Update on thrombolysis
Stroke update Manitoba 2019

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Director Stroke Program
Alberta, Canada

Competing Interests Declaration

- Competing interests
  - chair the steering committee of the SENTIS trial and FastFlo Trial and am an advisor to CoAxia. I am also on the steering committee of the DIAS III & DIAS IV trials, Impact-24 trial and the MASCI trial.
- In the past 5 years, I have received speaker fees from:
    - Sanofi-Aventis/BMS, BI, Pfizer, Merck, Roche, Servier, AstraZeneca, Bayer
- In the past 5 years, I have served on national and international advisory boards for:
    - AstraZeneca, BI, Lundbeck, Bayer, Sanofi-Aventis/BMS, Roche, Pfizer

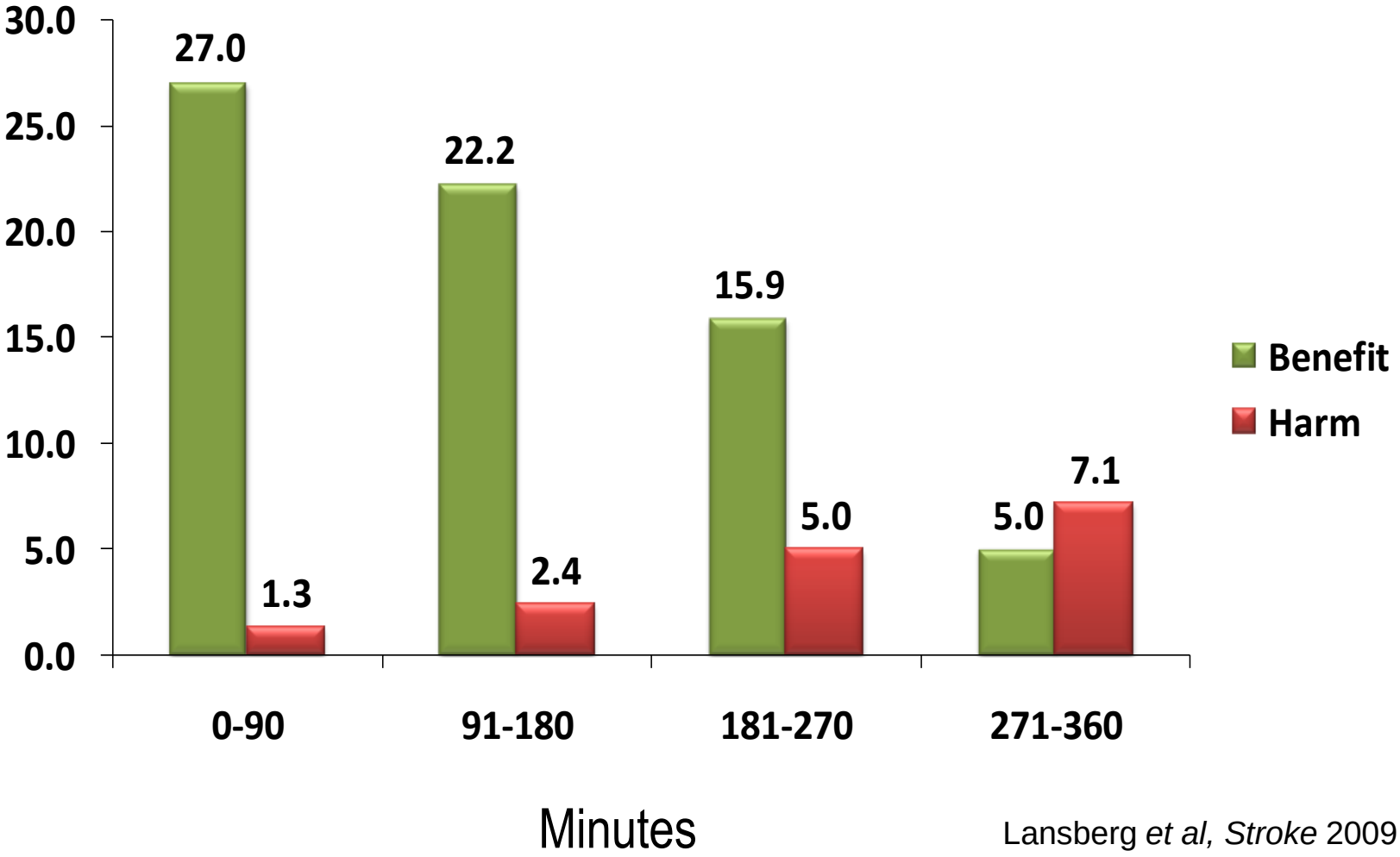
Assumptions

- **Treatment with iv-rtPA is highly effective in acute ischemic stroke**
- **Best outcomes require strict adherence to protocols (incl/excl guidelines)**
- **There is sufficient evidence for efficacy within a 4.5 hours time window**
- **Appropriate imaging essential to exclude ICH prior to treatment**

Outline of presentation

- **Rates of neuronal injury during acute stroke**
- Current time-window recommendations for thrombolysis
- Evidence for thrombolysis in the longer time windows
- Infra-structure and system change requirements for extending time window for thrombolysis

Number of Patients Who Benefit and Are Harmed per 100 Patients tPA Treated in Each Time Window



Lansberg *et al, Stroke* 2009

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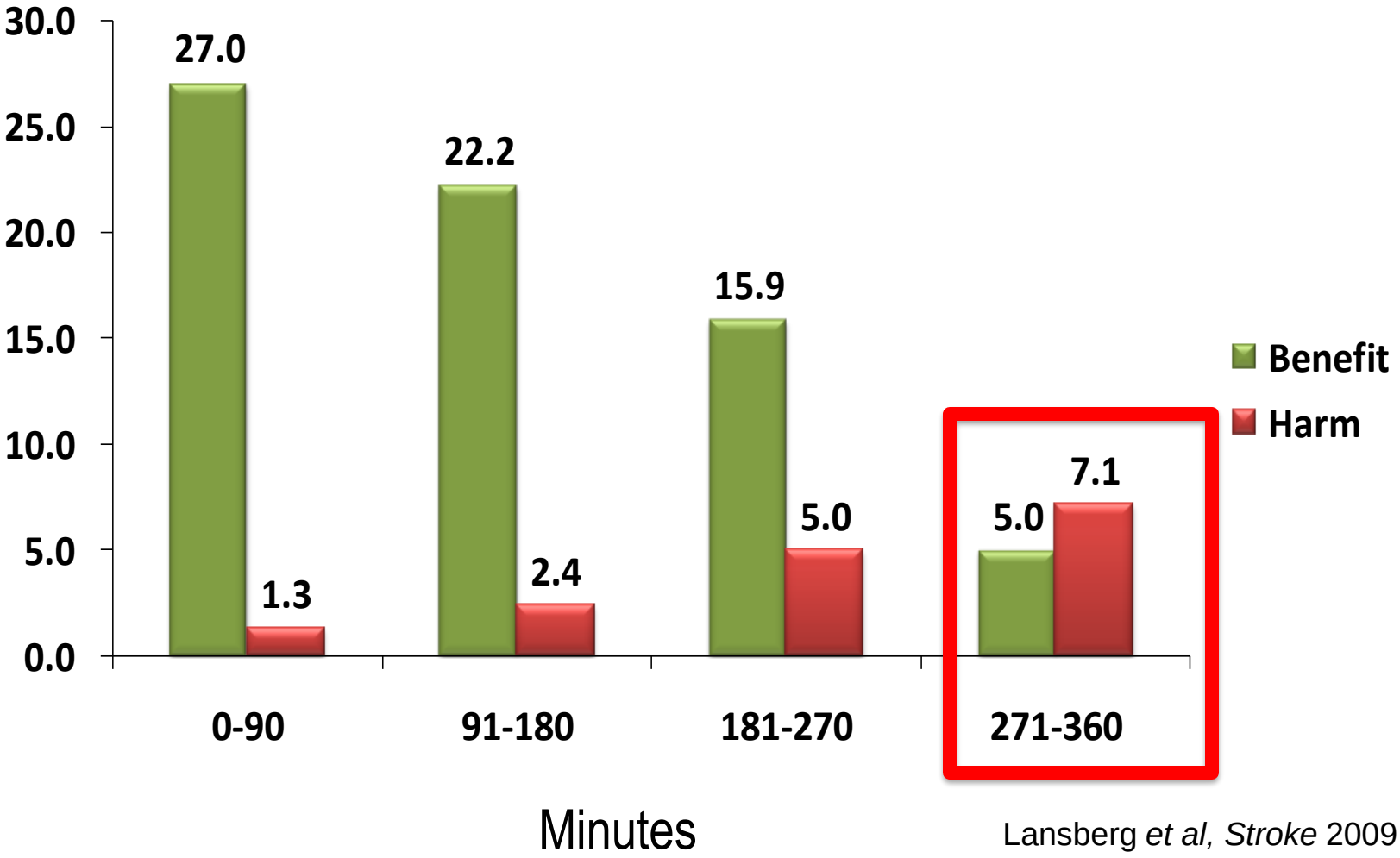


Lansberg *et al, Stroke* 2009

Times From Symptom Onset to Hospital Arrival in the Get With The Guidelines–Stroke Program 2002 to 2009

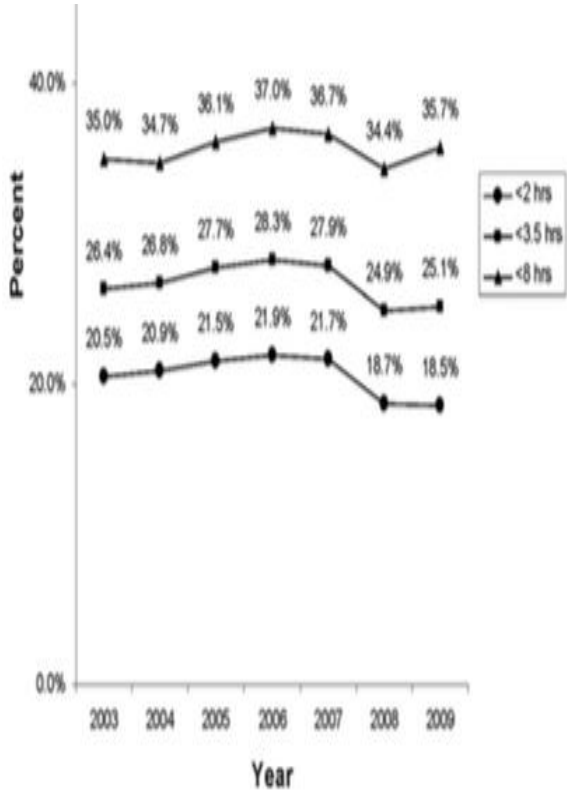
Temporal Trends and Implications

David Tong, MD; Mathew J. Reeves, PhD; Adrian F. Hernandez, MD, MHS; Xin Zhao, MS; DaiWai M. Olson, RN, PhD; Gregg C. Fonarow, MD; Lee H. Schwamm, MD; Eric E. Smith, MD, MPH

Conclusions—More than one fourth of patients with ischemic stroke arrive within the time window for tissue-type plasminogen activator therapy; however, this percentage has remained unchanged over recent years. Further efforts are needed to increase the portion of patients with acute ischemic stroke presenting within the time window for acute interventions. (***Stroke***. **2012;43:1912-1917.**)

Table 1. Characteristics of Patients According to Onset-to-Door Time Categories Among Patients With Documented Time of Arrival ≤24 h After Symptom Onset

	Onset-to-Door Time				
Characteristic	0–2 h (n=85 284)	>2–3.5 h (n=25 642)	>3.5–6 h (n=24 924)	>6–24 h (n=46 242)	*P* Value
Demographic					
Age, y	74 [62, 83]	74 [62, 83]	73 [61, 82]	72 [59, 81]	<0.001
Female sex	50.8	51.9	51.3	50.3	0.39
Race					
White	76.9	75.6	73.9	71.3	<0.001
Black	12.2	12.9	14.7	16.5	
Hispanic (any race)	4.9	5.0	4.7	5.4	
Other	6.0	6.4	6.8	6.8	
Arrival mode					
Emergency medical services	77.5	66.5	62.3	55.5	<0.001
Private transport	22.5	33.5	37.7	44.5	

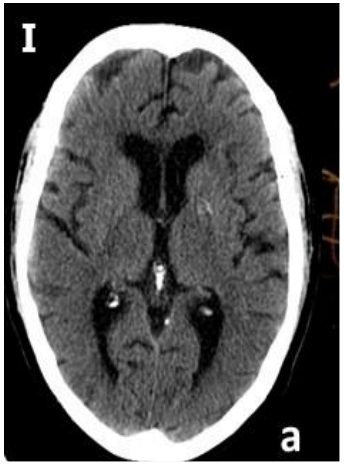


University of Alberta Hospital
Acute Stroke service activity covered by the fellow

Annual estimation*	Hyperacute treatment
1728 patients assessed (additional >1000 telestroke consults)	tPA in 15% of all patients
260 patients receiving tPA	EVT in 10% of all patients
186 patients receiving EVT	tPA and/or EVT in 23% of all patients

Mean acute consults/24h (range)
4,5 (0-9)

45% of patients seen within 4 hours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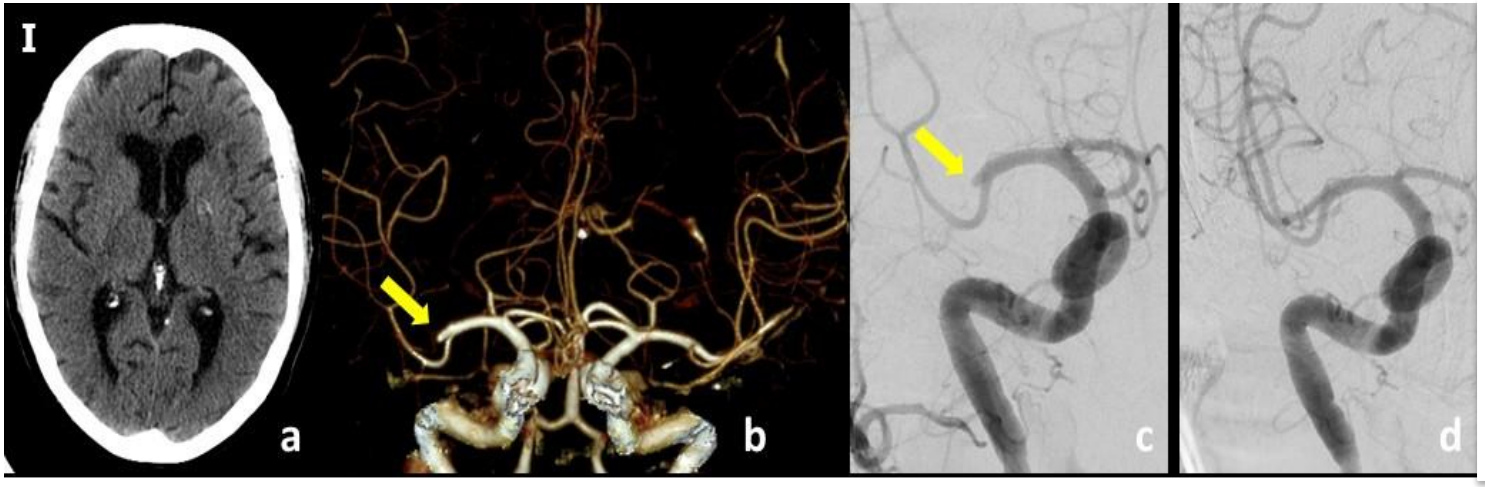
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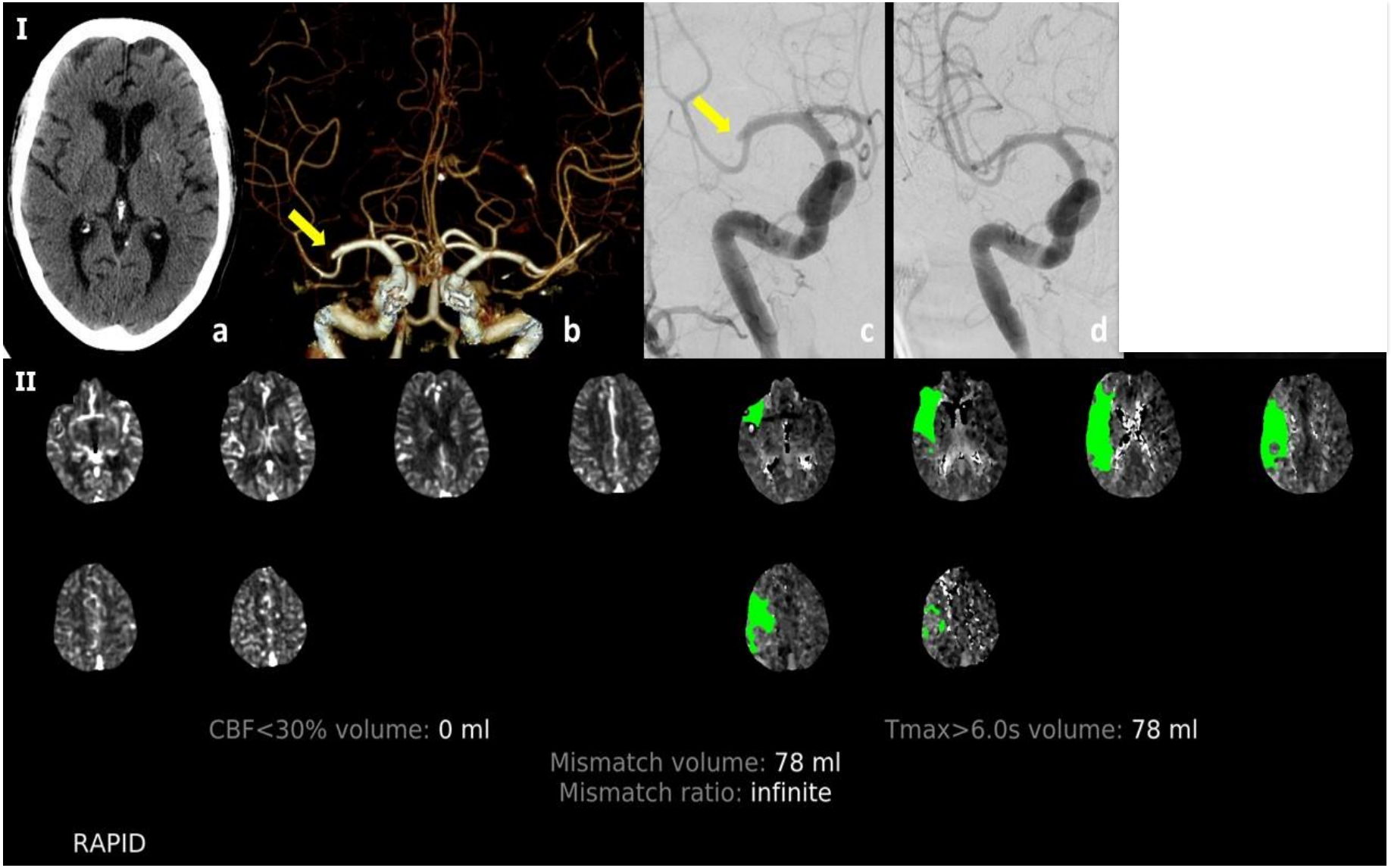
I
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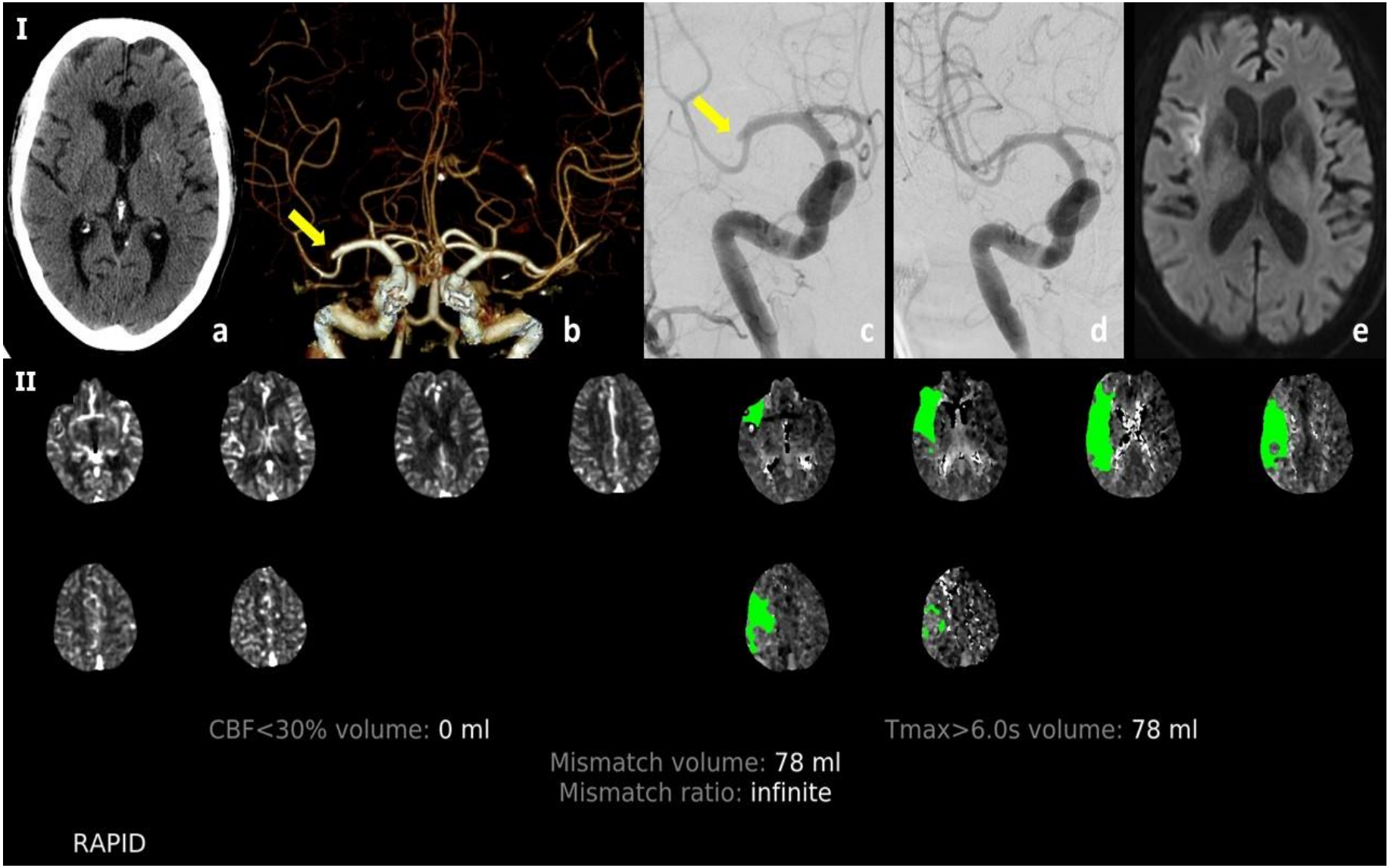
II
CBF<30% volume: 0 ml
Tmax>6.0s volume: 78 ml
Mismatch volume: 78 ml
Mismatch ratio: infinite
RAPID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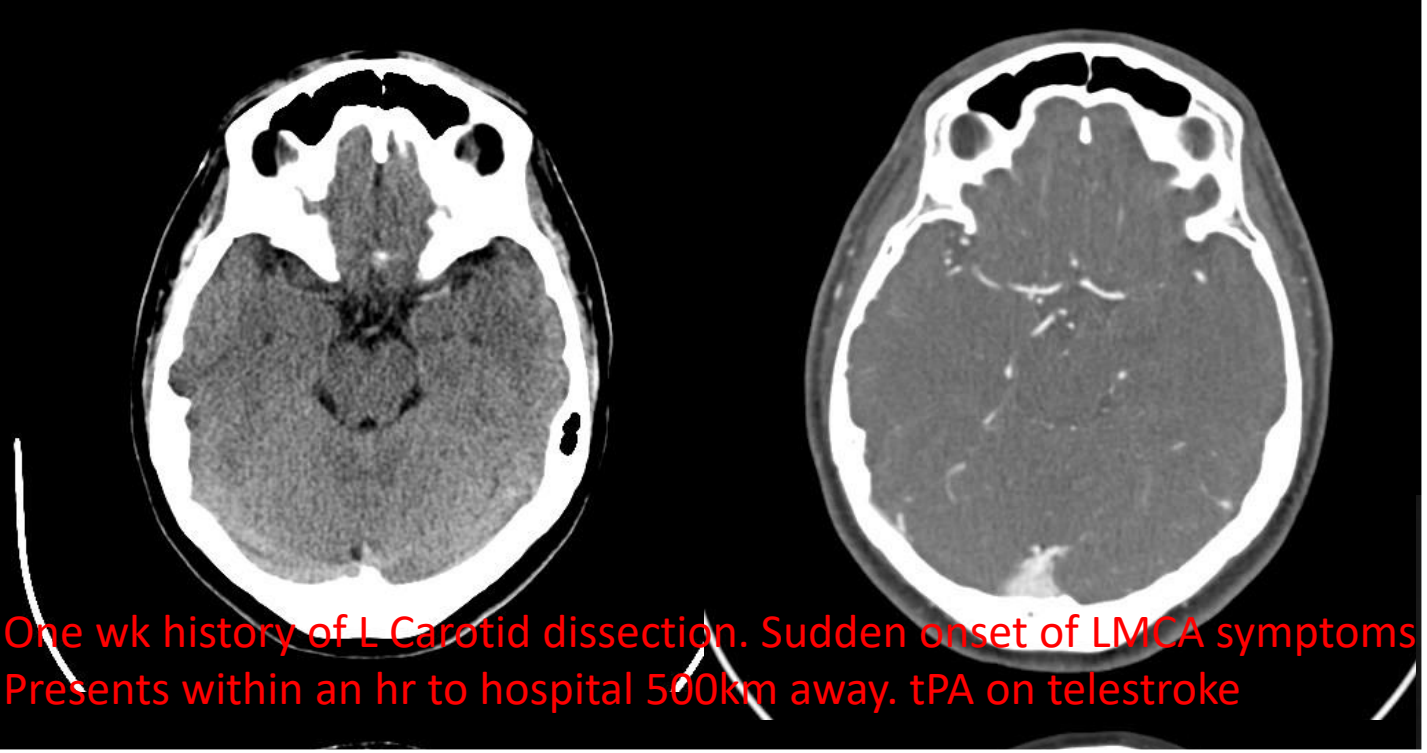
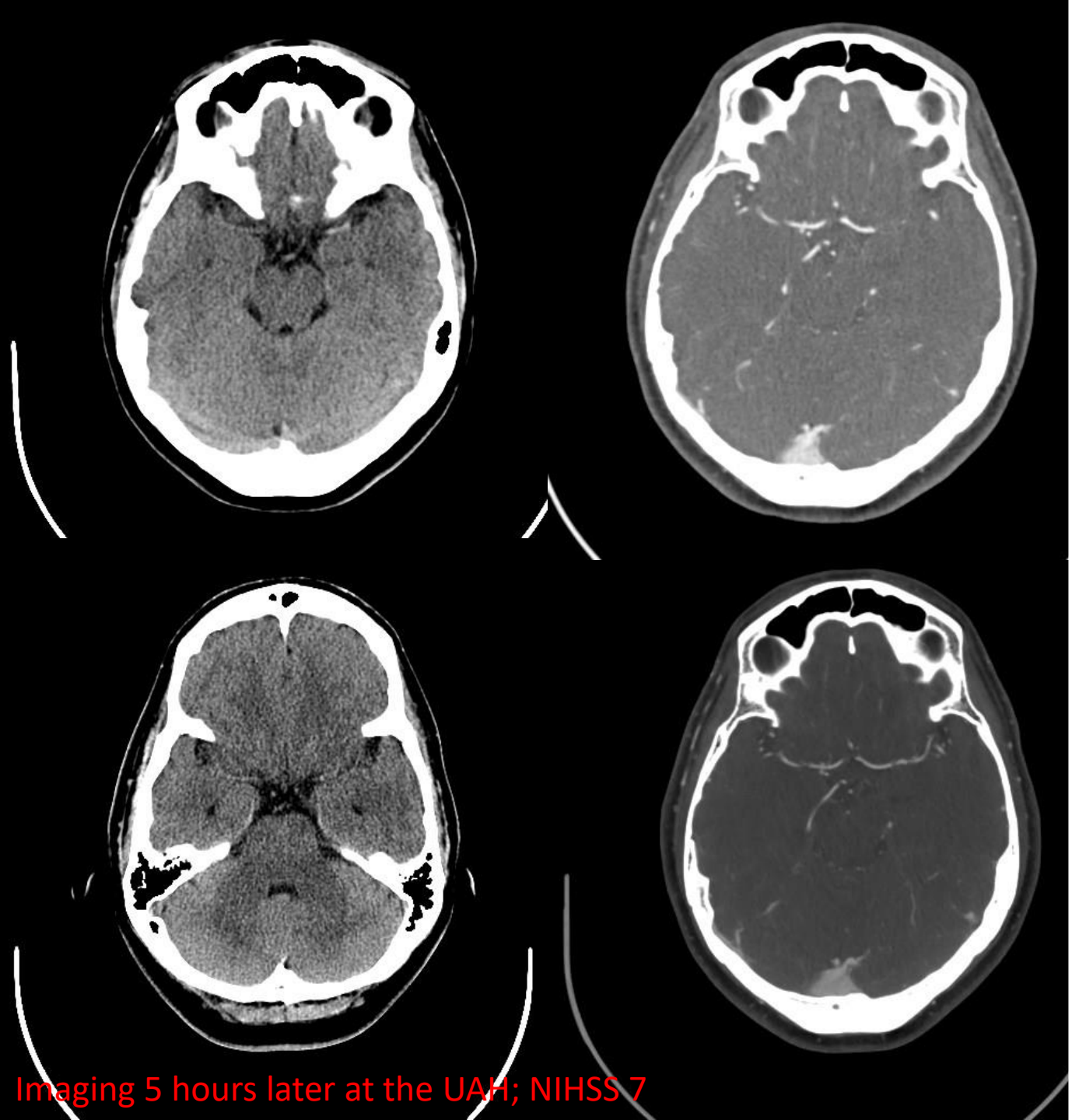
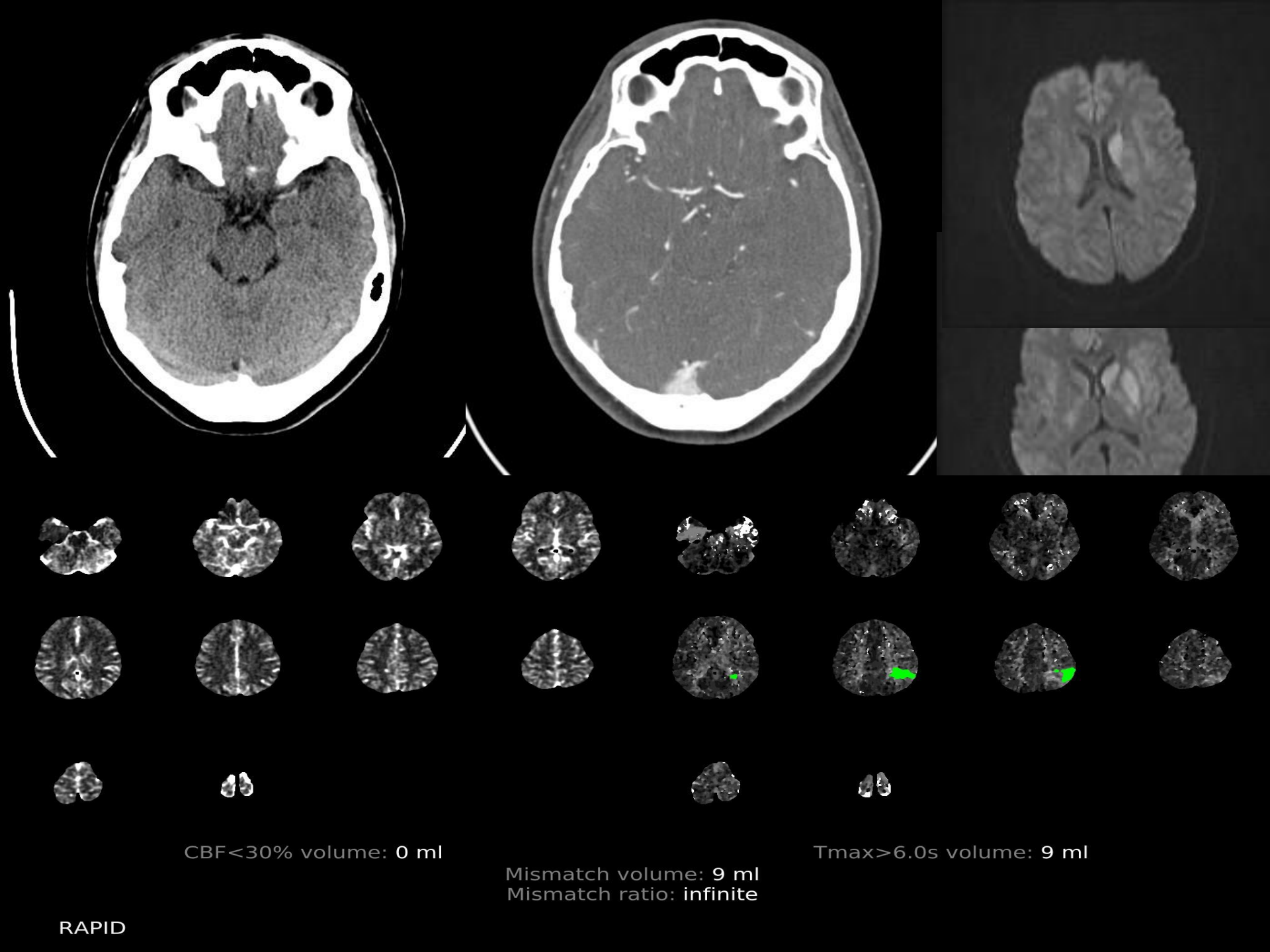

One wk history of L Carotid dissection. Sudden onset of LMCA symptoms
Presents within an hr to hospital 500km away. tPA on telestroke



Imaging 5 hours later at the UAH; NIHSS 7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Tmax>6.0s volume: 9 ml
Mismatch volume: 9 ml
Mismatch ratio: infinite
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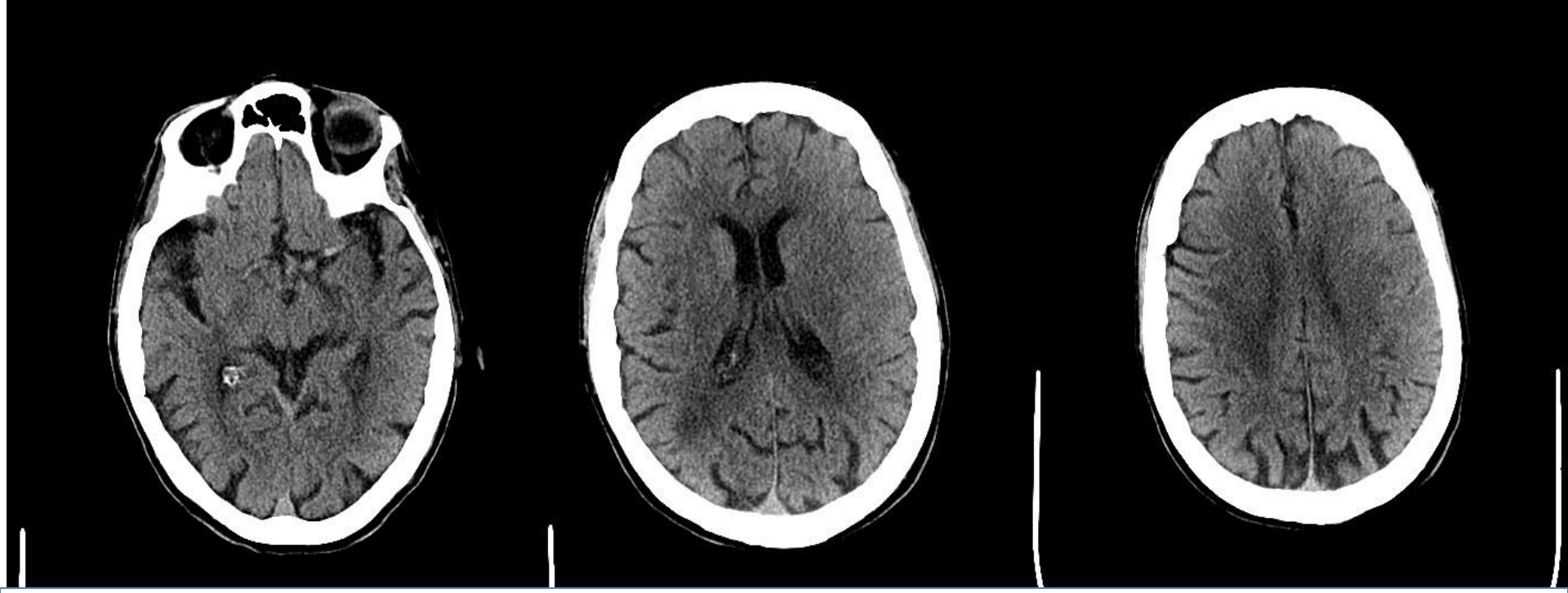
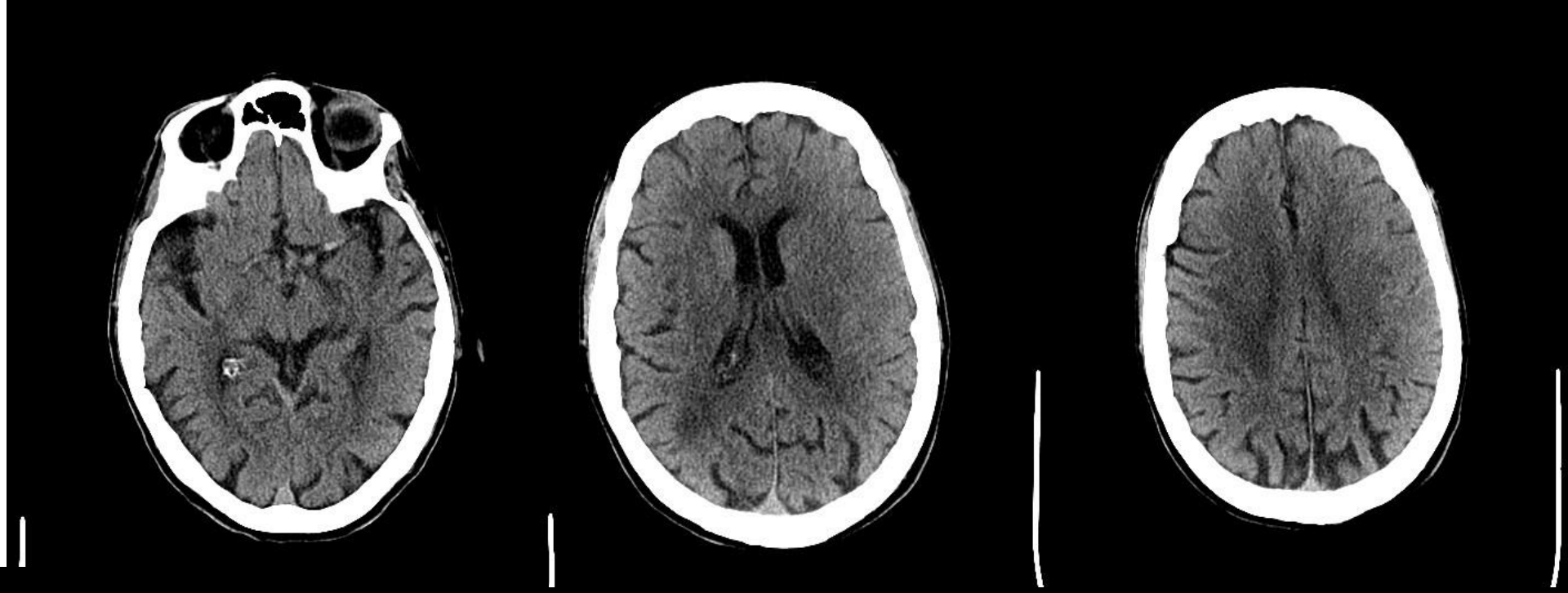
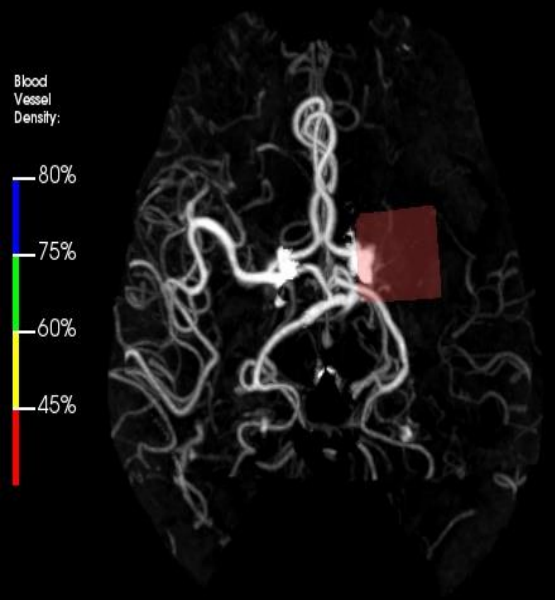
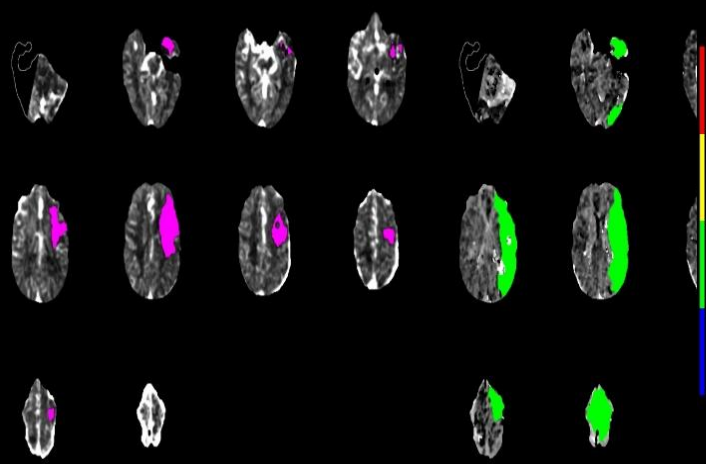


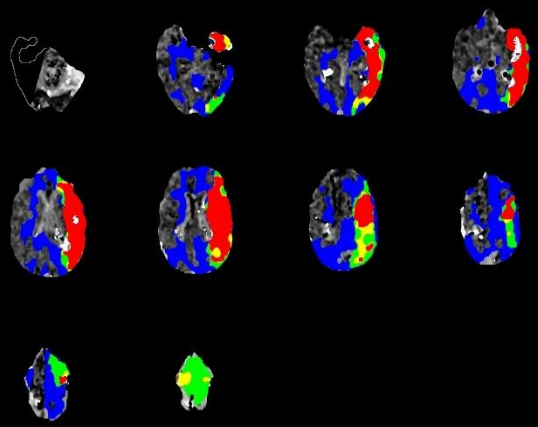
87 yrs old female with COPD and CAD
AF but not on AC

Patient seen by ambulance within 20 minutes.
Intubated in the ambulance for respiratory distress
CT and tPA in ambulance









CBF<30% volume: 45 ml

Tmax>6.0s volume

Mismatch volume: 144 ml
Mismatch ratio: 4.2

Tmax>10.0s volume: 112 ml
Tmax>8.0s volume: 134 ml
Tmax>6.0s volume: 189 ml
Tmax>4.0s volume: 417 ml
Hypoperfusion Index (Tmax>10s/Tmax>6s): 0.6

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Not for primary diagnosis.

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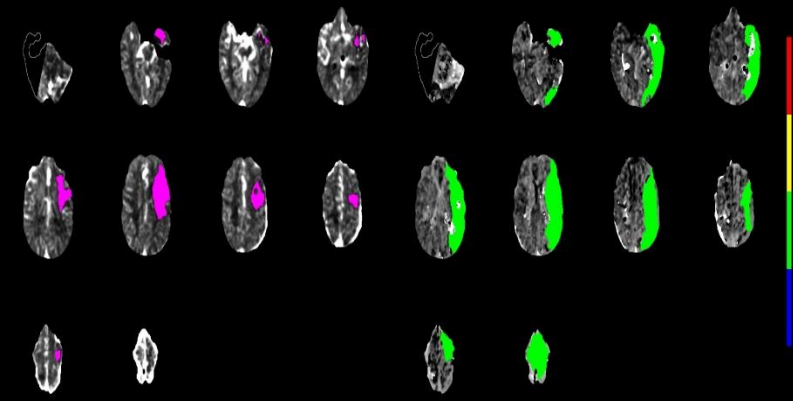

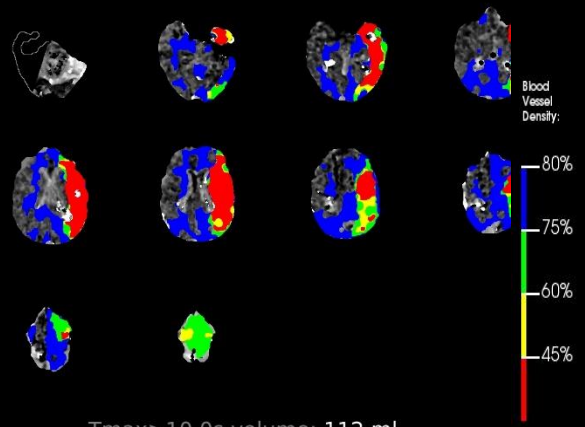

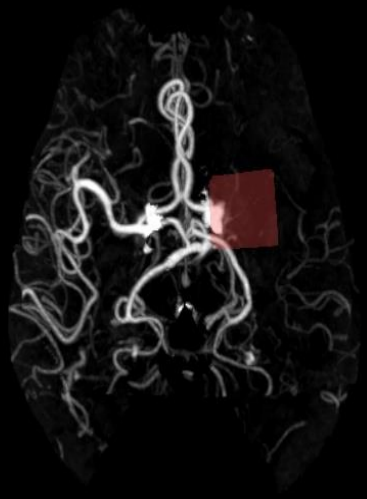

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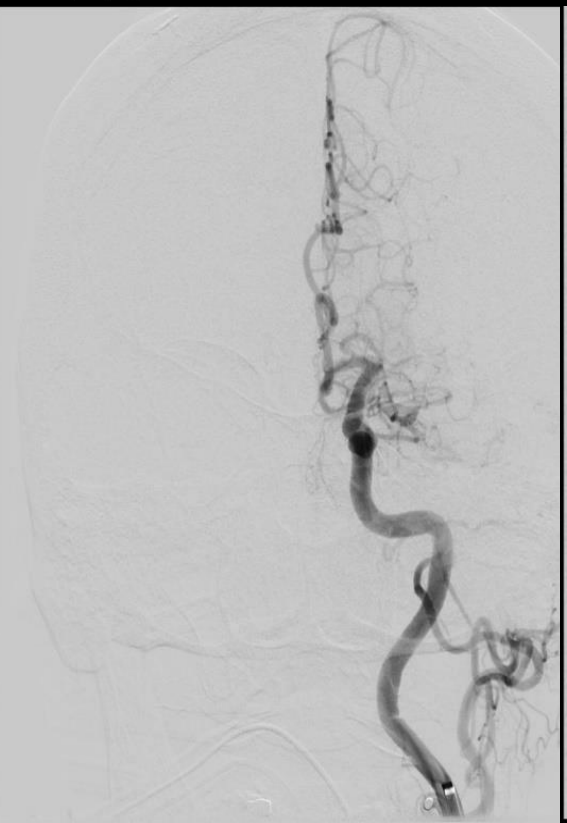

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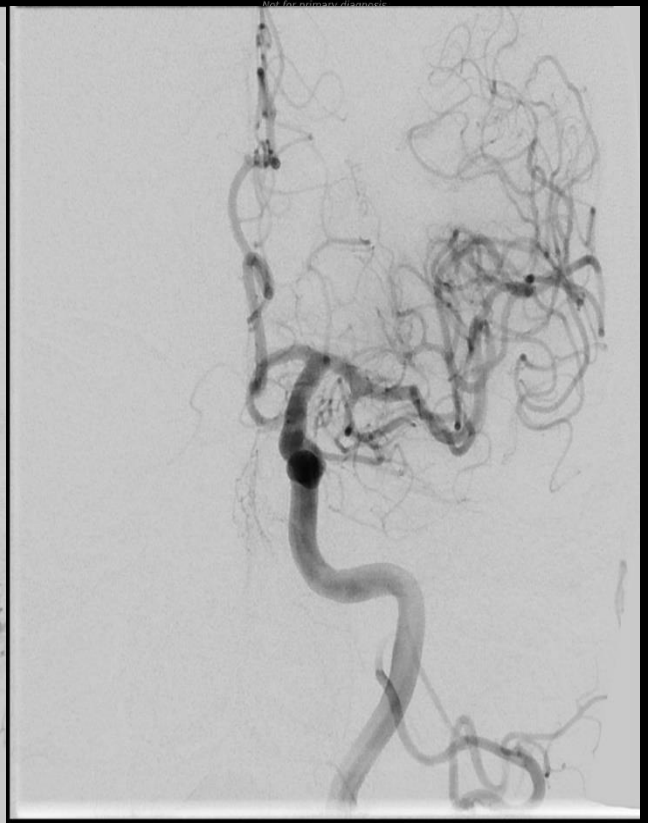

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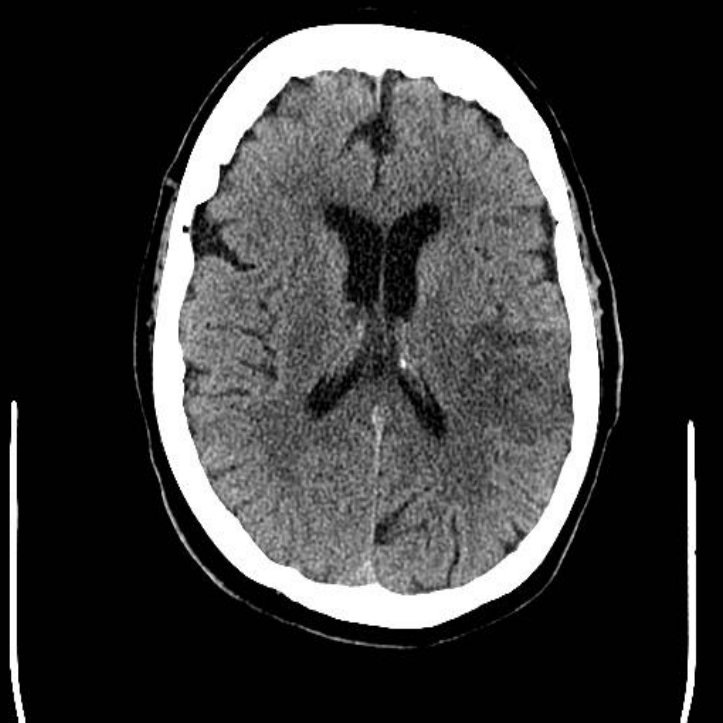
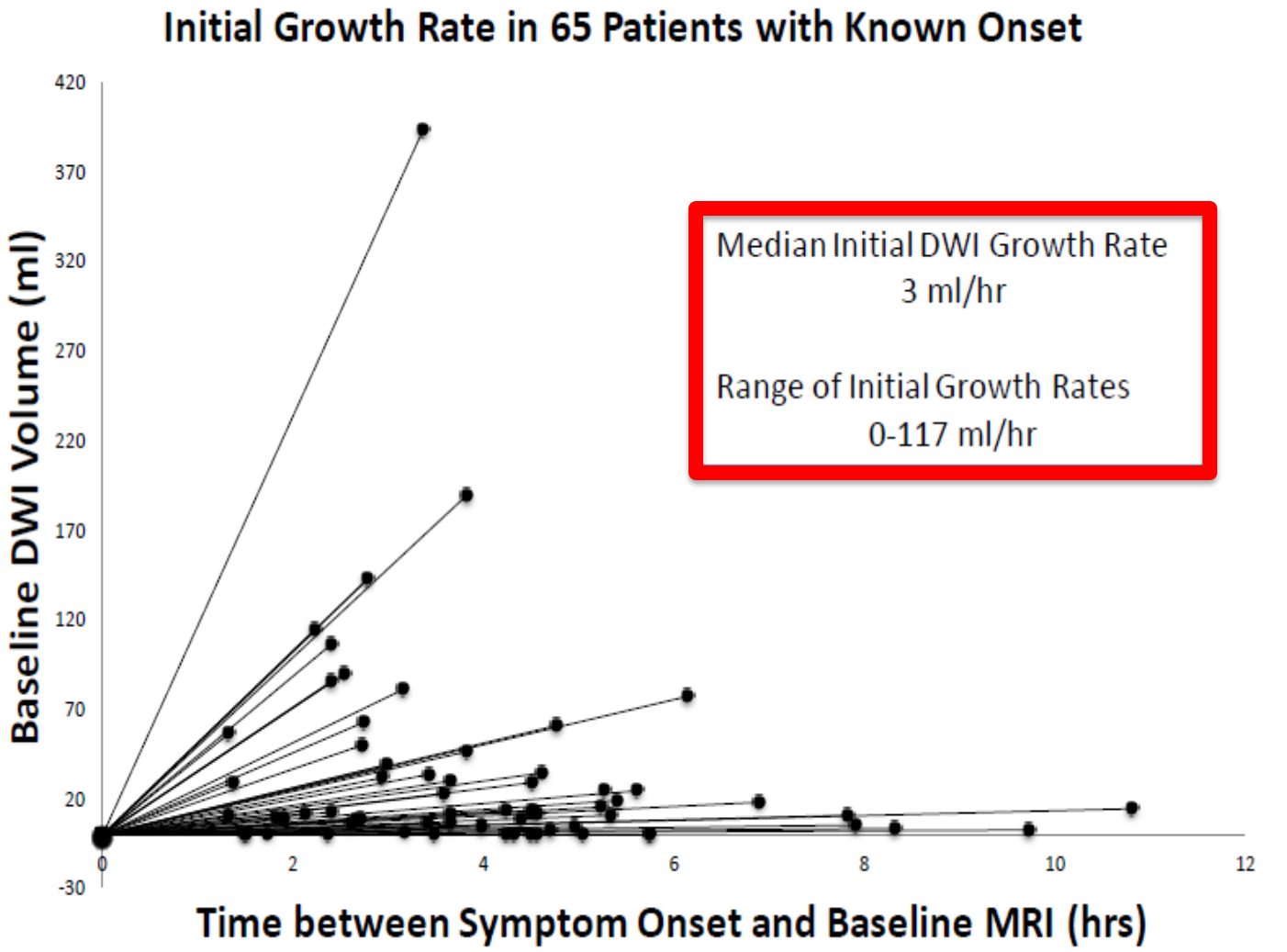


DEFUSE 2: Speed of progression

Part 1 Analysis



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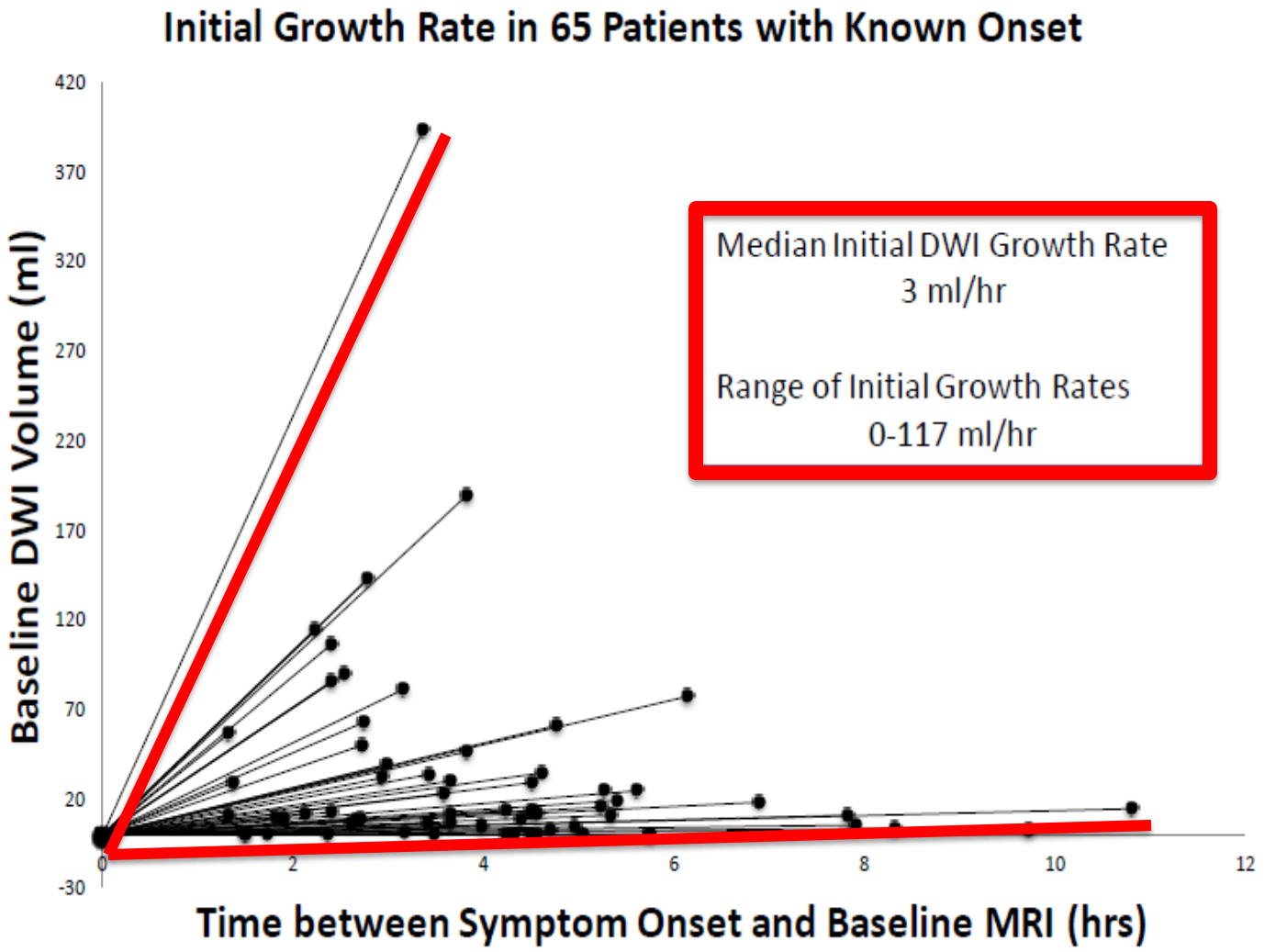
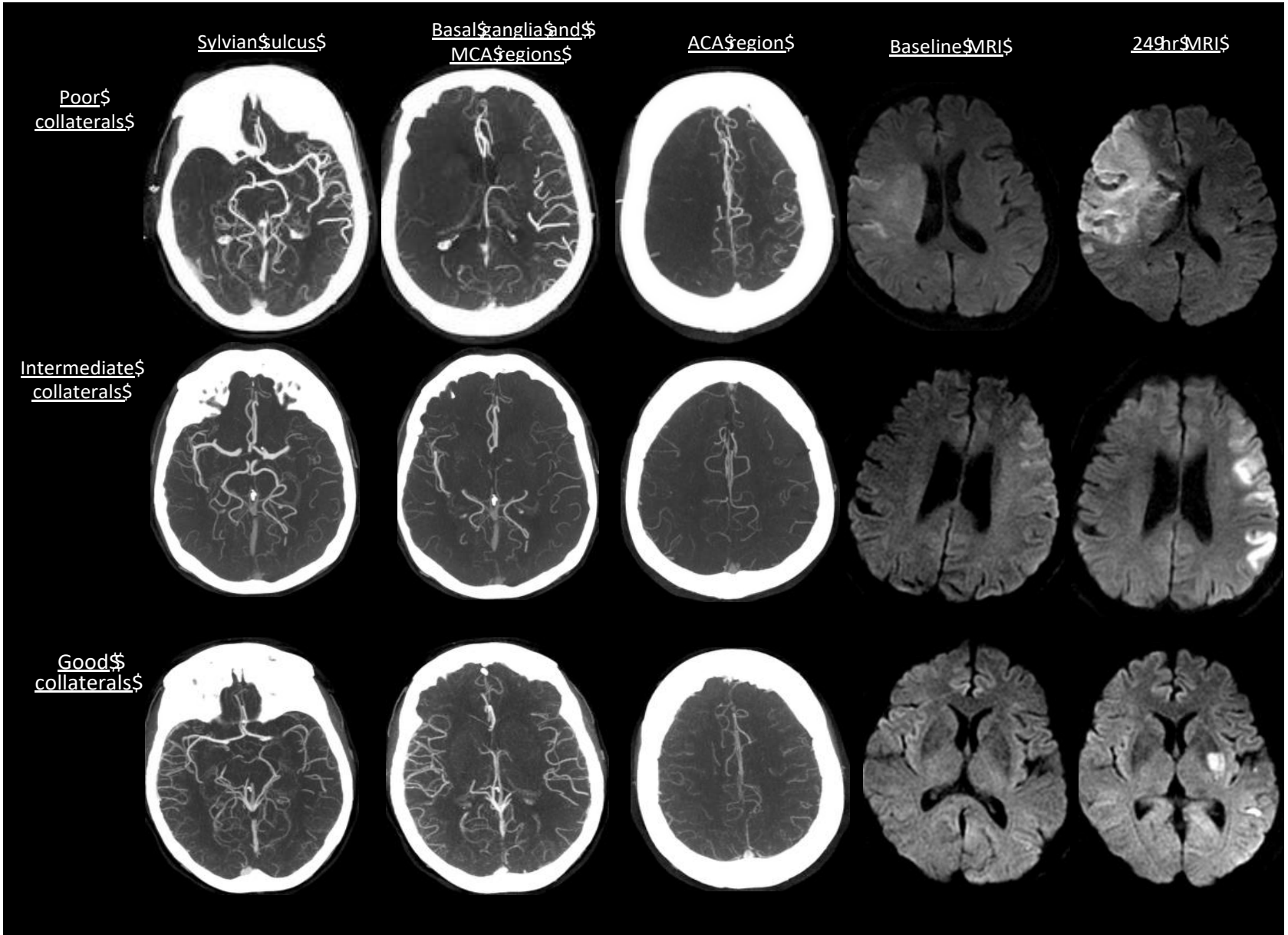


Collaterals Predict Imaging and Clinical Outcomes



Collateral Clock Is More Important Than Time Clock for Tissue Fate

A Natural History Study of Acute Ischemic Strokes

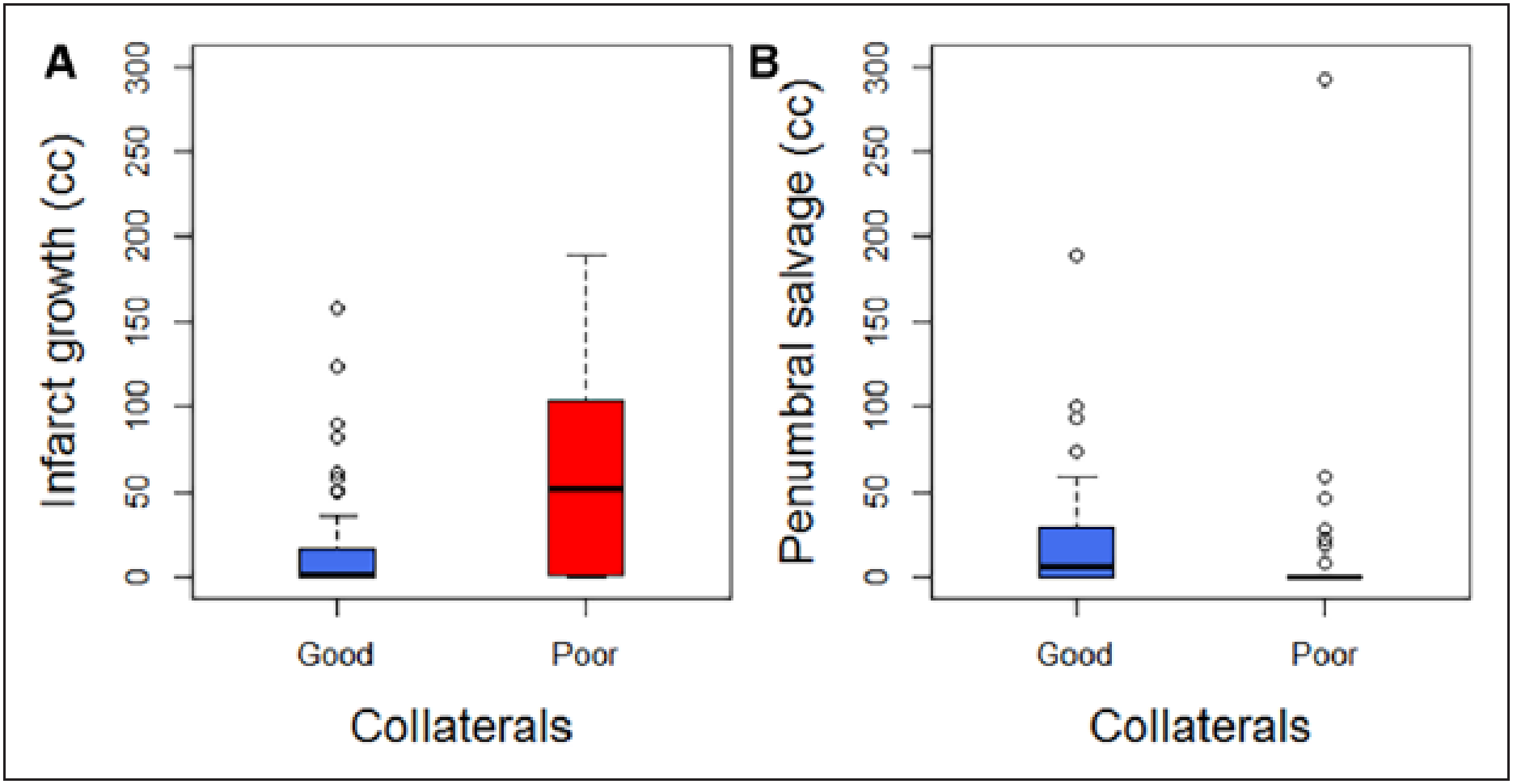
Achala Vagal, MD, MS; Richard Aviv, MD; Heidi Sucharew, PhD; Mahati Reddy, MD; Qinghua Hou, MD; Patrik Michel, MD; Tudor Jovin, MD; Thomas Tomsick, MD; Max Wintermark, MD; Pooja Khatri, MD, MSc

Background and Purpose—Although perfusion abnormality is an increasingly important therapeutic target, the natural history of tissue at risk without reperfusion treatment is understudied. Our objective was to determine how time affects penumbral salvage and infarct growth in untreated acute ischemic stroke patients and whether collateral status affects this relationship.

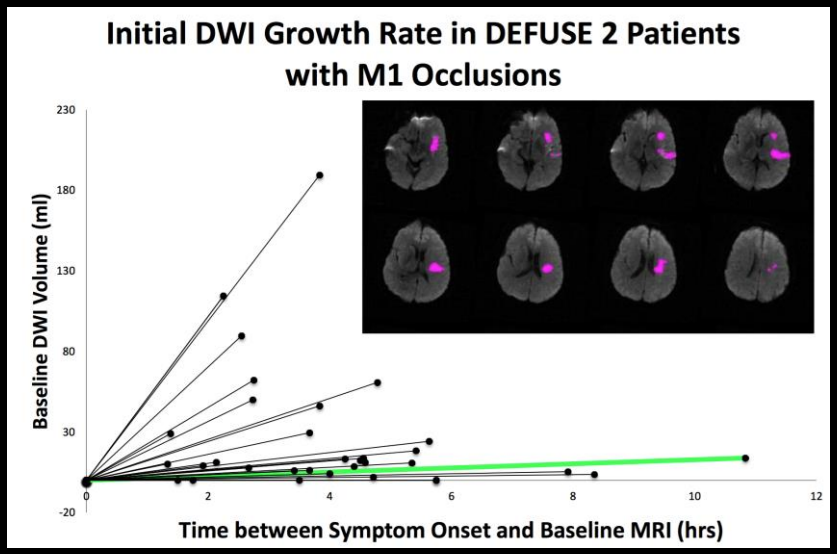
Methods—We used a prospectively collected, multicenter acute stroke registry to assess acute stroke patients who were not treated with intravenous thrombolysis or endovascular treatment. We analyzed baseline computed tomography angiogram and computed tomography perfusion within 24 hours of stroke onset along with follow-up imaging and assessed time from stroke onset to baseline imaging, ASPECTS (Alberta Stroke Program Early CT Score), vessel occlusion, collaterals, ischemic core, and penumbra. Penumbral salvage and infarct growth were calculated. Correlations between time and penumbral salvage and infarct growth were evaluated with Spearman correlation. Penumbral salvage and infarct growth were compared between subjects with good versus poor collateral status using the Wilcoxon rank-sum test. Clinical and imaging factors affecting penumbral salvage and infarct growth were evaluated by linear regression.

Results—Among 94 untreated stroke patients eligible for this analysis, the mean age was 65 years, median National Institutes of Health Stroke Scale score was 13, and median (range) time from stroke onset to baseline imaging was 2.9 (0.4–23) hours. There was no correlation between time and salvaged penumbra (r=0.06; P=0.56) or infarct growth (r=–0.05; P=0.61). Infarct growth was higher among those with poor collaterals versus those with good collaterals (median, 52.3 versus 0.9 cm^3; P<0.01). Penumbral salvage was lower among those with poor collaterals compared with those with good collaterals (poor, 0 [0–0]; good, 5.9 cm^3 [0–29.4]; P<0.01). Multivariable linear regression demonstrated that collaterals, but not time, were significantly associated with infarct growth and penumbral salvage.

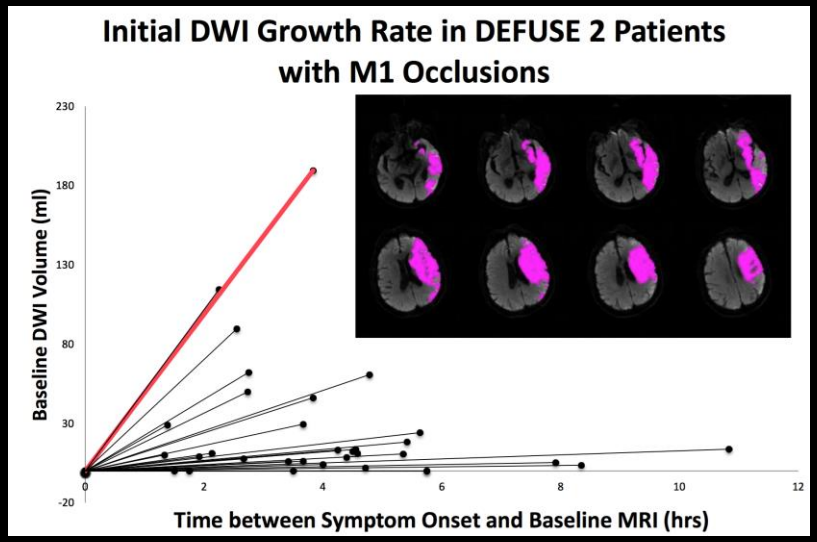
Conclusions—In this natural history study, penumbral salvage and infarct growth were less time dependent and more a measure of collateral flow. (***Stroke***. **2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021484.**)


A
Infarct growth (cc)
0
50
100
150
200
250
300
Good
Poor
Collaterals
B
Penumbral salvage (cc)
0
50
100
150
200
250
300
Good
Poor
Collaterals

Explaining the paradox:



Late Time
but
Good Collaterals
=
Good outcome
SLOW PROGRESSOR!



Early Time
but
Poor Collaterals
=
Poor outcome

FAST PROGRESSOR!

Other factors effecting speed of neuronal injury

- **Temperature**
- **Glucose**
- **Blood pressure (current and previous history of hypertension/medications)**
- **Diabetes**
- **Autonomic dysfunction**

Outline of presentation

- **Rates of neuronal injury during acute stroke**
- **Current time-window recommendations for thrombolysis**
- Evidence for thrombolysis in the longer time windows
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AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

William J. Powers, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, FAHA, Vice Chair;
Teri Ackerson, BSN, RN; Opeolu M. Adeoye, MD, MS, FAHA;
Nicholas C. Bambakidis, MD, FAHA; Kyra Becker, MD, FAHA; José Biller, MD, FAHA;
Michael Brown, MD, MSc; Bart M. Demaerschalk, MD, MSc, FAHA;
Brian Hoh, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Chelsea S. Kidwell, MD, FAHA;
Thabele M. Leslie-Mazwi, MD; Bruce Ovbiagele, MD, MSc, MAS, MBA, FAHA;
Phillip A. Scott, MD, MBA, FAHA; Kevin N. Sheth, MD, FAHA;
Andrew M. Southerland, MD, MSc, FAHA; Deborah V. Summers, MSN, RN, FAHA;
David L. Tirschwell, MD, MSc, FAHA; on behalf of the American Heart Association Stroke Council

Time From Symptom Onset: Recommendations

1. The time from last seen normal to treatment with intravenous alteplase should be <3 hours for eligible patients with the use of standard eligibility criteria (*Class I; Level of Evidence A*).
2. Intravenous alteplase treatment in the 3- to 4.5-hour time window is also recommended for those patients <80 years of age without a history of both diabetes mellitus and prior stroke, NIHSS score <25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one third of the MCA territory (*Class I; Level of Evidence B*).

3. Patients with a positive stroke screen or who are strongly suspected to have a stroke should be transported rapidly to the closest healthcare facilities that are able to administer IV alteplase.	**I**	**B-NR**

The 2013 recommendation referred to initial emergency care as described elsewhere in the guidelines, which specified administration of IV alteplase as part of this care. The current recommendation is unchanged in intent but reworded to make this clear.

4. When several IV alteplase–capable hospital options exist within a defined geographic region, the benefit of bypassing the closest to bring the patient to one that offers a higher level of stroke care, including mechanical thrombectomy, is uncertain.	**IIb**	**B-NR**
5. Effective prehospital procedures to identify patients who are ineligible for IV thrombolysis and have a strong probability of large vessel occlusion (LVO) stroke should be developed to facilitate rapid transport of patients potentially eligible for thrombectomy to the closest healthcare facilities that are able to perform mechanical thrombectomy.	**IIb**	**C-EO**

2.2.2. IV Alteplase Eligibility (Continued)	COR	LOE	New, Revised, or Unchanged
2. In patients eligible for IV alteplase, because benefit of therapy is time dependent, treatment should be initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT and MRI perfusion imaging.	I	B-NR	New recommendation.
NCCT was the only neuroimaging modality used in the NINDS rt-PA trial and in ECASS III and is therefore sufficient neuroimaging for decisions about IV alteplase in most patients.[48,49] Multimodal CT and MRI, including diffusion and perfusion imaging, are not necessary when the diagnosis of ischemic stroke is very likely, and their performance may delay time-sensitive administration of IV alteplase. In some cases, particularly when there is substantial diagnostic uncertainty, advanced imaging may be beneficial.			See Table XX in online Data Supplement 1.
3. In patients with AIS who awake with stroke symptoms or have unclear time of onset > 4.5 hours from last known well or at baseline state, MRI to identify diffusion-positive FLAIR-negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition.	IIa	B-R	New recommendation.

A summary of the *Canadian Stroke Best Practice Recommendations,* Sixth Edition (2018): Updates relevant to prehospital and emergency medicine providers

- **<4.5 hours:** potentially alteplase (tPA) eligible and should undergo *immediate* NCCT (Evidence Level A; Section 4.2.ii).

- **<6 hours**: potentially EVT eligible and should undergo *immediate* NCCT and CT angiography (CTA) from aortic arch to vertex, including extracranial and intracranial circulation (Evidence Level A; Section 4.2.iii).
- **6-24 hours**: potentially EVT eligible (including late presentation and stroke on awakening) and should undergo *immediate* brain imaging with NCCT, CTA, and CT perfusion or MRI with MR angiography (MRA) and MR perfusion (MRP) (Evidence Level B; Section 4.2.iv).

Outline of presentation

- **Rates of neuronal injury during acute stroke**
- **Current time-window recommendations for thrombolysis**
- **Evidence for thrombolysis in the longer time windows**
- Infra-structure and system change requirements

Table. Previous Randomized Clinical Trials of Intravenous Thrombolysis and Thrombectomy Based on Imaging Biomarkers in Extended Time Windows (>4.5 Hours Since Onset)

Trial	Year	Time Window	Imaging Methods
Intravenous thrombolysis			
DIAS[4]	2005	3–6 h	MRI diffusion-perfusion mismatch
DEDAS[5]	2006	3–9 h	MRI diffusion-perfusion mismatch
EPITHET[6]	2008	3–9 h	MRI diffusion-perfusion mismatch
DIAS-2[7]	2009	3–9 h	MRI diffusion-perfusion mismatch or CTP
DIAS-3[8]	2015	3–9 h	Intracranial large vessel occlusion
DIAS-4[9]	2016	3–9 h	Intracranial large vessel occlusion
EXTEND[10]	2018	4.5–9 h	CTP
WAKE-UP[11]	2018	4.5 h after waking	MRI diffusion-FLAIR mismatch
ECASS-4[12]	2019	4.5–9 h	MRI diffusion-perfusion mismatch

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ECASS-4[12]	2019	4.5–9 h	MRI diffusion-perfusion mismatch

MRI or CTP: small core and large penumbra

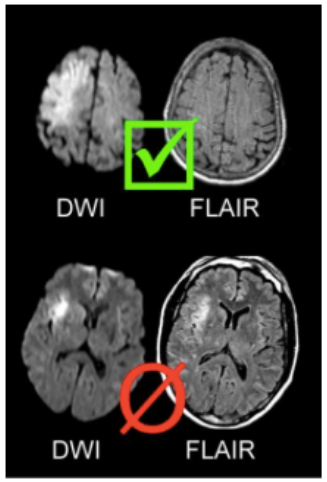
Intravenous Thrombombolysis in Stroke Patients with Unknown Time of Onset –

Results of the Multicentre, Randomized, Double-blind, Placebo-Controlled WAKE-UP Trial

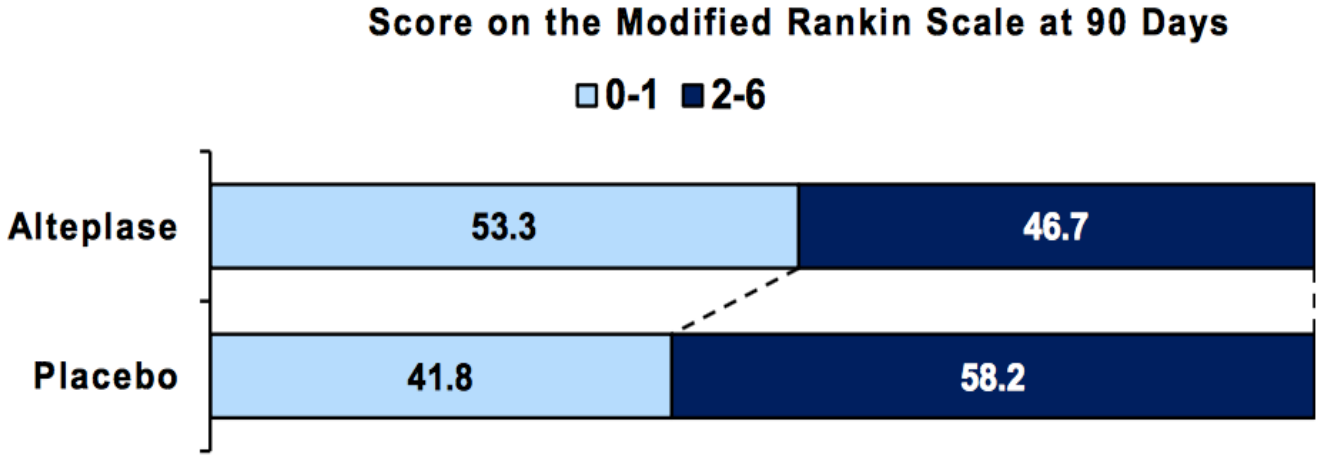
G. Thomalla, C.Z. Simonsen, F. Boutitie, B. Cheng, T.H. Cho, M. Ebinger, M. Endres, J.B. Fiebach, J. Fiehler, I. Ford, I. Galinovic, R. Lemmens, K. Muir, N. Nighoghossian, S. Pedraza, J. Puig, P. Roy, V. Thijs, C. Gerloff,

on behalf of the WAKE-UP Investigators

- **Aim**: To prove efficacy and safety of MRI-based thrombolysis in patients with unknown time of symptom onset
- **Design**: randomised, placebo-controlled clinical trial (Alteplase vs. Placebo 1:1)
- **Planned sample**: 800 ischemic stroke patients (unknown symptom onset)
- **Inclusion criteria**:
  - Acute stroke with unknown symptom onset, disabling neurological deficit
  - Last known well >4.5 hours (ie not eligible for IV alteplase by licence)
  - Age 18-80 years
  - Treatment can be started within 4.5 h of symptom recognition
  - Written informed consent
  - MRI completeted and indicative of lesion age ≤4.5 h: “DWI-FLAIR-mismatch”
- **Exclusion criteria**:
  - Planned thrombectomy
  - Any contradindication against treatment with alteplase (except for unknown time window)



Primary Endpoint



Endpoint	Alteplase (n=254)	Placebo (n=249)	Effect Variable	Adjusted Value (95% CI) *	P-Value
Favorable outcome (mRS 0-1) at 90 days	131/246 (53.3%)	102/244 (41.8%)	Odds ratio	**1.61 (1.09-2.36)**	**0.02**

** Adjusted for age and NIHSS at baseline*

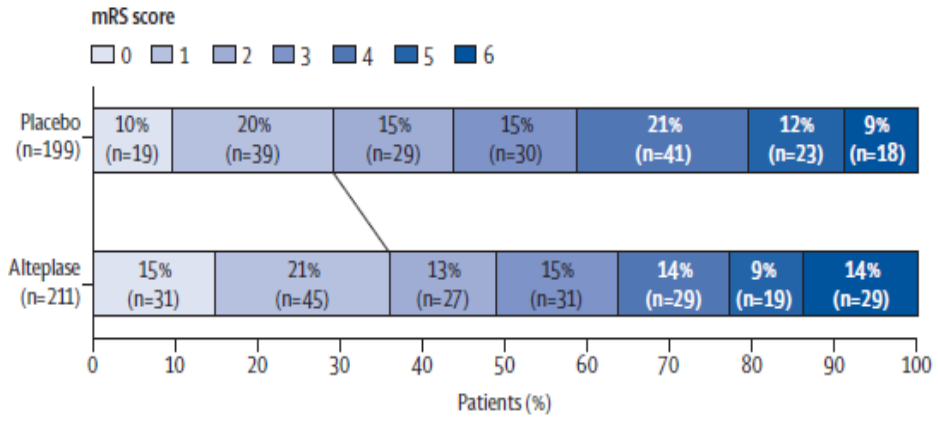
WAKE-UP trial

Table 3. Safety Outcomes.

Outcome	Alteplase Group (N=251)	Placebo Group (N=244)	Adjusted Odds Ratio (95% CI)*	P Value
	no. (%)			
Primary†				
Death or dependency at 90 days	33 (13.5)	44 (18.3)	0.68 (0.39–1.18)	0.17
Death at 90 days	10 (4.1)	3 (1.2)	3.38 (0.92–12.52)	0.07
Secondary				
Symptomatic intracranial hemorrhage				
As defined in SITS-MOST‡	5 (2.0)	1 (0.4)	4.95 (0.57–42.87)	0.15
As defined in ECASS II§	7 (2.8)	3 (1.2)	2.40 (0.60–9.53)	0.21
As defined in ECASS III¶	6 (2.4)	1 (0.4)	6.04 (0.72–50.87)	0.10
As defined in NINDS‖	20 (8.0)	12 (4.9)	1.78 (0.84–3.71)	0.13
Parenchymal hemorrhage type 2**	10 (4.0)	1 (0.4)	10.46 (1.32–82.77)	0.03
Other††				
Space-occupying brain infarction or edema with clinical deterioration	6 (2.4)	2 (0.8)		
Recurrent ischemic stroke				
Asymptomatic‡‡	58 (23.1)	55 (22.5)		
Symptomatic	17 (6.8)	8 (3.3)		
Major extracranial bleeding	3 (1.2)	0		
Severe anaphylactic reaction	0	1 (0.4)		

Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data

Bruce C V Campbell, Henry Ma*, Peter A Ringleb*, Mark W Parsons, Leonid Churilov, Martin Bendszus, Christopher R Levi, Chung Hsu, Timothy J Kleinig, Marc Fatar, Didier Leys, Carlos Molina, Tissa Wijeratne, Sami Curtze, Helen M Dewey, P Alan Barber, Kenneth S Butcher, Deidre A De Silva, Christopher F Bladin, Nawaf Yassi, Johannes A R Pfaff, Gagan Sharma, Andrew Bivard, Patricia M Desmond, Stefan Schwab, Peter D Schellinger, Bernard Yan, Peter J Mitchell, Joaquín Serena, Danilo Toni, Vincent Thijs, Werner Hacke†, Stephen M Davis†, Geoffrey A Donnan†, on behalf of the EXTEND, ECASS-4, and EPITHET Investigators‡*



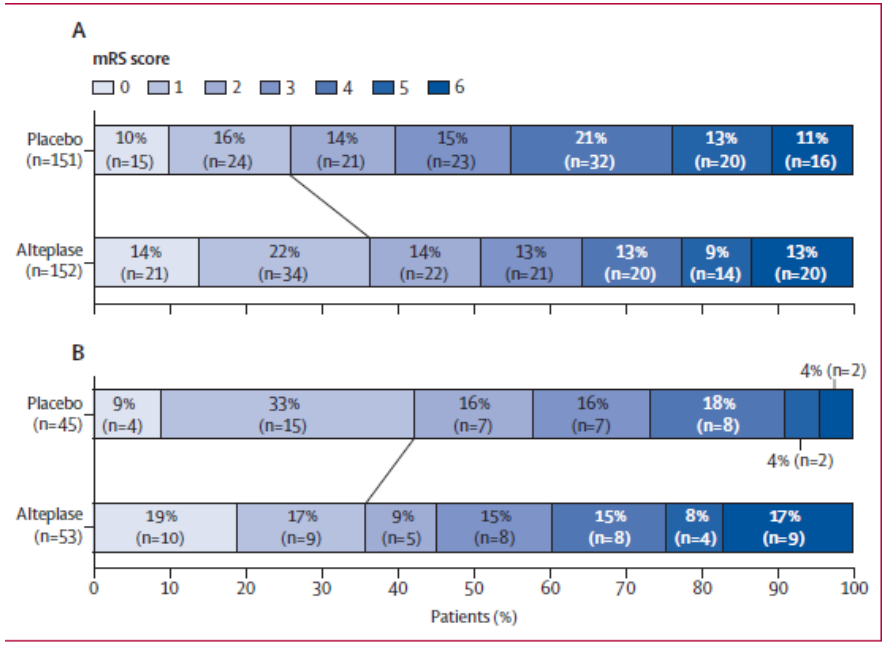
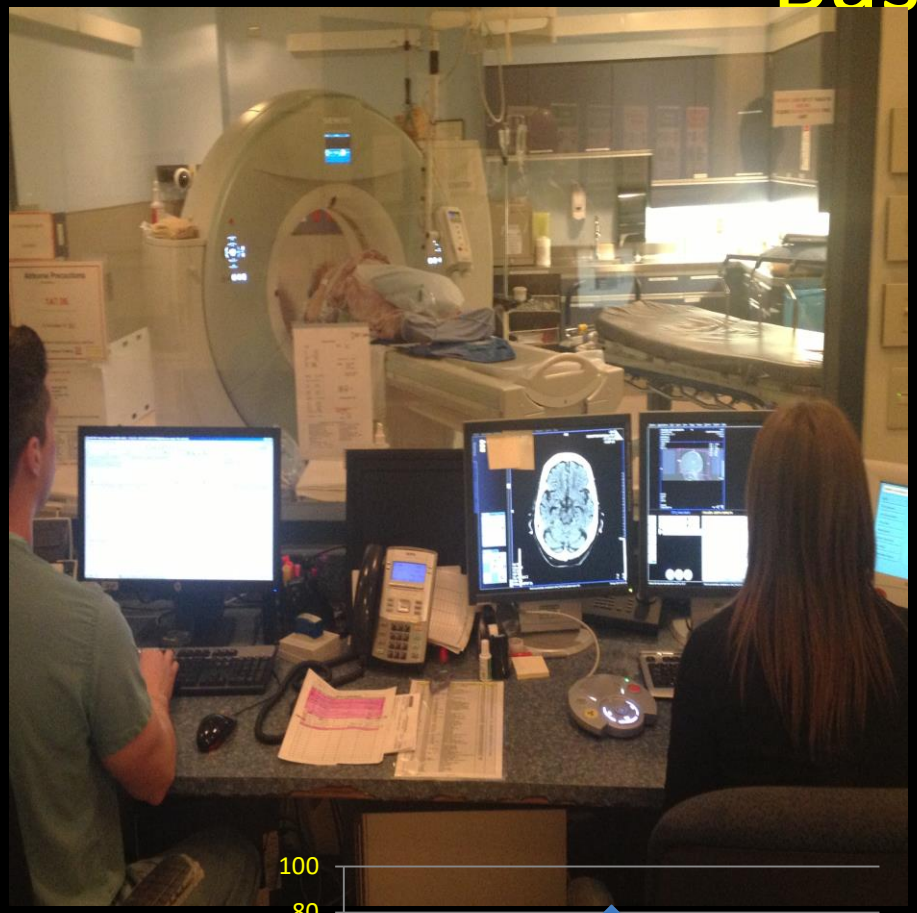


Figure 3: mRS score at 3 months by perfusion mismatch subgroup

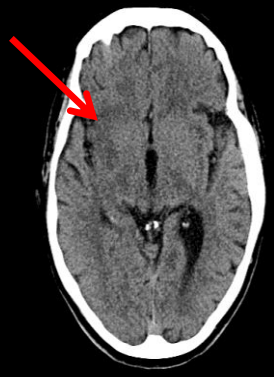
Outline of presentation

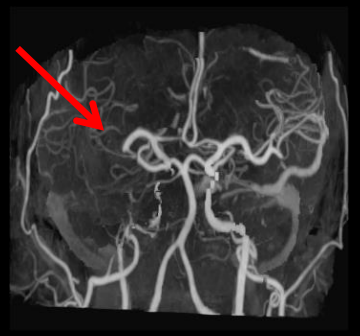
- Rates of neuronal injury during acute stroke
- Current time-window recommendations for thrombolysis
- Evidence for thrombolysis in the later time windows
- Infra-structure and system change requirements for extending time window for thrombolysis

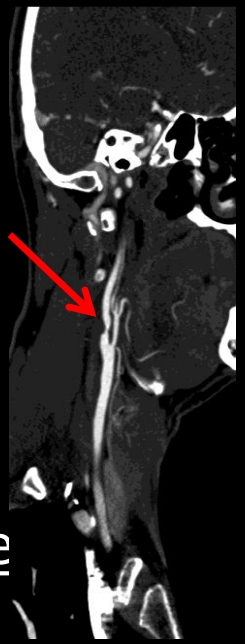
UAH Stroke Diagnosis and Treatment: CT Based



Treatment starts here

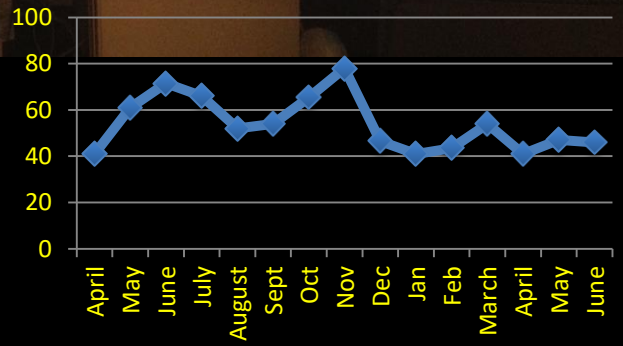






CT + CTA + CTP:

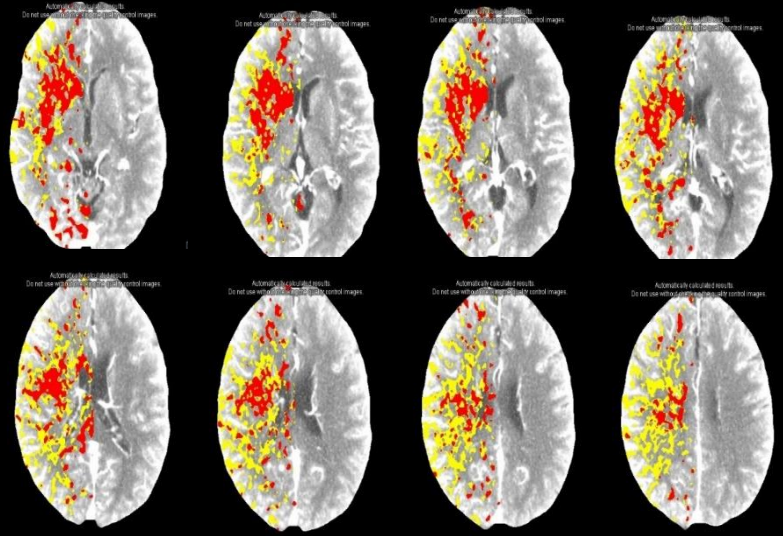
10 min: total table time



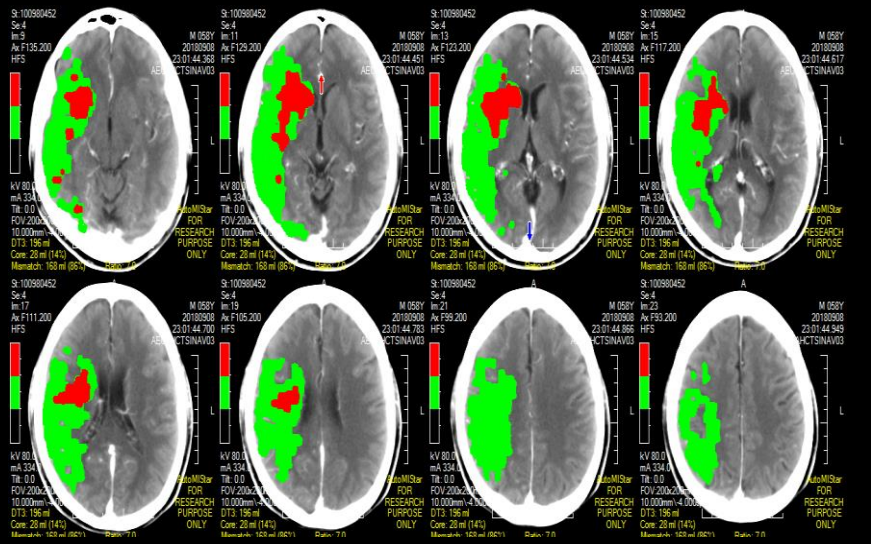
QuICR

Penumbral Mapping Software Options

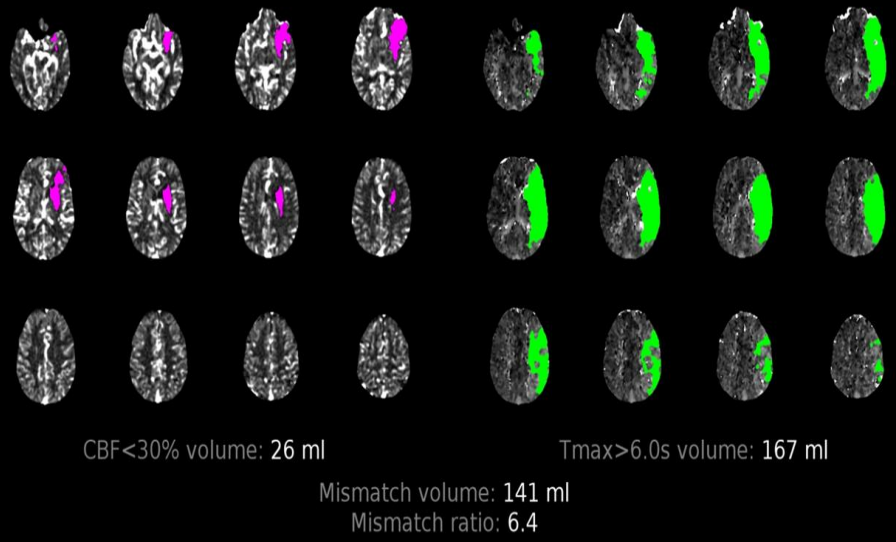
Siemens (no volumes)



MiStar (Apollo Imaging

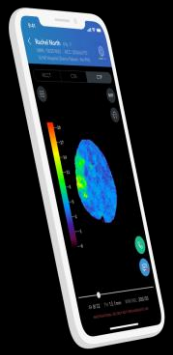


iSchemaView)

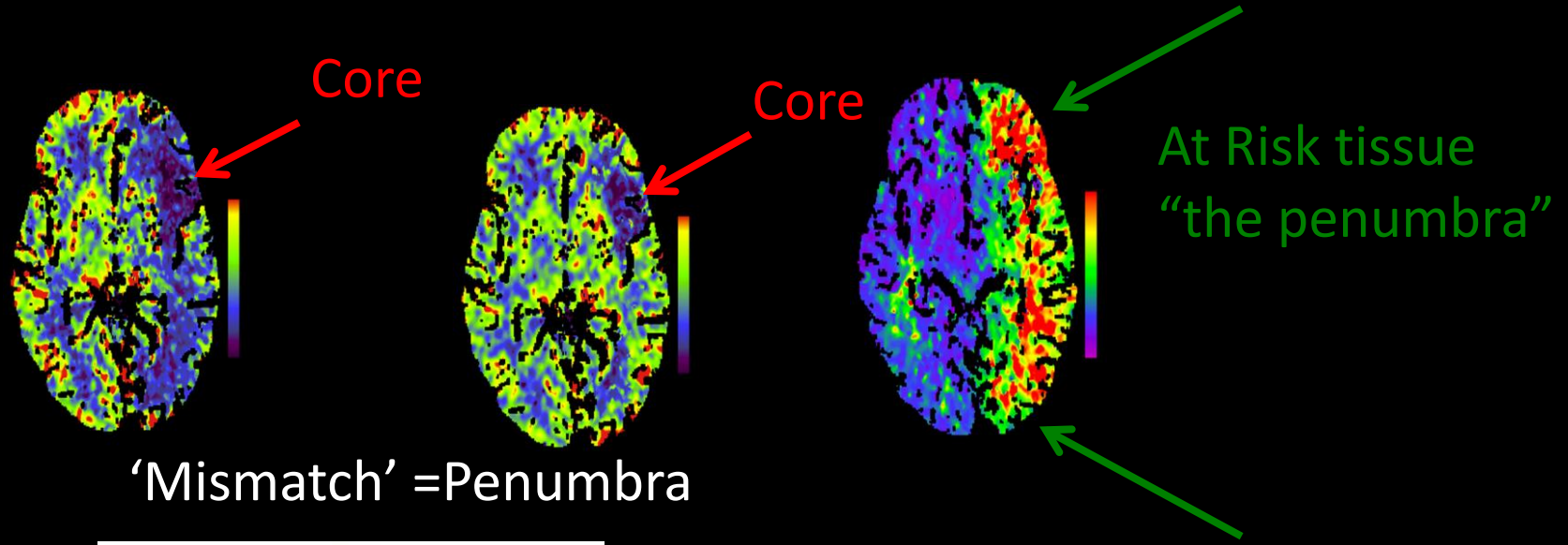


Olea Medical

Viz CTP



I asked for the time...not how the watch works!



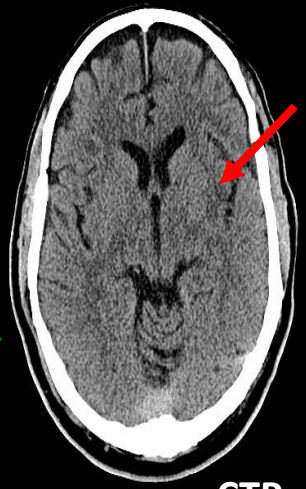
'Mismatch' =Penumbra

Courtesy Dr Ken Butcher

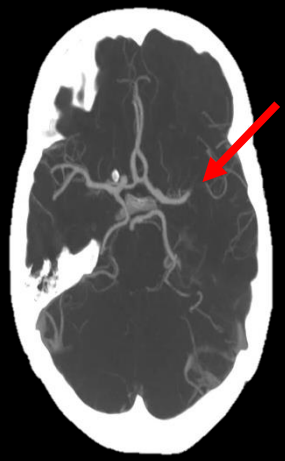
Penumbral Patterns in the ESCAPE Trial

71 yrs male
NIHSS 22
Onset 5.5 hours

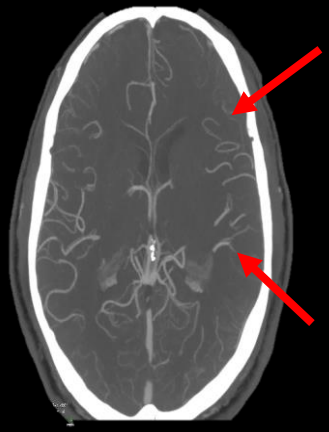
NCCT: ASPECTS 9



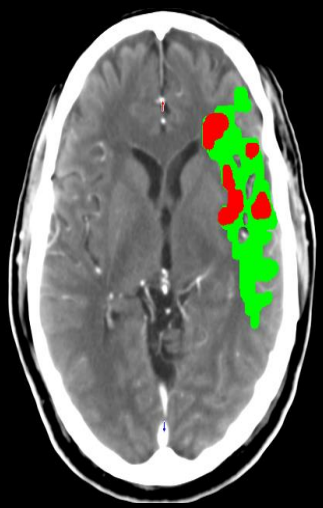
CTA: M1 Occlusion

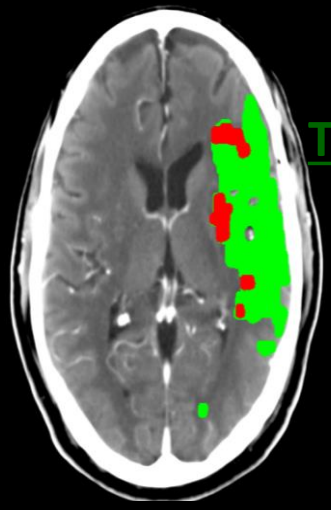


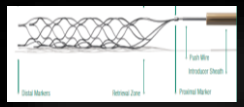
CTA Collaterals: Good



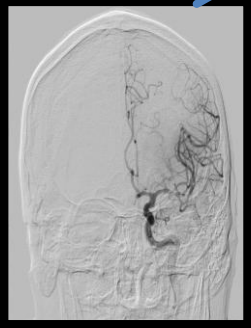
CTP: Penumbral Pattern



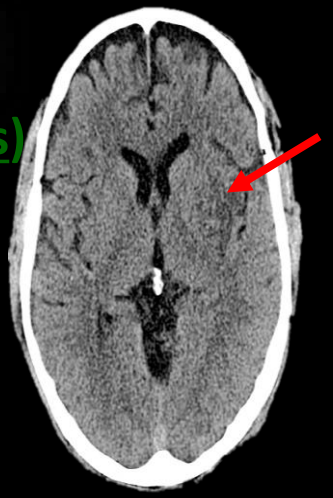




TICI 3 (7.7 hours)

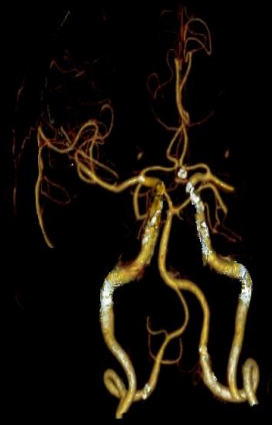


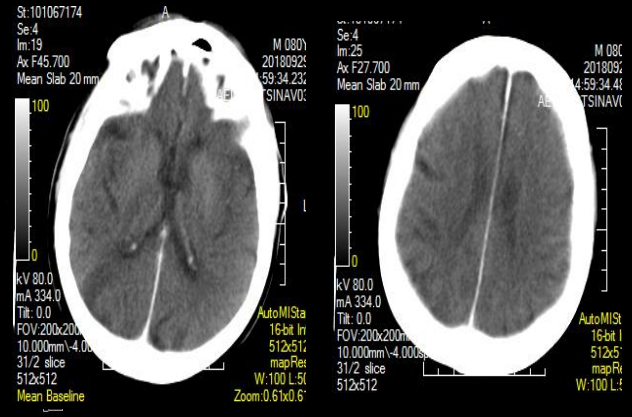
24 Hour NCCT

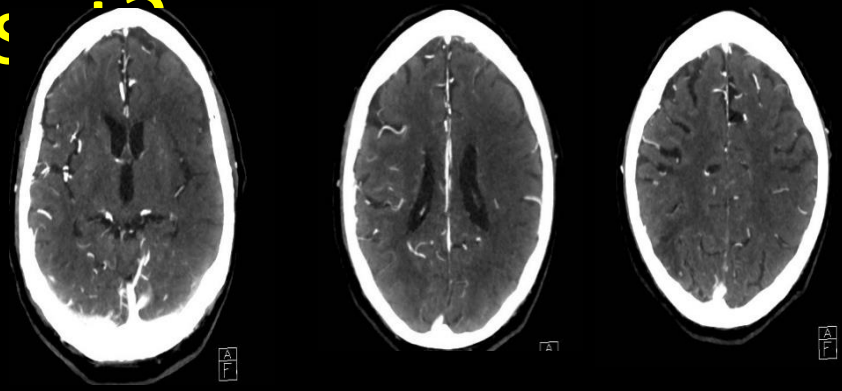


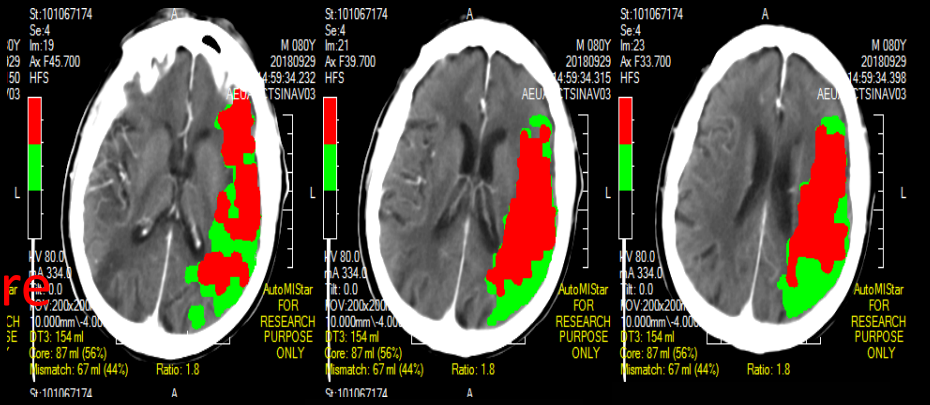
Does CTP Have a Role < 6 h From Ons

79 M: 1.5 h after onset



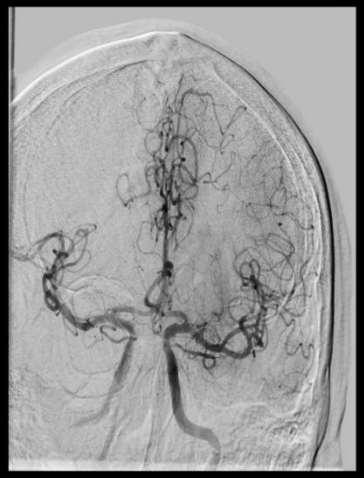


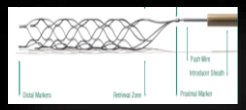




2.10 h (residual M2 after tPA)

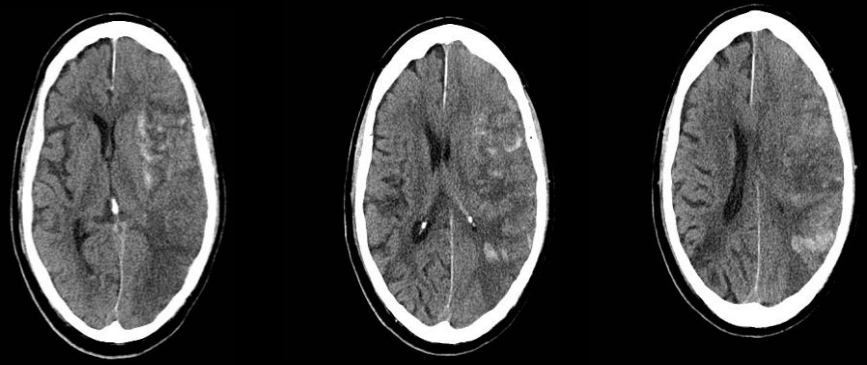
87 ml core





TICI 3 (3.20 hours)

24 h CT



Edmonton Stroke Program

- 24/7 comprehensive program with, pre-hospital ambulance and tele-stroke
- Immediate availability of advanced imaging
- Careful clinical evaluation by the stroke team
- Rapid access to angio-suite and an enthusiastic interventionist critical for success
- After treatment care very important
- Follow-up evaluation to determine recovery

Conclusions

- **Highly effective treatment including thrombolysis and thrombectomy for acute stroke patients available**
- **Treatment is time-dependent very early**
- **Effective treatment available up to or later than 24 hours in some patients**
- **For patients presenting late, imaging essential to determination “slow-progressors”**
- **Comprehensive stroke program essential**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