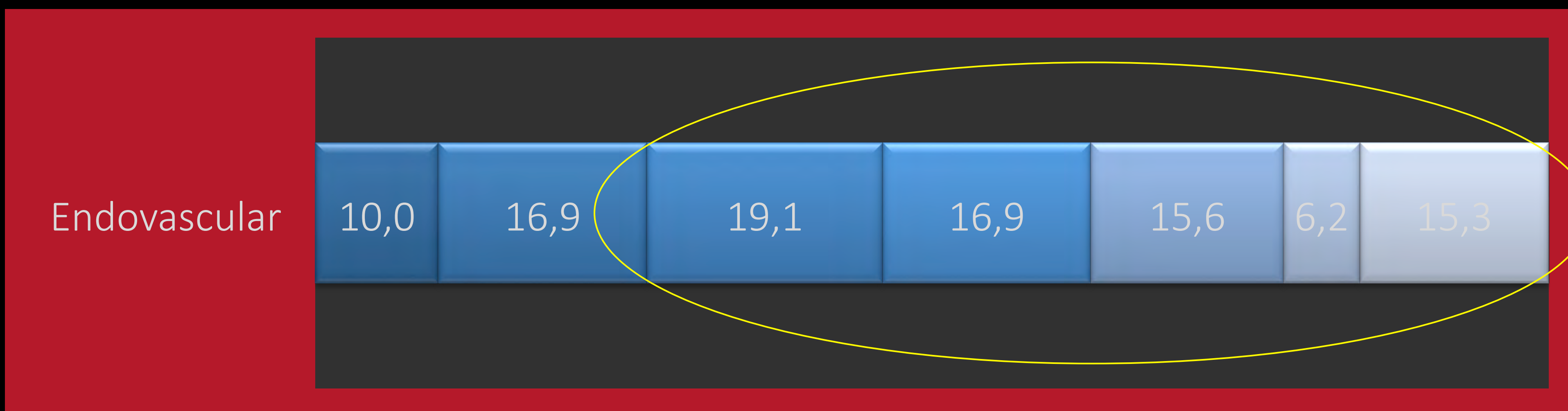

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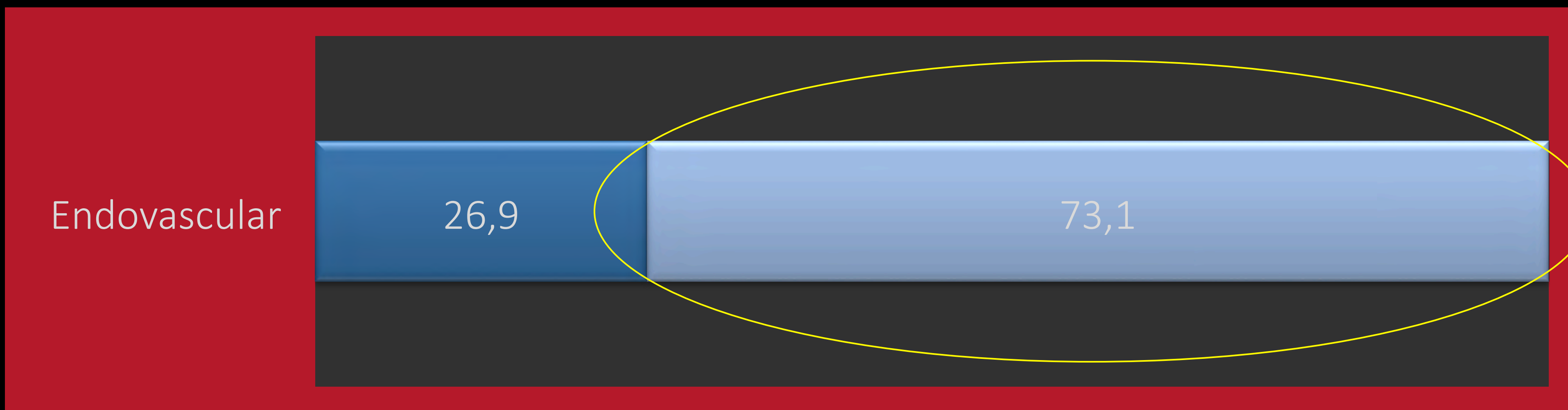

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What Do We Need

- More REPERFUSION
- More SALVAGEABLE BRAIN
- Less BLEEDING
- More PATIENTS

What Do We Need

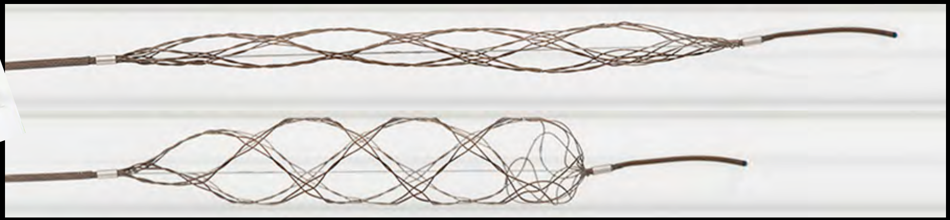
- More REPERFUSION
  - » Better devices
  - » Better combinations of lytics and devices
- More SALVAGEABLE BRAIN
  - » Preprocedure neuroprotection / collateral enhancement
  - » Faster onset to puncture
    - Hospital processes of care
    - EMS systems of care
- Less BLEEDING
  - » Skip tPA (?)
  - » Deter reperfusion injury
- More PATIENTS
  - » Expand time window with standard selection
  - » Expand time window with imaging selection

Building Next Generation of Clinical Trials that Will Positively Impact an Emerging Field

Intervention Type	Special Trial Aspects	Example Comparisons	Target Patients
New Devices	TICI reperfusion as primary surrogate endpoint	Device A vs B	Large artery occlusions
Reperfusion Strategies	Active Comparator	IVT+ERT vs ERT alone	ICA occlusions
		IVT+ERT vs IVT alone	M2 occlusions
Prehospital Neuroprotection	ED imaging endpoints	NA1, hypothermia, RIPC, NTG vs control	EMS transported patients
Systems of Care	Cluster randomization; stepped wedge	EMS routing – PSCs first versus CSCs first	Severe deficits
Deter Reperfusion Injury	IA admin	Free radical scavengers vs control	Post-successful TICI 2b/3 reperfusion
Imaging Selection	6-24h	ERT vs no ERT	Wake-up and late

Improved Reperfusion Rates via Novel Devices

- Retrievers
  - » Solitaire (Medtronic)
  - » Trevo (Stryker)
  - » Catch (Balt)
  - » Preset (Phenox)
  - » EmboTrap (Neuravia)
  - » Separator 3D (Penumbra)
  - » Revive (Codman)
  - » Mindframe (Medtronic)
  - » Golden (Amnis)
  - » Tigertriever (Rapid Medical)
- Aspiration catheters
  - » Max ACE (Penumbra)
  - » Arc (Medtronic)
  - » SOFIA (Microvention)
  - » Cat-6 (Stryker)



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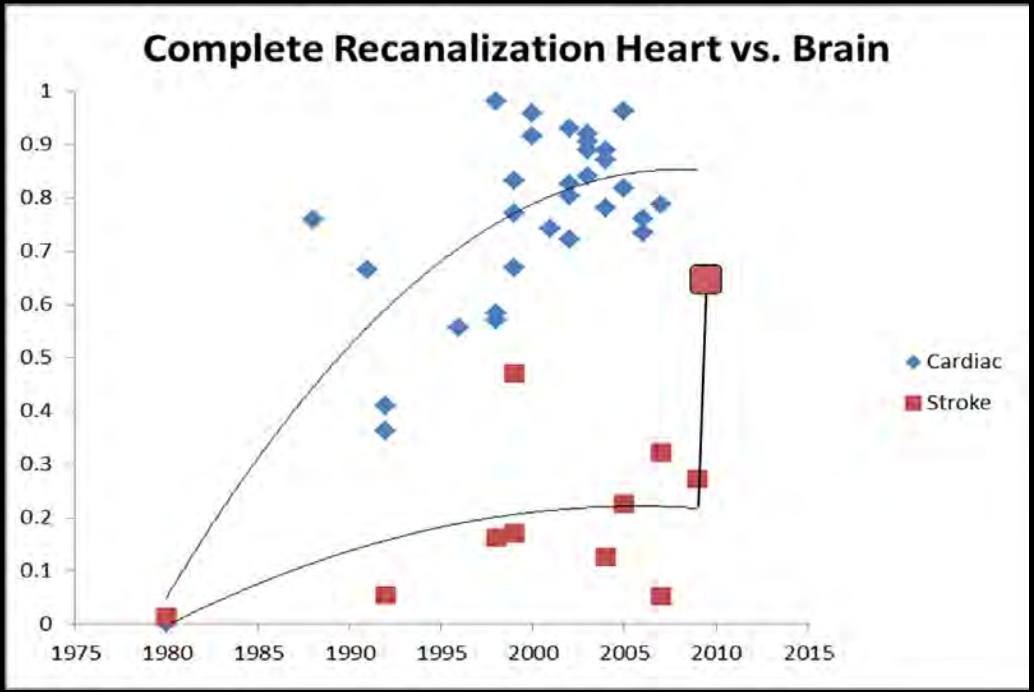

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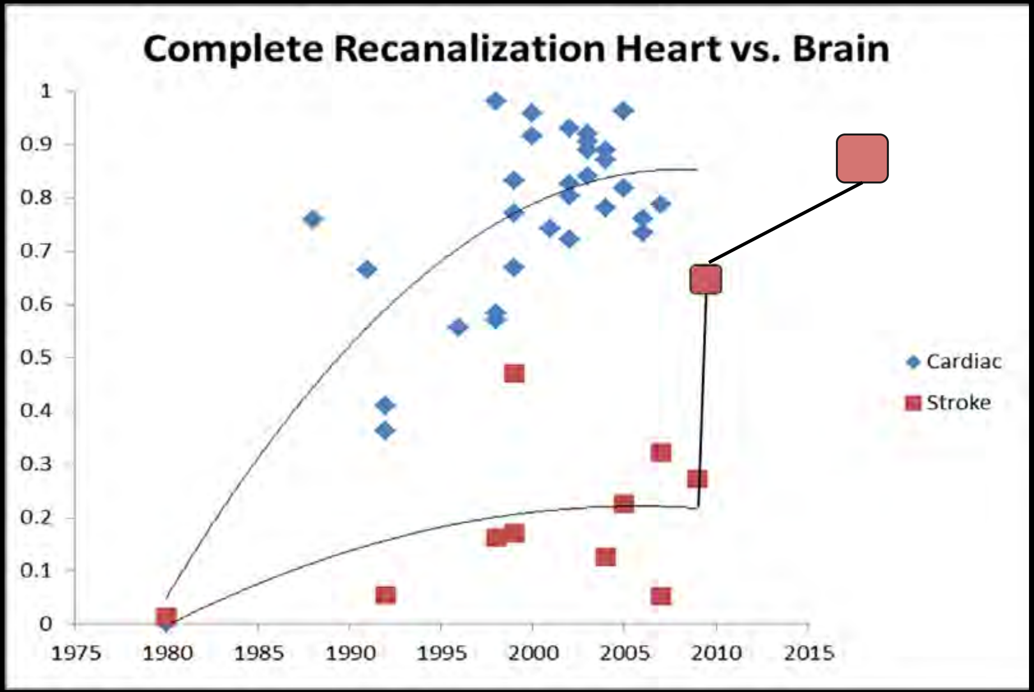

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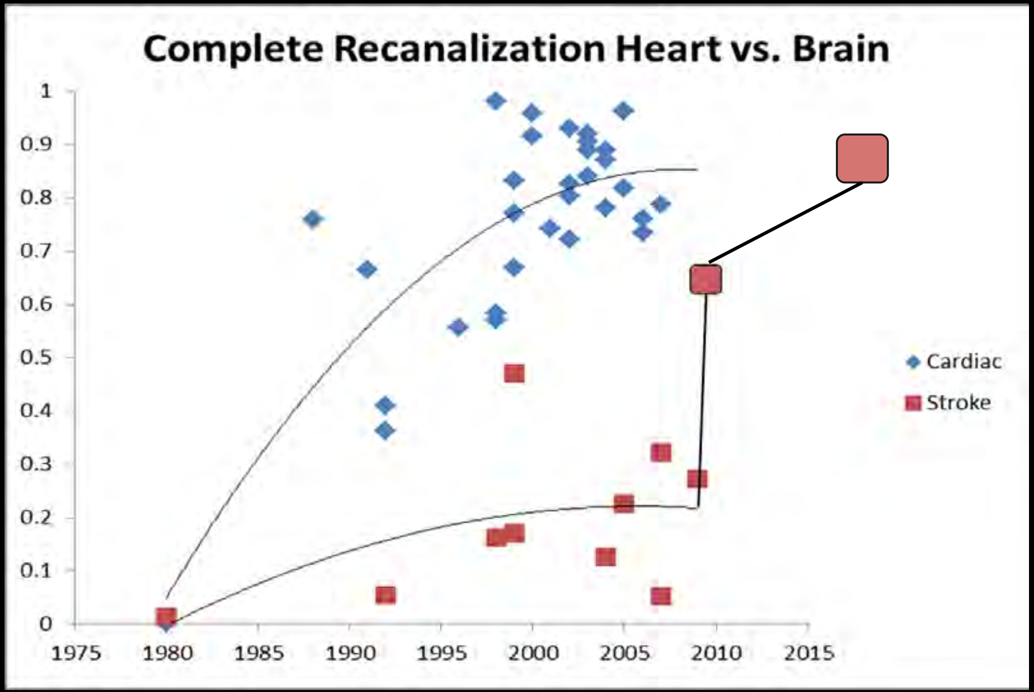

- LVO
- MVO - M2, M3/4, P1/2 PCA, A1/2 ACA

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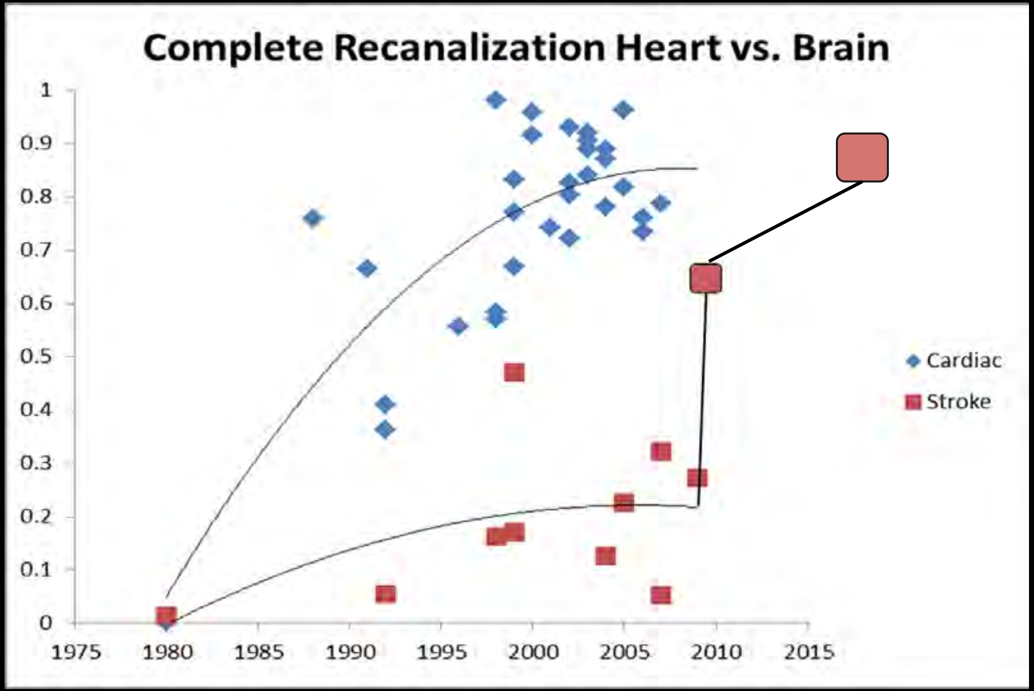

<u>Trials</u>

ARISE II

ASTER / Penumbra 3D / COMPASS

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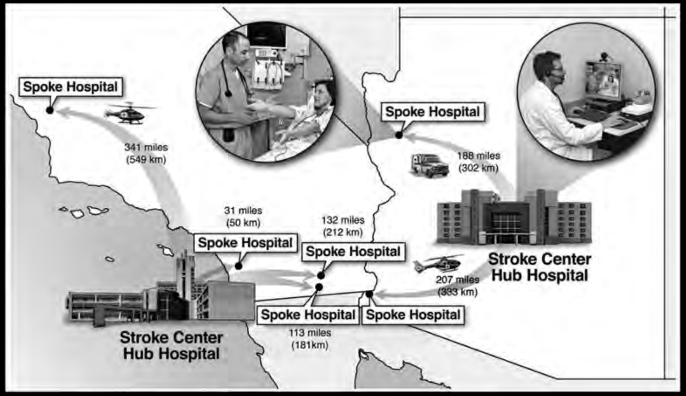
Neuroprotective Trial Designs in the Thrombectomy Era

NP in the Ambulance

FAST-MAG	Number of Patients	NP to Reperf Tx Start Time
IV tPA	452 (27%)	1h 32m
EVT	76 (5%)	3h 50m

NP during Hosp Tx



- Enroll at PSCs, ASRHs
  - » Tele-enrollment
- NP infusion during interval from OSH to endovascular hospital
- “Drip, ship, NiP, and grip”

NP Door to Reperf

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<u>Trials</u>

RIGHT-2

ESCAPE NA1

Give or Skip IV tPA

Pro Combination

- Faster reperfusion
  - Faster start of IV Rx - faster reperfusion in IV responders
  - Increased first-pass response
- More reperfusion
  - Higher ERT reperfusion rate
  - Reperfusion in ERT non-deployable pts
  - High IV Rx reperfusion in EMVO
- Cleaner distal vessels
  - Dissolve distal thrombus fragments from ERT
- Target occlusion characterization
  - Reveal *in situ* athero

Against Combination

- Slower reperfusion
  - Consent and set-up of IV Rx may slow start of ERT
- Little additional reperfusion
  - Low IV Rx reperfusion in ELVO
- More hemorrhage
- Higher cost

Give or Skip IV tPA

Pro Combination

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<u>Trials</u>

MR CLEAN Family

SWIFT Direct

"The outcome of any serious research can only be to make two questions grow where only one grew before" (Veblen)

Intervention Type	Special Trial Aspects	Example Comparisons	Target Patients
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Judy Guzy, RN
Ileana Grunberg, RN
Rodel Aflonso, RN

Stroke Fellows and Residents

UCLA Stroke Center

UCLA Ronald Reagan Medical Center