ENDOVASCULAR ACUTE STROKE THERAPY: INTEGRATING IMAGING INTO TREATMENT DECISIONS

TUDOR G. JOVIN, M.D.

ASSOCIATE PROFESSOR OF NEUROLOGY AND NEUROSURGERY

DIRECTOR, UPMC STROKE INSTITUTE

DIRECTOR UPMC CENTER FOR NEUROENDOVASCULAR THERAPY

UNIVERSITY OF PITTSBURGH MEDICAL CENTER

DISCLOSURES

Consultant/Advisory Board: Ownership Interest: Silk Road Medical – modest

Consultant/Advisory Board: Covidien/Medtronic: unpaid

Consultant: Stryker Neurovascular unpaid

PI: REVASCAT (Fundacio Ictus Malaltia Vascular), unpaid

PI: DAWN (Stryker Neurovascular), unpaid

UPMC Stroke Institute

ROLE OF IMAGING IN SELECTION FOR ACUTE STROKE REPERFUSION THERAPIES IN THE HYPERACUTE TIME WINDOW (0-6 hours)

- **Rule out** hemorrhage

- **Rule out** absence of occlusion

- **Rule out** large core

- **Rule out** absence or small of "at risk" tissue

MAIN ROLE OF IMAGING IS TO EXCLUDE PATIENTS FROM TREATMENT !!!

Ischemic Penumbra
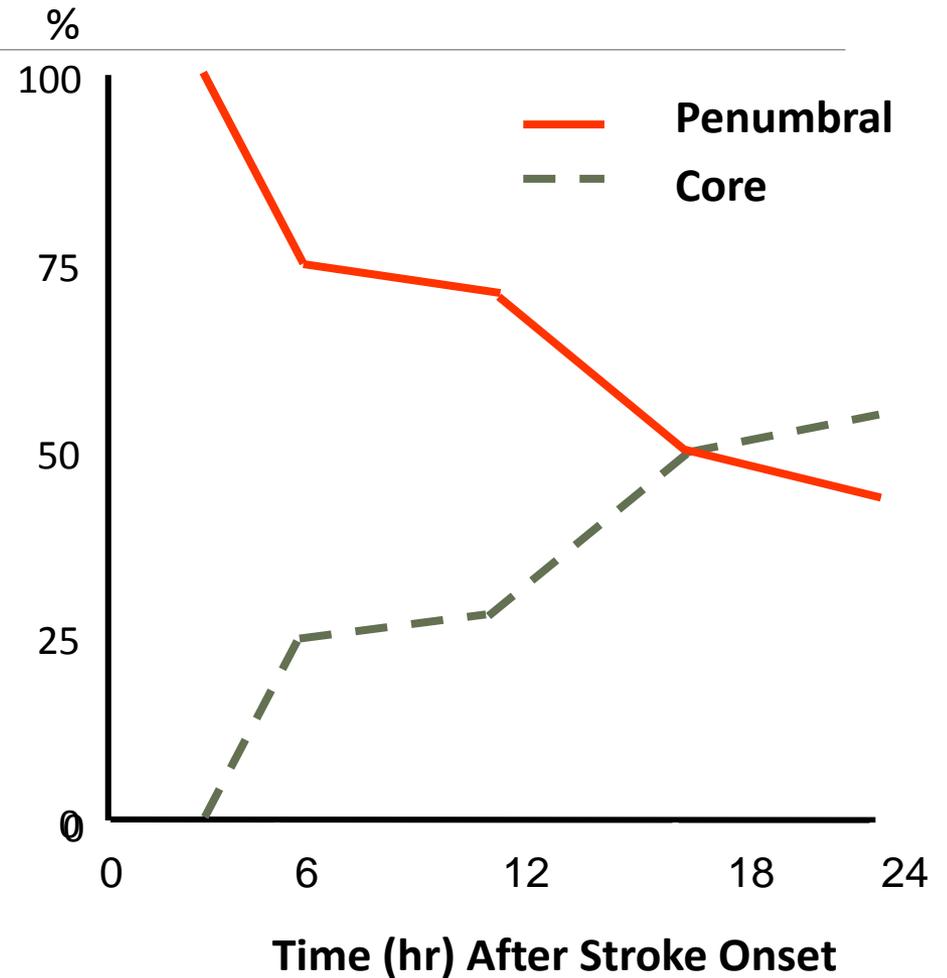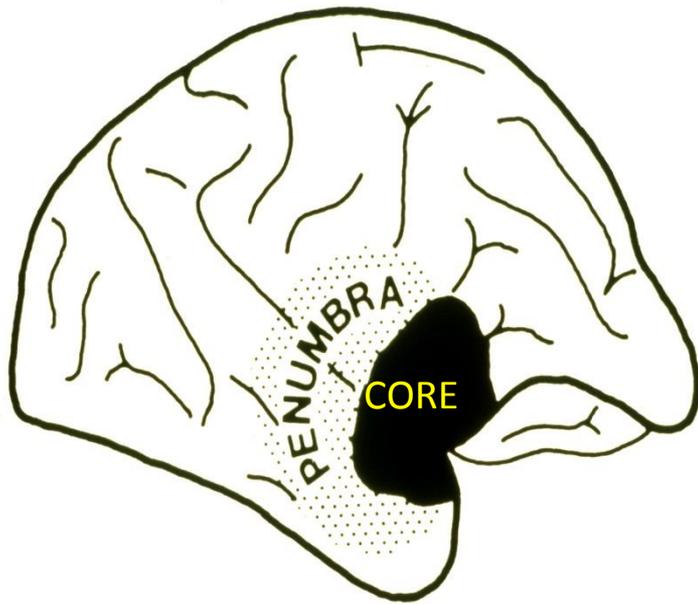
Initial Growth Rate: Known Onset & M1 Occlusion

Wheeler HM, et al. Int J Stroke. 2015

Initial Growth Rate: Known Onset & M1 Occlusion

Baseline DWI Volume (ml)

Time between Symptom Onset and Baseline MRI (hrs)
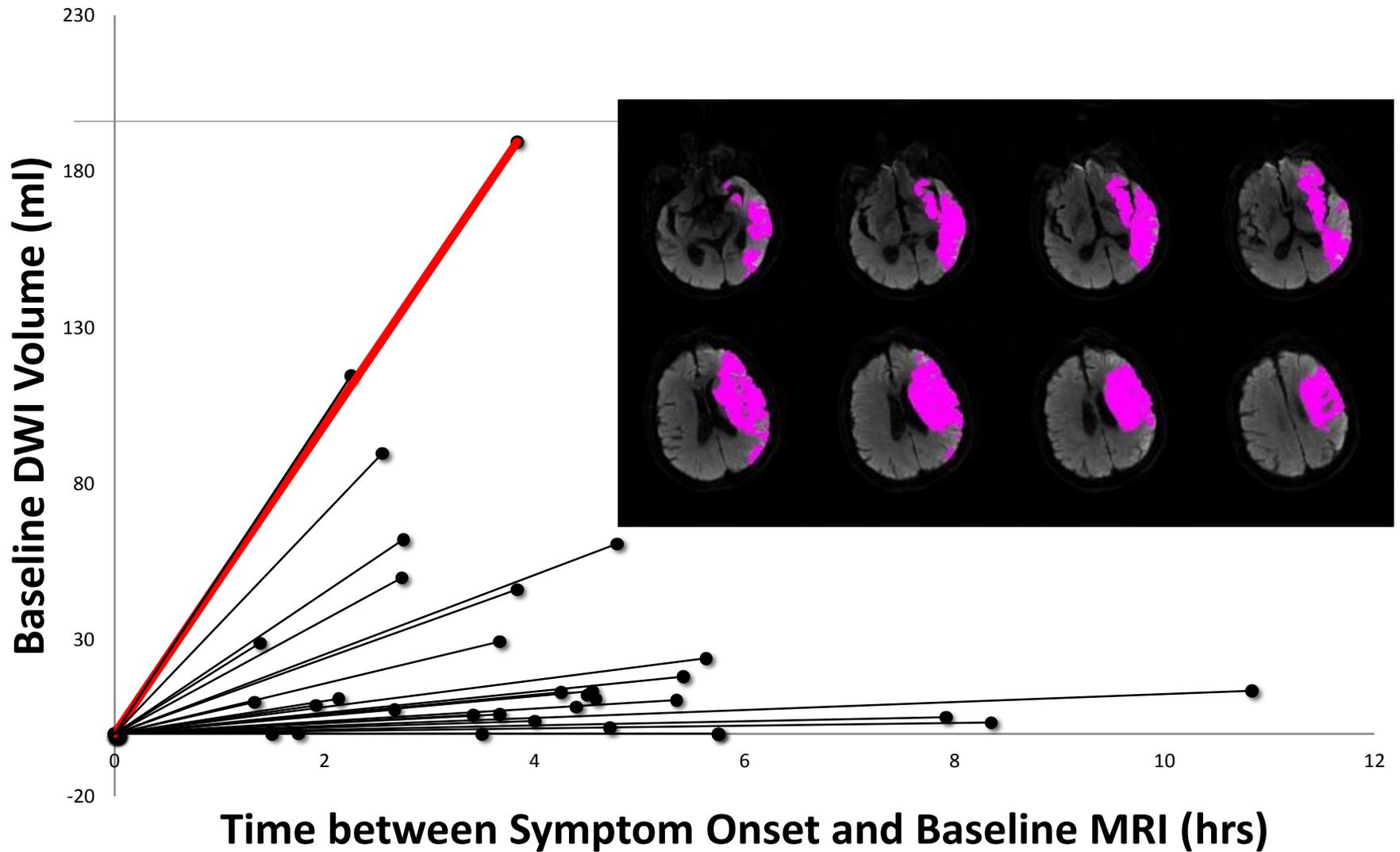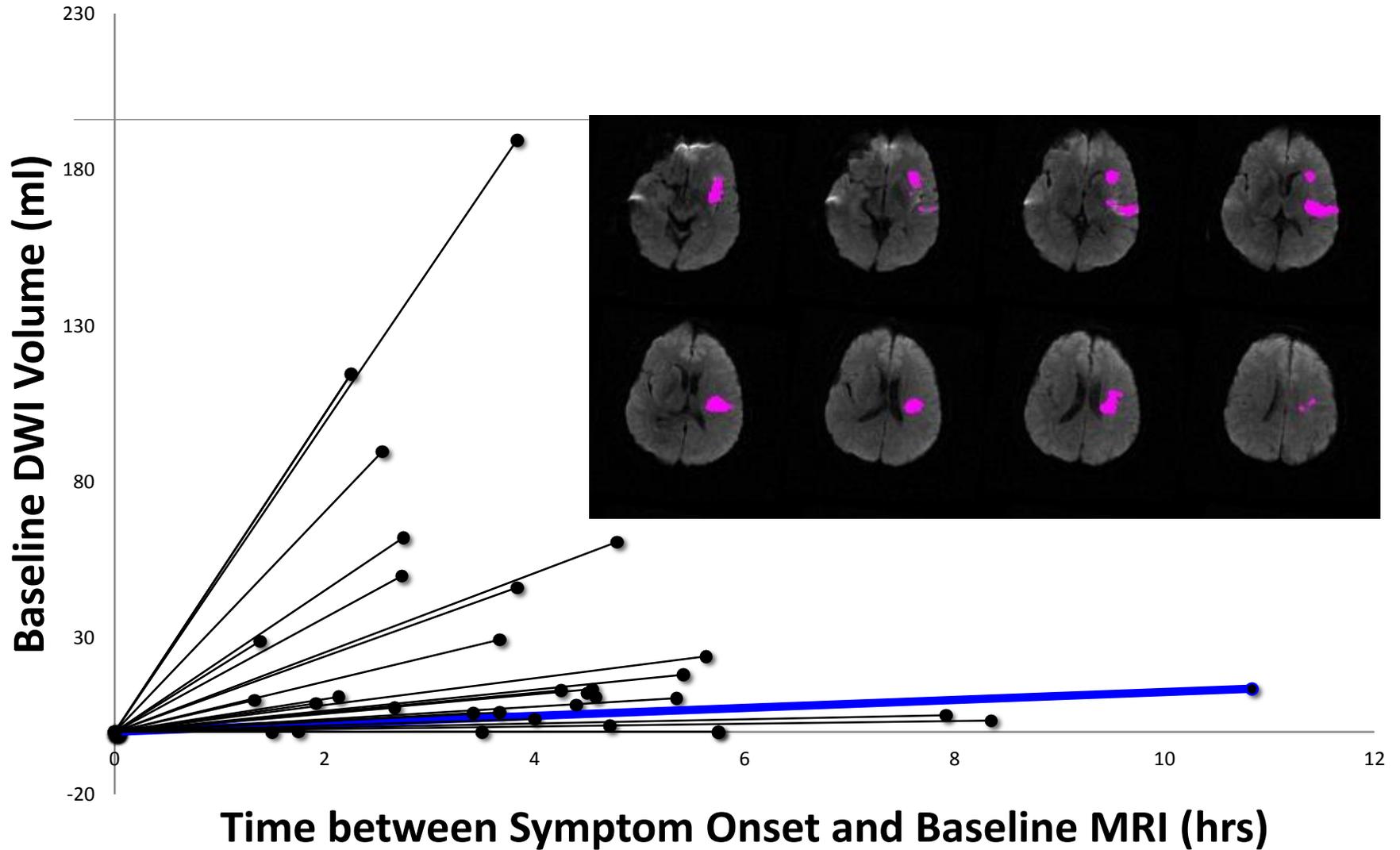
SELECTION FOR REPERFUSION IN PATIENTS WITH LARGE VESSEL OCCLUSION

Likely to Benefit	Unlikely to Benefit
Small core	Any size core (usually large)
Large penumbra	Small penumbra
MISMATCH	NO MISMATCH

IMS 3 — 24 hour infarct volume by 90 days mRS categories

* Median 24 hr volume   P < 0.0001 by ANOVA   Jovin et al., ISC 2015
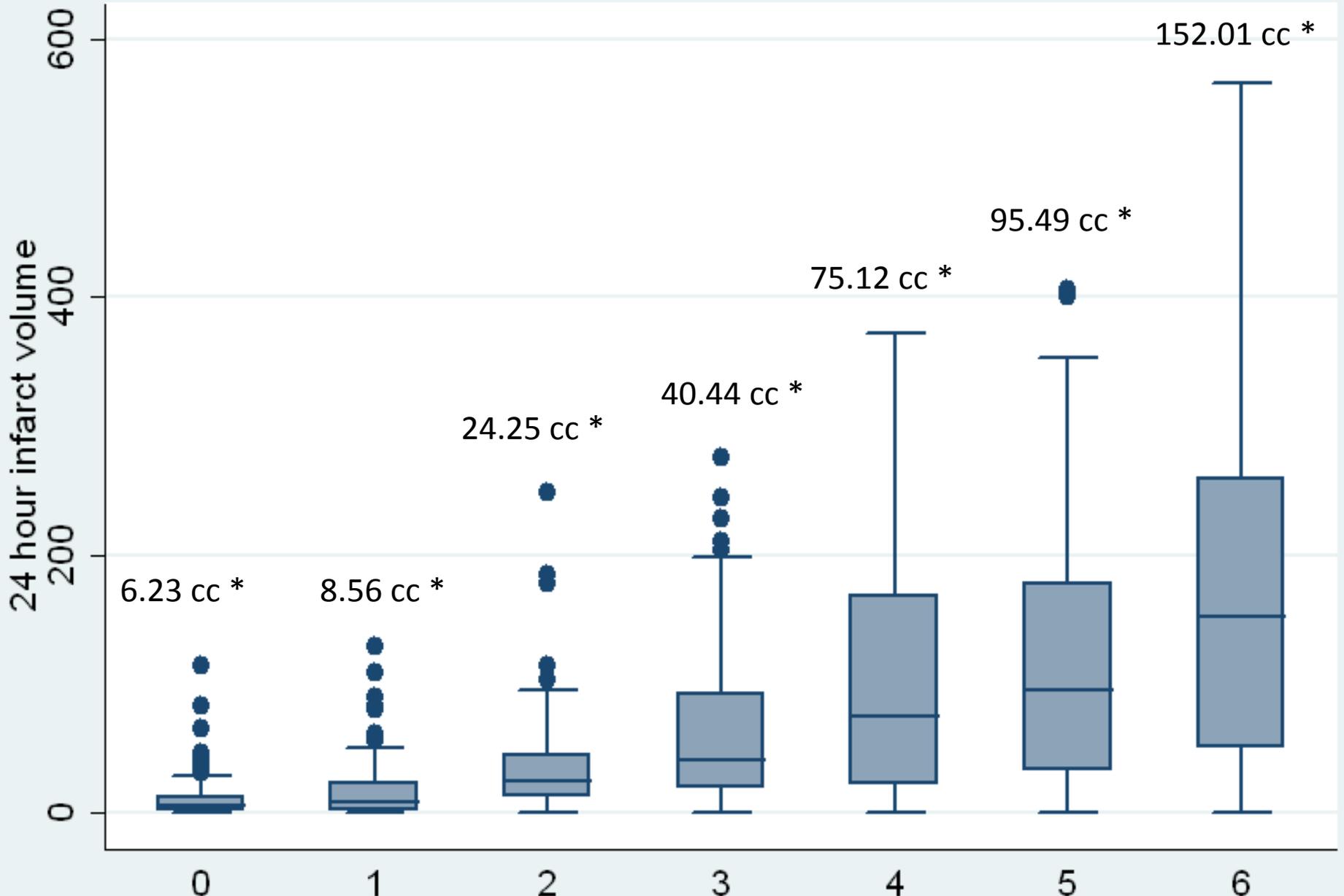
# PRE-TREATMENT ISCHEMIC CORE A POWERFUL DETERMINANT OF OUTCOME IN ACUTE STROKE

- CT based (ASPECTS), Hill et al., Stroke 2003

- CTP based (CBV), Lev at al., Stroke 2001

- Xenon-CT-CBF based (core voxels), Jovin et al, Stroke 2003

- MRI based (DWI), Yoo et al., Stroke 2009 (DWI cutoff of 70 cc's predicts poor outcome)

- MRI based (DWI), Parsons et. al, Journal Cereb Blood Metab 2010 (DWI cut off 25 cc)

ASPECTS Score and Infarct Core
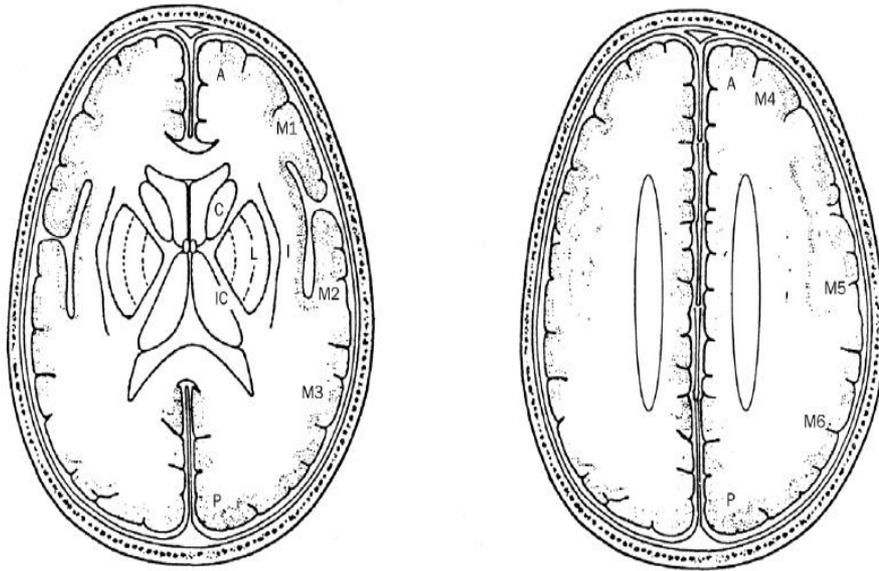
Figure 1: **ASPECTS study form**

A=anterior circulation; P=posterior circulation; C=caudate; L=lentiform; IC=internal capsule; I=insular ribbon; MCA=middle cerebral artery; M1=anterior MCA cortex; M2=MCA cortex lateral to insular ribbon; M3=posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia.

Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5, and M6).

Barber et al., Lancet 2002
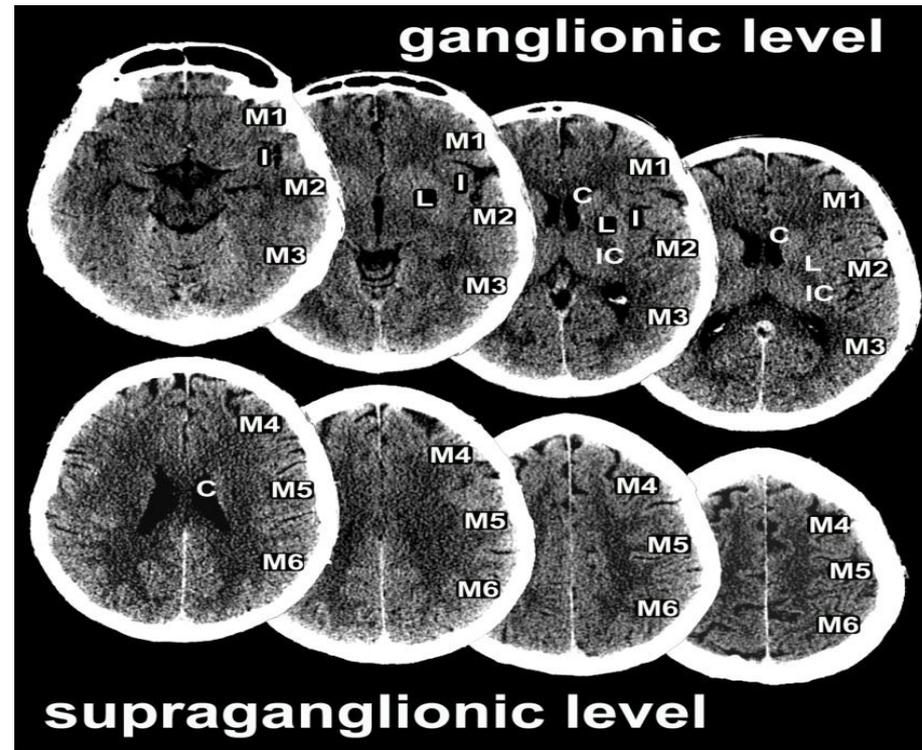
CLINICAL EXAM (NIHSS): A GOOD ESTIMATION OF THE AT RISK TERRITORY ??

The clinical–DWI mismatch

A new diagnostic approach to the brain tissue at risk of infarction

A. Dávalos, MD, PhD; M. Blanco, MD, PhD; S. Pedraza, MD; R. Leira, MD, PhD; M. Castellanos, MD; J.M. Pumar, MD, PhD; Y. Silva, MD; J. Serena, MD, PhD; and J. Castillo, MD, PhD

Abstract—*Objective:* To evaluate the usefulness of a mismatch between the severity of acute clinical manifestations and the diffusion-weighted imaging (DWI) lesion in predicting early stroke outcome and infarct volume. *Methods:* One hundred sixty-six patients with a hemispheric ischemic stroke of <12 hours' duration were studied. The NIH Stroke Scale (NIHSS) score and the volume of DWI lesion were measured on admission and at 72 ± 12 hours. Infarct volume was measured on T2-weighted or fluid-attenuated inversion recovery images at day 30. Early neurologic deterioration (END) was defined as an increase of ≥ 4 points between the two NIHSS evaluations. Thirty-eight patients received IV thrombolysis or abciximab. Clinical–DWI mismatch (CDM) was defined as NIHSS score of ≥ 8 and ischemic volume on DWI of ≤ 25 mL on admission. The adjusted influence of CDM on END, DWI lesion enlargement at 72 hours, and infarct growth at day 30 was evaluated by logistic regression analysis and generalized linear models. *Results:* CDM was found in 87 patients (52.4%). Patients with CDM had a higher risk of END than patients without CDM because NIHSS < 8 (odds ratio [OR], 9.0; 95% CI, 1.9 to 42) or DWI lesion > 25 mL (OR, 2.0; 95% CI, 0.8 to 4.9). CDM was associated with an increase of 46 to 68 mL in the mean volume of DWI lesion enlargement and infarct growth in comparison with non-CDM. All the effects were even greater and significant in patients not treated with reperfusion therapies. *Conclusions:* Acute stroke patients with an NIHSS score of ≥ 8 and DWI volume of ≤ 25 mL have a higher probability of infarct growth and early neurologic deterioration. The new concept of CDM may identify patients with tissue at risk of infarction for thrombolytic or neuroprotective drugs.

SWIFT PRIME: Infarct Prediction using RAPID

RAPID ischemic core and hypoperfusion volumes predicted infarct size

→ Baseline core predicts infarct volume in reperfusers

→ Baseline hypoperfusion predicts infarct in non-reperfusers

→ Malignant profile predicts infarct growth despite reperfusion

Albers GW, et al. In press, Annals of Neurology
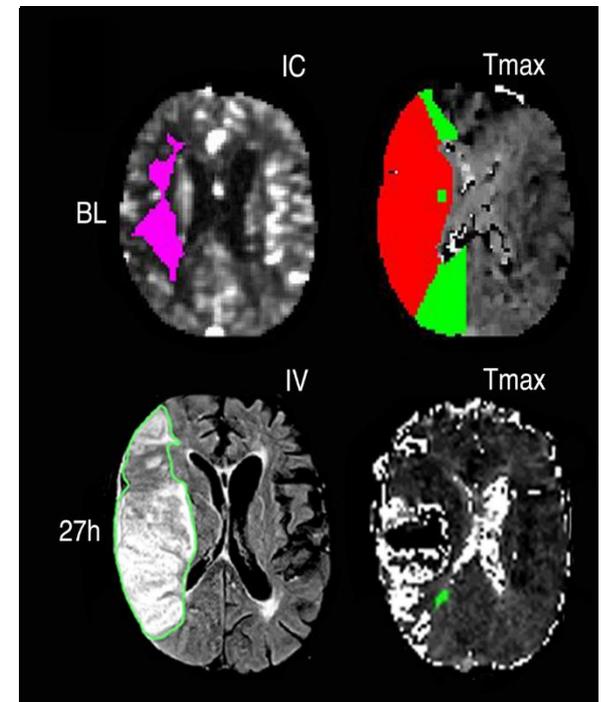
CT VS CTP AS SELECTION TOOL FOR ENDOVASCULAR THERAPY- A MULTICENTER STUDY

N=338 patients from 7 US centers

Mean age 67, mean NIHSS 18

Occlusion location: 248 (73%) M1, 55 (17%) ICA terminus, 35 (10%) M2

sICH rates: CTP vs CT 6.8% vs. 6.6%, p=0.82

Good outcomes: CTP vs. CT 36.5% vs. 38.9%, p=0.72

Final infarct volume: 80±64 cm^3 vs. 88±62 cm^3, p=0.32

CT acquisition to groin puncture times: 132±57 mins. vs. 97±60 mins., p=0.01

CT acquisition to reperfusion times: 227±109 mins. vs. 199±91 mins., p<0.001

Gupta et al., JNIS 2012

Median TIMES across recent trials (min median)

	ESCAPE	SWIFT PRIME	REVASCAT
Imaging to puncture	50	63	68
Imaging to perfusion	82	100	138
Onset to puncture (MR CLEAN 260)	180	224	270
Onset to perfusion (IMS 325)	213	268	356
Door to groin	89	95	109

# WHAT IS THE PRICE WE PAY FOR THE ADDITIONAL TIME REQUIRED FOR IMAGING ???
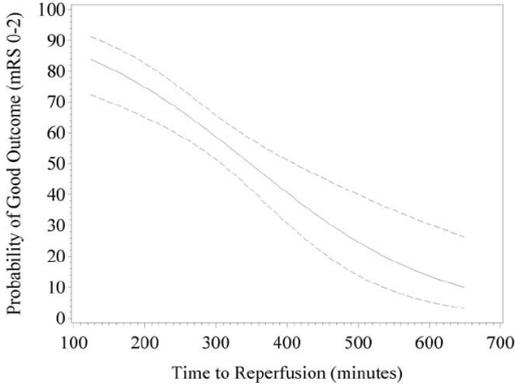
FIGURE 3: Predicted probability and confidence interval of good neurological outcome (mRS 0–2) at 90 days from logistic regression with time as a continuous variable. Probability of mRS 0 to 2 is plotted against onset to recanalization. Dashed lines demonstrate 95% confidence intervals. mRS = modified Rankin Scale.
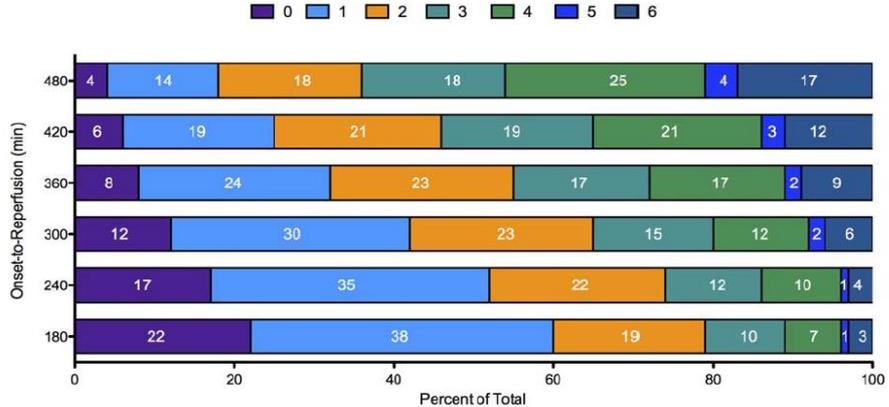

FIGURE 4: Predicted 90-day mRS outcomes from adjusted ordinal logistic regression. Stacked bar graphs represent the predicted mRS outcome distributions for each incremental 60-minute change in onset-to-reperfusion time, beginning with 180 minutes. Numbers within each colored region represent the percentage of patients with the corresponding mRS outcome grade for that time window. mRS = modified Rankin Scale. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 4. Benefit Associated With Every 15-Minute Acceleration of Substantial Reperfusion

	Number Needed to Treat	Benefit Per Thousand Treated
For transitions across multiple mRS levels		
All seven levels (0, 1, 2, 3, 4, 5, 6)	30	34
Best six levels (0, 1, 2, 3, 4, 5/6)	30	34
For individual dichotomizations of the mRS		
0 vs. 1–6	104	10
0–1 vs. 2–6	48	21
0–2 vs. 3–6	46	22
0–3 vs. 4–6	58	17
0–4 vs. 5–6	115	9
0–5 vs. 6	140	7
mRS = modified Rankin Scale.		

SWIFT AND STAR, N=202

Sheath et al., Ann Neurol 2015

REVASCAT :OUTCOMES BY CTP/MRI vs NO CTP/MRI

REVASCAT

FUNDACIÓ ICTUS
MALALTIA VASCULAR

1 mRS by CTP or MRI					
		CTP or MRI		Not CTP and MRI	
		Intervention	**Control**	**Intervention**	**Control**
mRS					
Total no-missing	n	31	33	72	70
0-2	n (%)	14 (45.2%)	10 (30.3%)	31 (43.1%)	19 (27.1%)
3-6	n (%)	17 (54.8%)	23 (69.7%)	41 (56.9%)	51 (72.9%)
Missing	n	0	0	0	0

14.9%   16%

Logistic Regression mRS 0-2 (OR 95%) / CMH			
	OR (95% CI) for mRS 0-2	OR IC 95% for mRS 0-2 CMH	OR (95% CI) shift analysis
Variables			
Treatment (Exp vs Med)	1.985 (1.111 – 3.546)	1.985 (1.112 -3.546)	1.685 (1.032 – 2.751)
CTP or MRI (No vs Yes)	0.889 (0.487 – 1.654)		1.158 (0.684 - 1.963)

IMAGING BASED EXCLUSION AND TREATMENT EFFECT
Absolute difference between groups in mRS 0-2

%

EXTEND IA[2] NNT=3

SWIFT PRIME[3] NNT=4

ESCAPE[1] NNT=4

† ‡

REVASCAT [5] NNT=6

MR CLLEAN[4] NNT=8
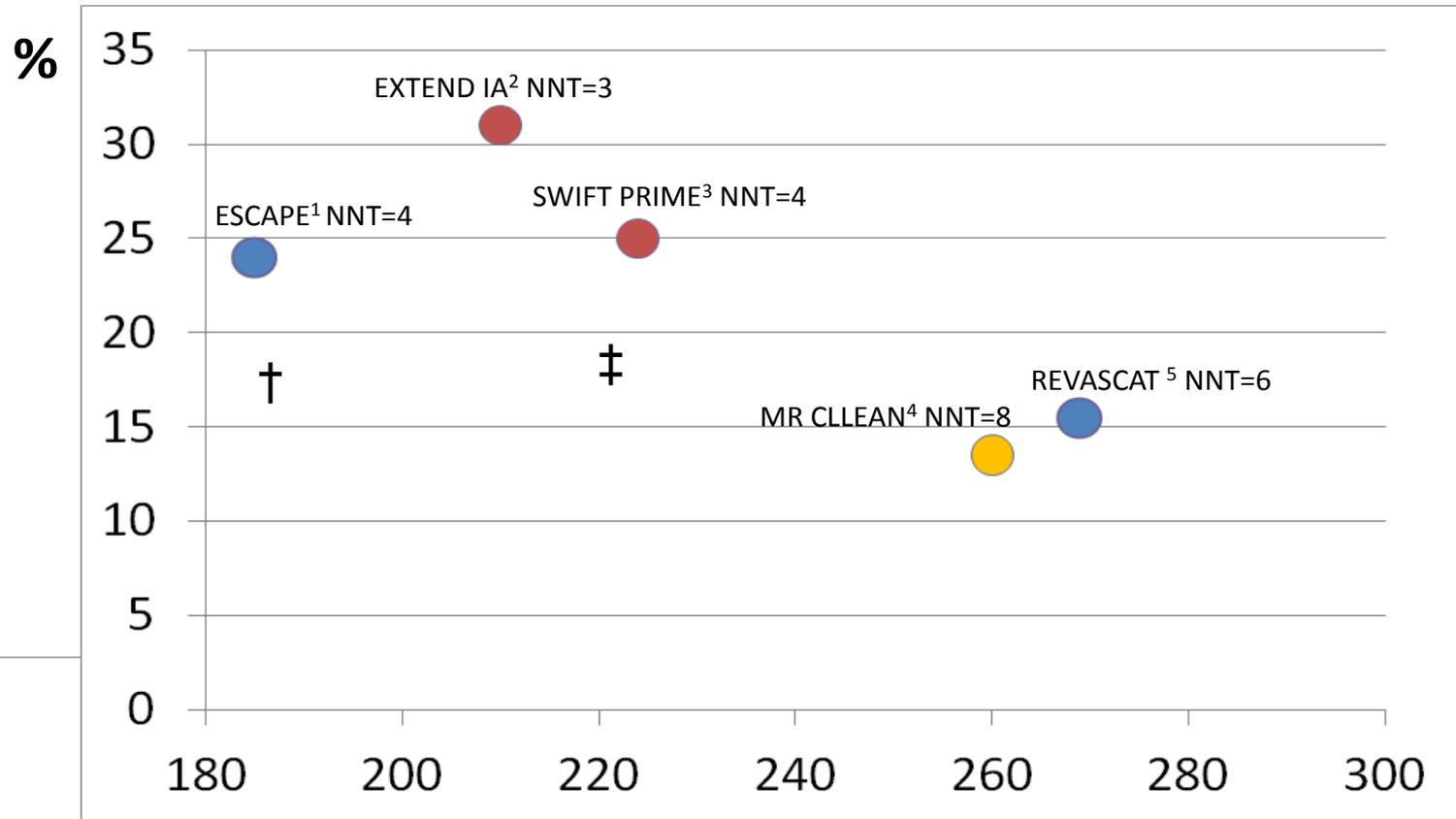
Median time from onset to groin puncture, min

● Perfusion imaging/mismatch   ● ASPECT score ≥ 6   ● No CT/MRI criteria

‡ Performed in 81% of patients   † Moderate-good collaterals

[1]Goyal et. al , NEJM 2015, [2]Campbell et. al., NEJM 2015, [3]Saver et.al, NEJM 2015, [4]Berkhemmer et al., NEJM 2015, [5]Jovin et al., NEJM 2015

23 Randomized Trials of PCI vs Lytics: 30 day Events (n=7739)

PCI **Lytic**

ARR 6%, NNT= 29

Frequency (%)

P=0.0002

P=0.0003

P<0.0001

P=0.0004

P<0.0001

	PCI	Lytic
Death	7	9
Death (shock excl.)	5	7
Non-Fatal MI	2.5	6.8
CVA	1	2
Death CVA/MI	8	14

Keeley & Grines, *Lancet* 2003;361:13-20
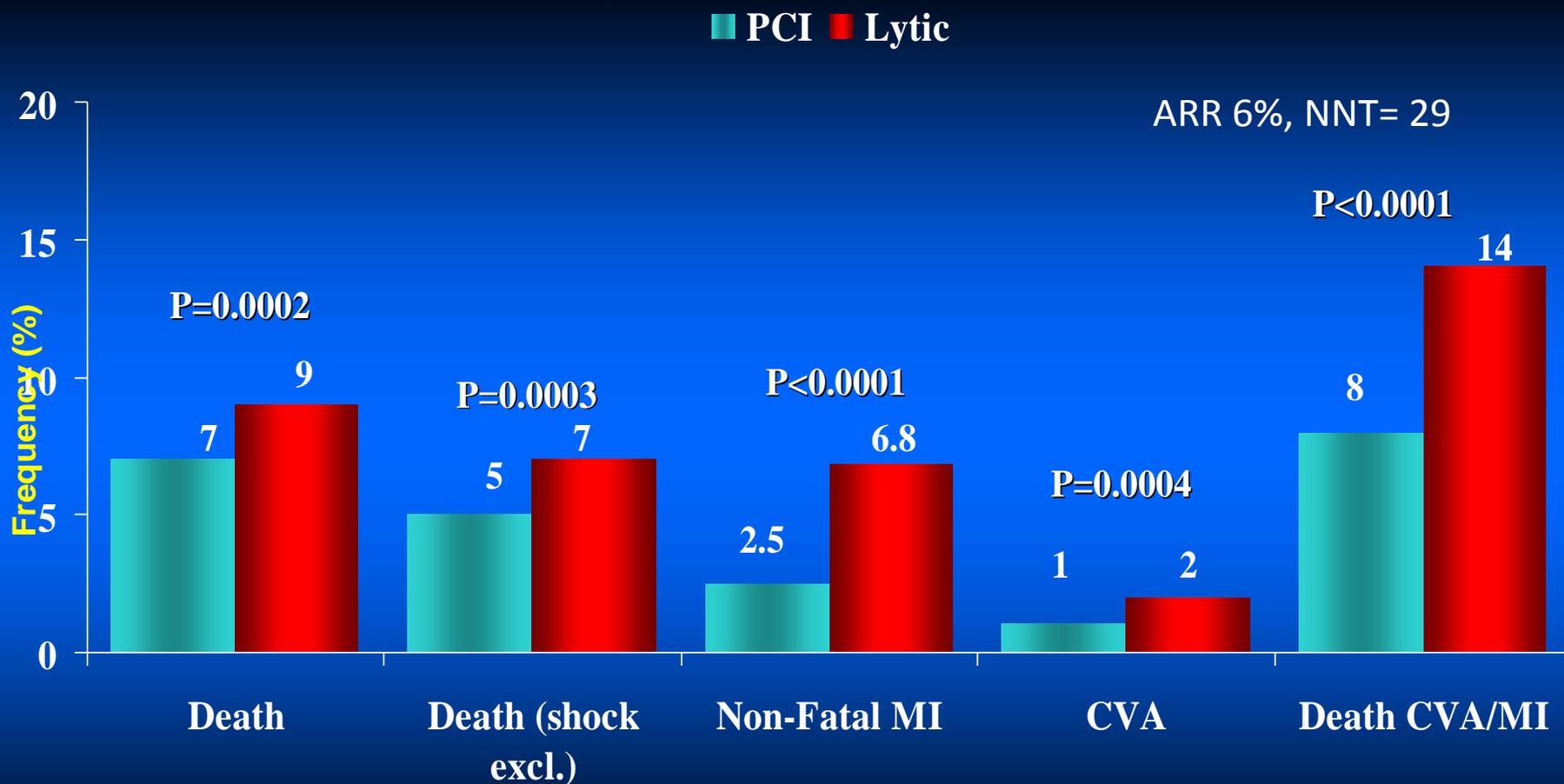
Clinical Vignette #2

59 year old man who presented with NSTEMI and heart failure in the setting of RCA occlusion requiring CABG and valve repair.

After extubation: NIHSS 16 (1 LOCC, 2 VF, 2 gaze, 4 LLE, 4 LUE, 1 sensation, 2 neglect).

What next?

Tpa?

Additional imaging?

Thrombectomy?

Clinical Vignette

CT head obtained on angio table: No hemorrhage

DSA reveals right M1 occlusion and favorable collaterals.
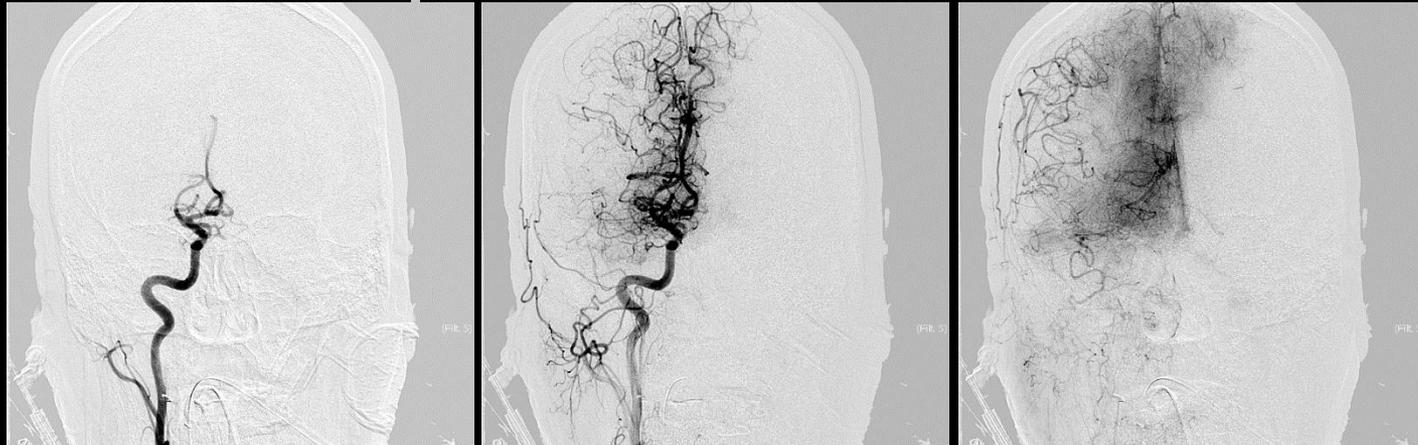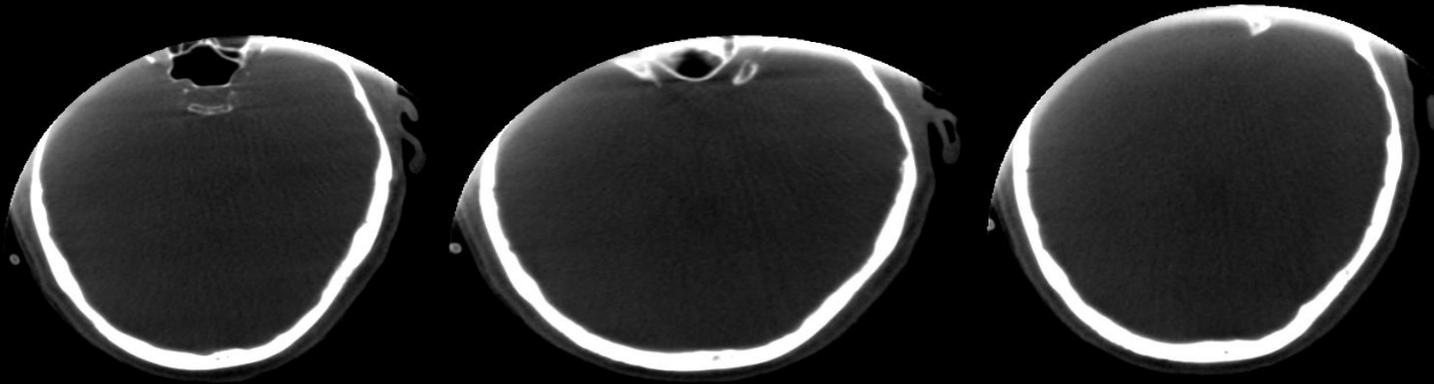
Clinical Vignette

Last seen well	Symptoms	Angio suite	CT head	Access	Recanalization
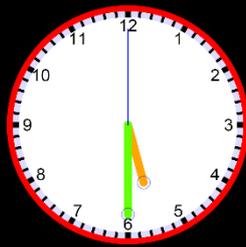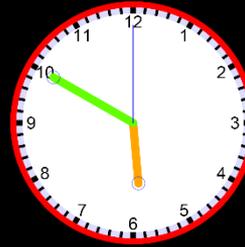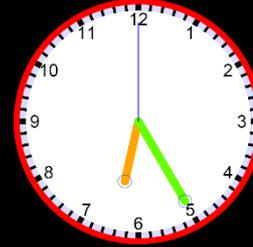
9.5 hours → **50 minutes** → **20 minutes** → **5 minutes** → **30 minutes**
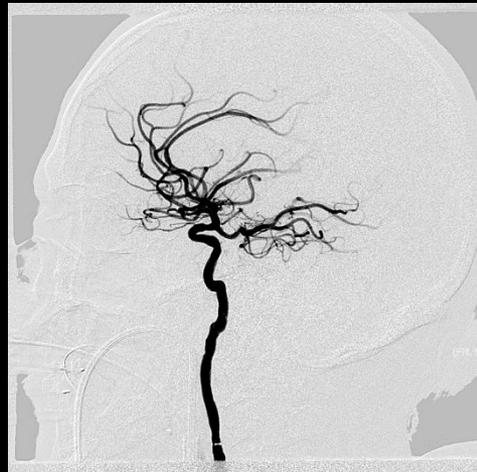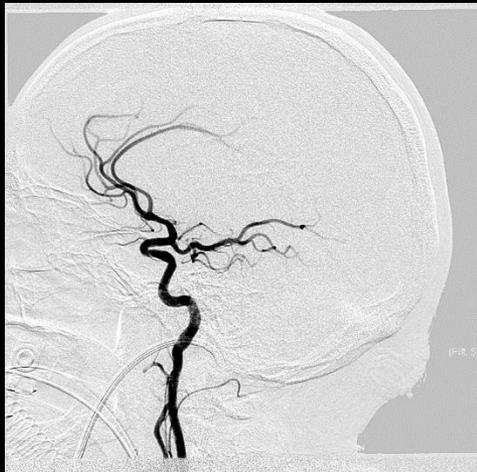
Dual energy CT

Process
Symptom-CT: 70 minutes
Picture-Puncture: 5 minutes
Puncture-Treatment: 30 minutes

Direct transfer to angiosuite

➢ Jan 2013 to July 2015: review of 379 patients undergoing endovascular therapy at UPMC

➢ 8.9% were triage directly from helipad to the angio-suite

➢ Mean door to puncture time: 21.1 minutes

Example workflow of left MCA occlusion
Comparison with "gold standard": CT-Perfusion

SIEMENS

CBF

CBV

CT at presentation
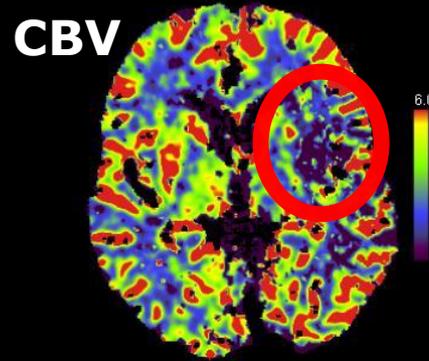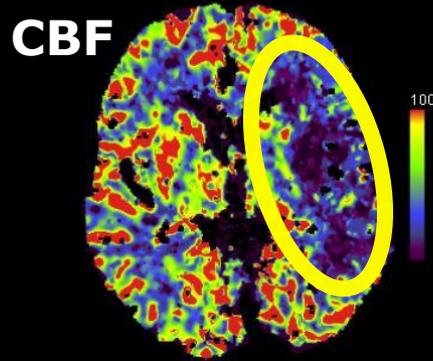
CT 24h

Artis at presentation

DynaCT-Angio

DynaPBV Neuro

(Image courtesy of Prof. Dörfler and Dr. Struffert, Neuroradiology, Erlangen)

Overview

Title	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN)
Sponsor	Stryker Neyrovascular Inc.
PIs	Tudor G. Jovin, MD and Raul G. Nogueira, MD
Funding	Stryker Neurovascular Inc.
Study device	Trevo® ProVue™ and Trevo® XP ProVue™ Retrievers
Control intervention (IV-tPA yes/no?)	Best medical therapy including iv t-PA in eligible patients (which will be estimated to make up maximum 20% of total)
Study population	Acute stroke patients with no upper age limit presenting in the 6-24 hour time window with proximal anterior circulation occlusions (M1, ICA T) and substantial clinical/core mismatch
Objective	To evaluate the hypothesis that Trevo thrombectomy plus medical management leads to superior clinical outcomes at 90 days as compared to medical management alone in appropriately selected subjects experiencing an acute ischemic stroke when treatment is initiated within 6-24 hours after last seen well.

Conclusions

- In the hyperacute time window we are still excluding patients from treatment who may benefit even when selection is based on plain CT (ASPECTS)

- Advanced imaging only excludes more patients without a clear safety advantage

- Advanced imaging is associated with delays that translate into fewer favorable outcomes

- Characterization of core thresholds beyond which there is no benefit or harm is a priority for the field

- In the meantine focus should be on time with imaging only used to exclude large core (ASPECTS < 5 or > 1/3 MCA hypodensity)

- In the > 6 hour time window target population consists of "slow progresors". Time to reperfusion less impactful and info derived from imaging may be worth it

UPMC *Stroke Institute*

UPMC ACUTE ENDOVASCULAR STORKE TEAM

Stroke/Interventional Neurology

- Tudor Jovin, MD
- Ashu Jadhav, MD PhD
- Lawrence Wechsler, MD
- Maxim Hammer, MD
- Vivek Reddy, MD
- Matt Starr, MD
- Viktoria Totoraitis, MD
- Nima Aghaebrahim, mD
- Dan Victor Giurgiutiu, MD

Vascular Endovascular Neurosurgery

- Brian Jankowitz, MD
- Andrew Ducruet, MD
- Robert Friedlander, MD
- Paul Gardner, MD
- Dan Wecht, MD

Stroke Institute Nursing Staff

- Lori Massaro – CRNP
- Susan Kim - CRNP
- Maria Abraham – PA
- Christina Bonaccorsi – PA
- Kathy Seiler, RN
- Cherie Adams RN
- Jonya Brooks, RN
- Ken Coval ,RN
- Patti Williams, RN

Neurocritical Care

- Brad Molyneaux, MD
- Lori Shutter, MD
- Sherry Chou, MD
- Ruchi Jha, MD
- Kees Polderman, MD

Neuroanesthesia

- Coleen Moran, MD
- Frank Gyulai, MD
- Theresa Gelzinis , MD

Emergency Medicine

- Charissa Pacella, MD
- Frank Guyette, MD
- Chris Gill-Martin, MD
- Cliff Callaway, MD
- Don Yealy, MD
- Mike Turturro, MD
- Maria Guyette, MD

Neuroradiology

- Bill Delfyett, MD
- Char Branstetter, MD
- Emanuel Kanal, MD

Stroke Institute Research Staff

- Lisa Baxendell – Research coord
- Carlynn Graves – Research coord
- Patricia Porter – Research coord
- Kara Armbruster – Research coord
- Yvonne Cannon – Research coord
- Holly Kromer- Data Management

NeuroIR Radiology Techs & Nursing Staff

- Kitty O'Toole, RTVI
- Casey Foster, RTVI
- Jennifer Hamil, RTVI
- Jim Bozak,RTVI
- Jason Paul,RTVI
- Candace Acklin, RN
- Josie Stashko, RN

Neurorahabiltiation

- Jennifer Shen
- Cara Camiolo
- Mike Bonimnger

Neuroscience Nursing

- Melanie Smith, RN
- Ben Morrow, RN
- Kate Spiering, RN
- Therese Dawson, RN