Thrombolysis in acute stroke management

Ashfaq Shuaib, MD FRCPC FAHA

Professor of Medicine and Neurology

University of Alberta

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

No conflict of interest to declare with this presentation

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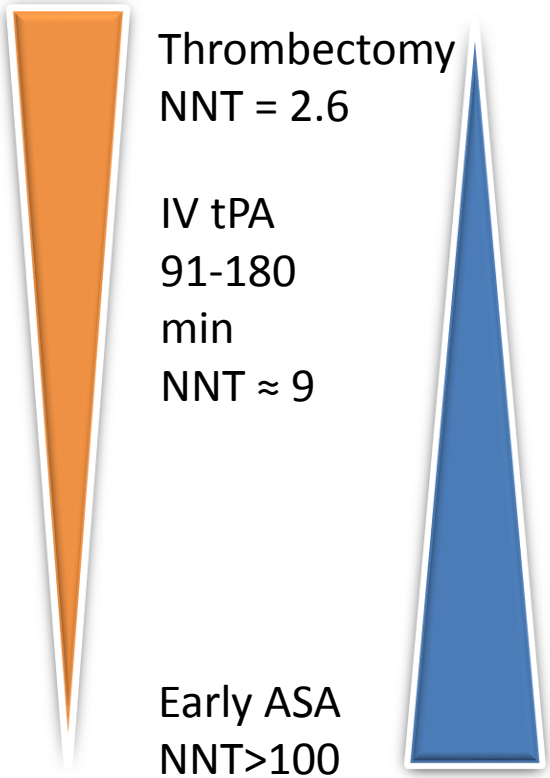
Outline of presentation

- **Rationale for reperfusion-treatment time windows in acute stroke**
- Current recommendations and guidelines
- Extending the time window for thrombolysis
- What's new !

Overview of Acute Stroke Therapies

Greatest Efficacy
Lowest NNT

Fewer strokes benefit

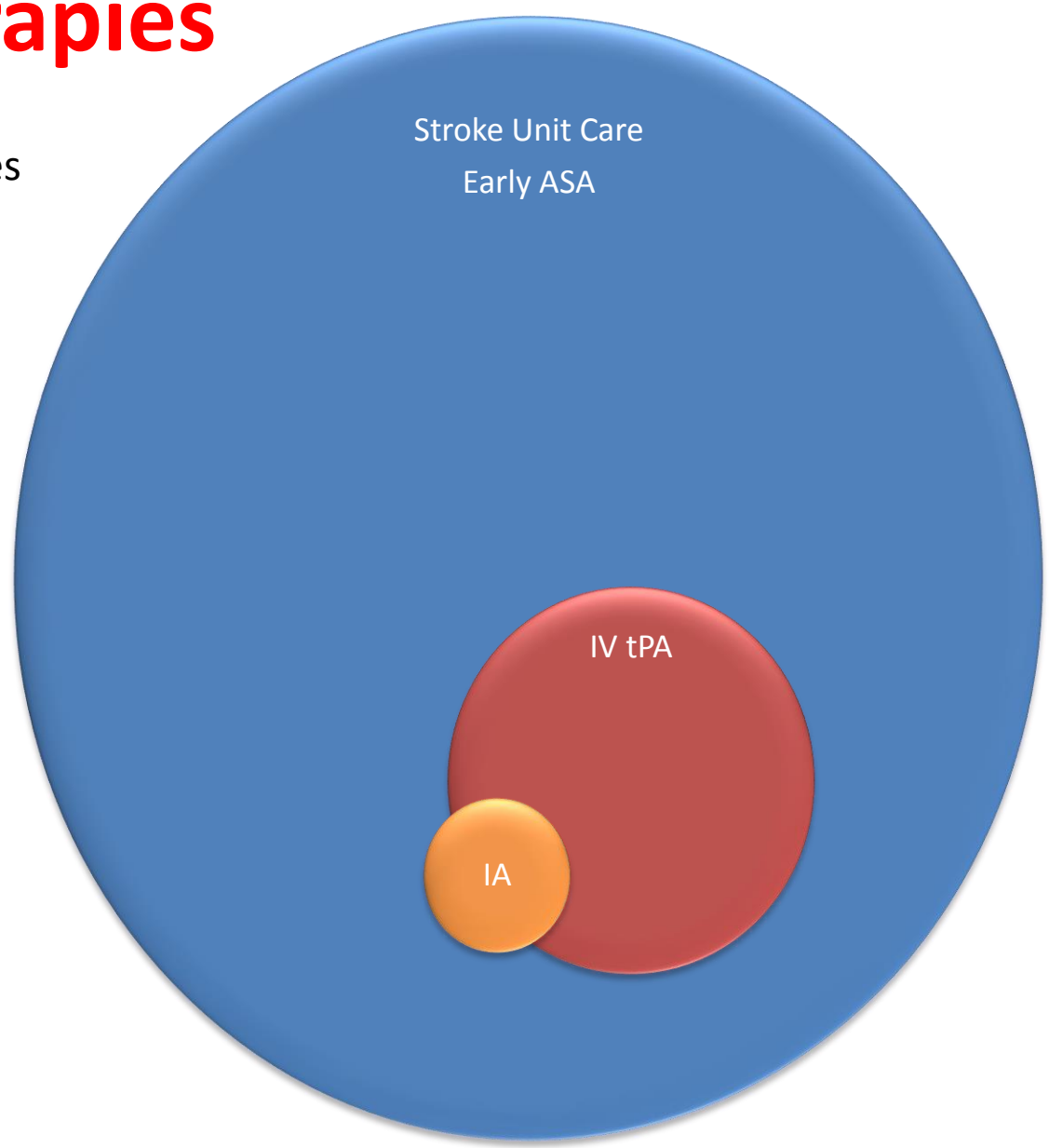


Thrombectomy
NNT = 2.6

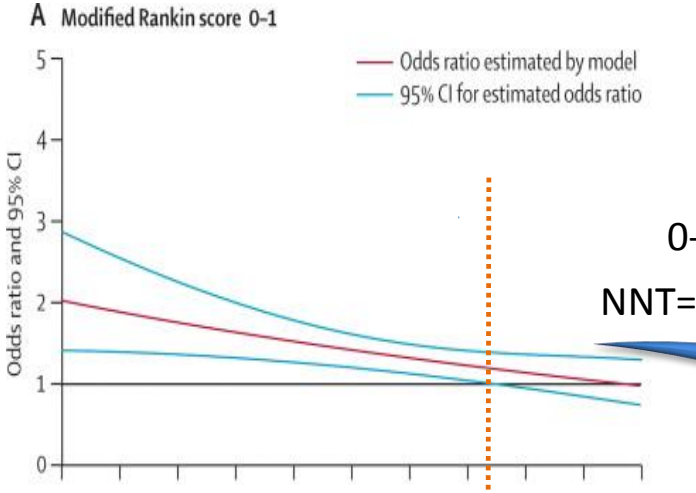
IV tPA
91-180 min
NNT ≈ 9

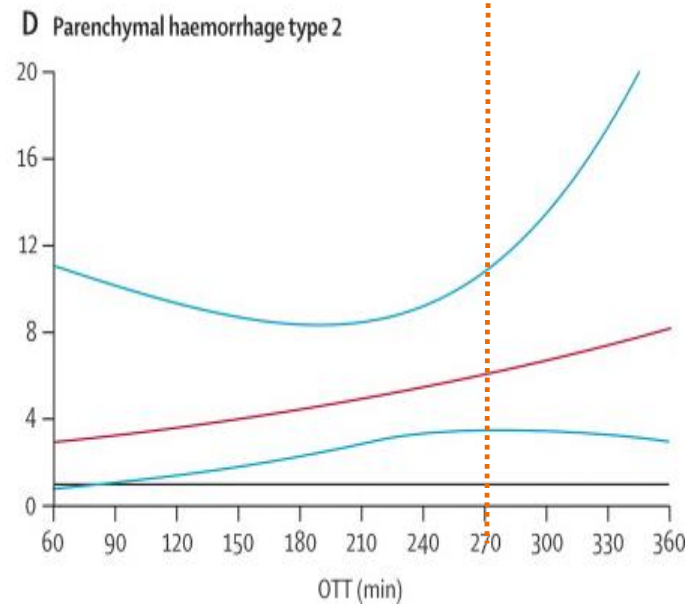
Early ASA
NNT>100

Almost all strokes benefit



Benefits of tPA decay rapidly over time: Time to IV tPA treatment and outcome, pooled analysis 8 trials (n=3670)





0-90 minutes

NNT=4.5 for mRS 0-1

91-180 min

NNT=9.0

181-270 min

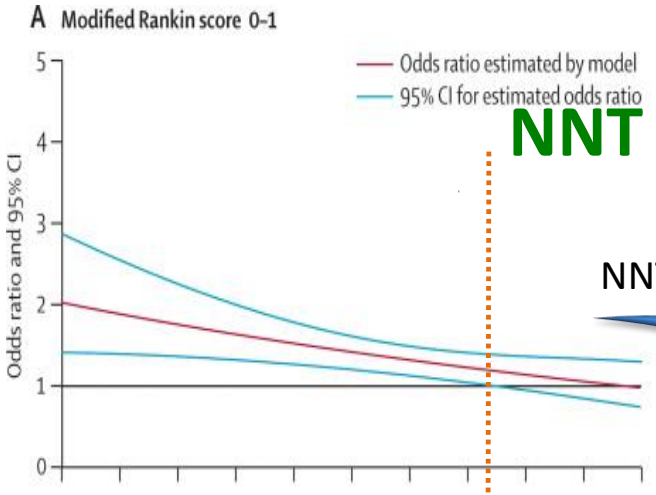
NNT=14.9

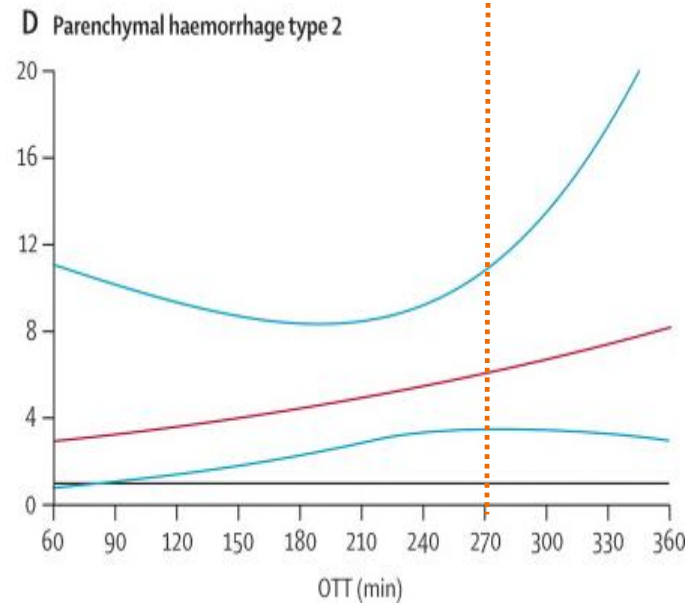
270-360 min

NNT=28.7

Lancet 2010 Vol 375, Issue 9727, Pages 1695–1703

Benefits of tPA decay rapidly over time: Time to IV tPA treatment and outcome, pooled analysis 8 trials (n=3670)





NNT increase by 1 per 20 min delay

0-90 minutes

NNT=4.5 for mRS 0-1

91-180 min

NNT=9.0

181-270 min

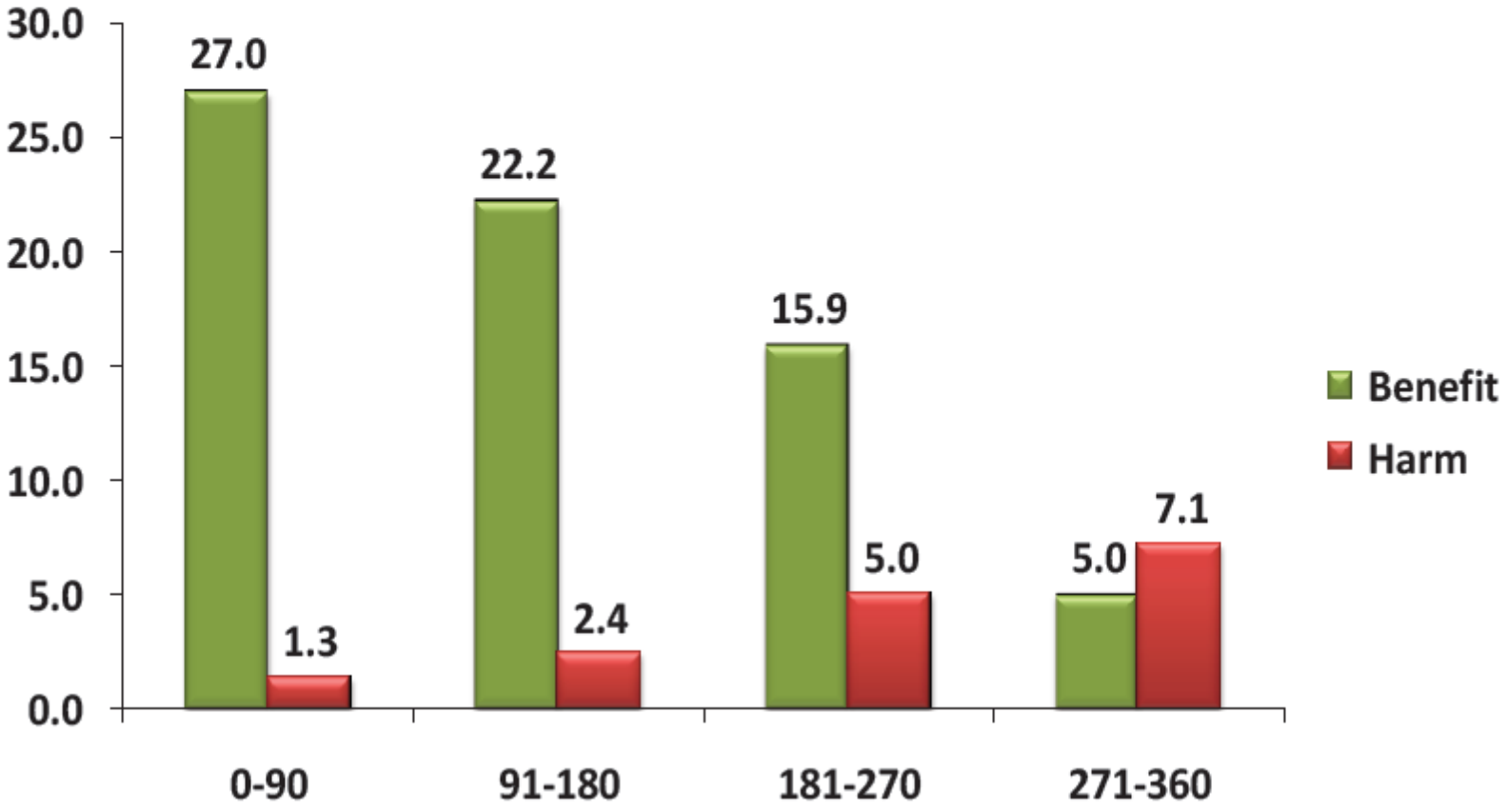
NNT=14.9

270-360 min

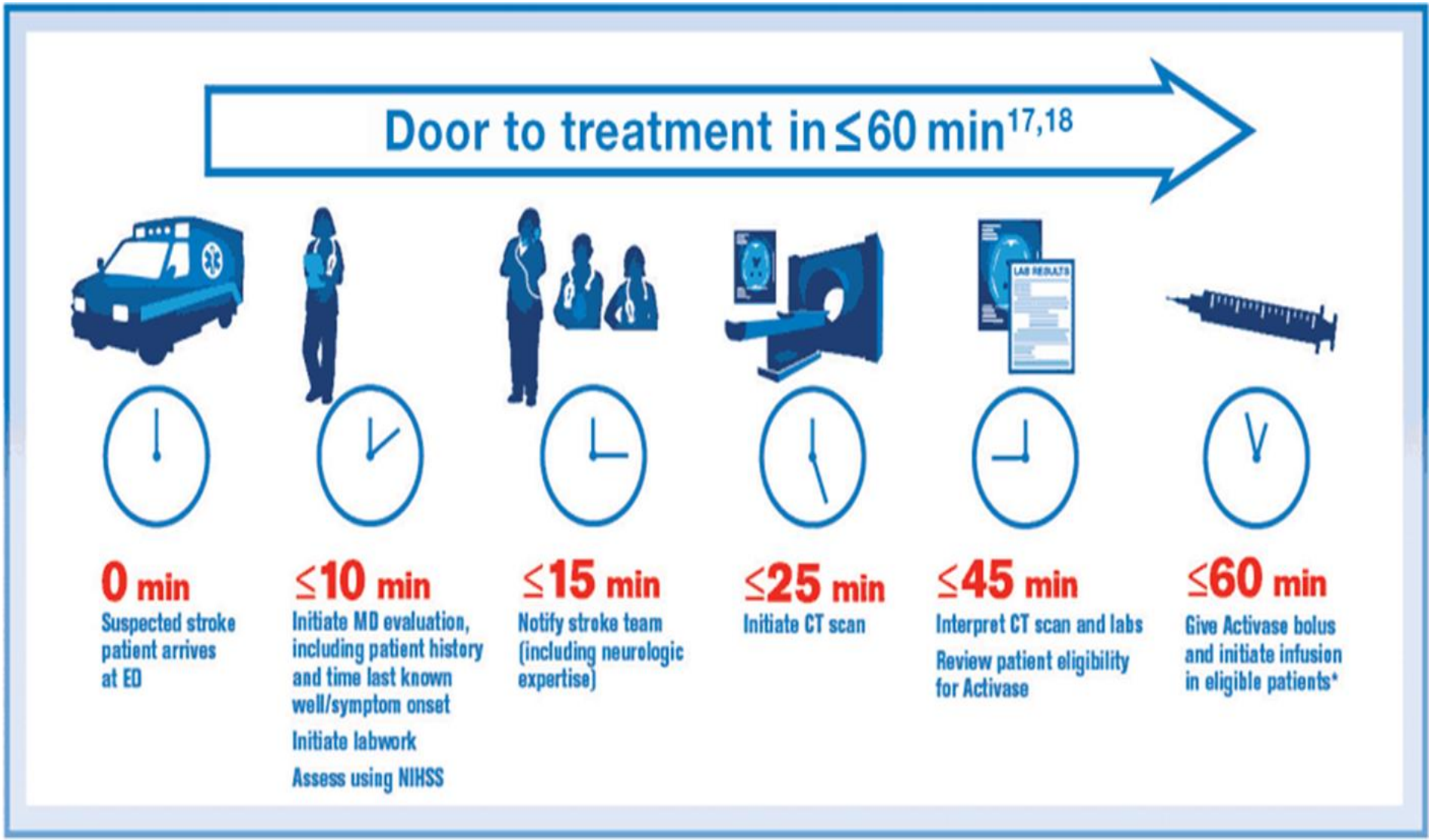
NNT=28.7

Lancet 2010 Vol 375, Issue 9727, Pages

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

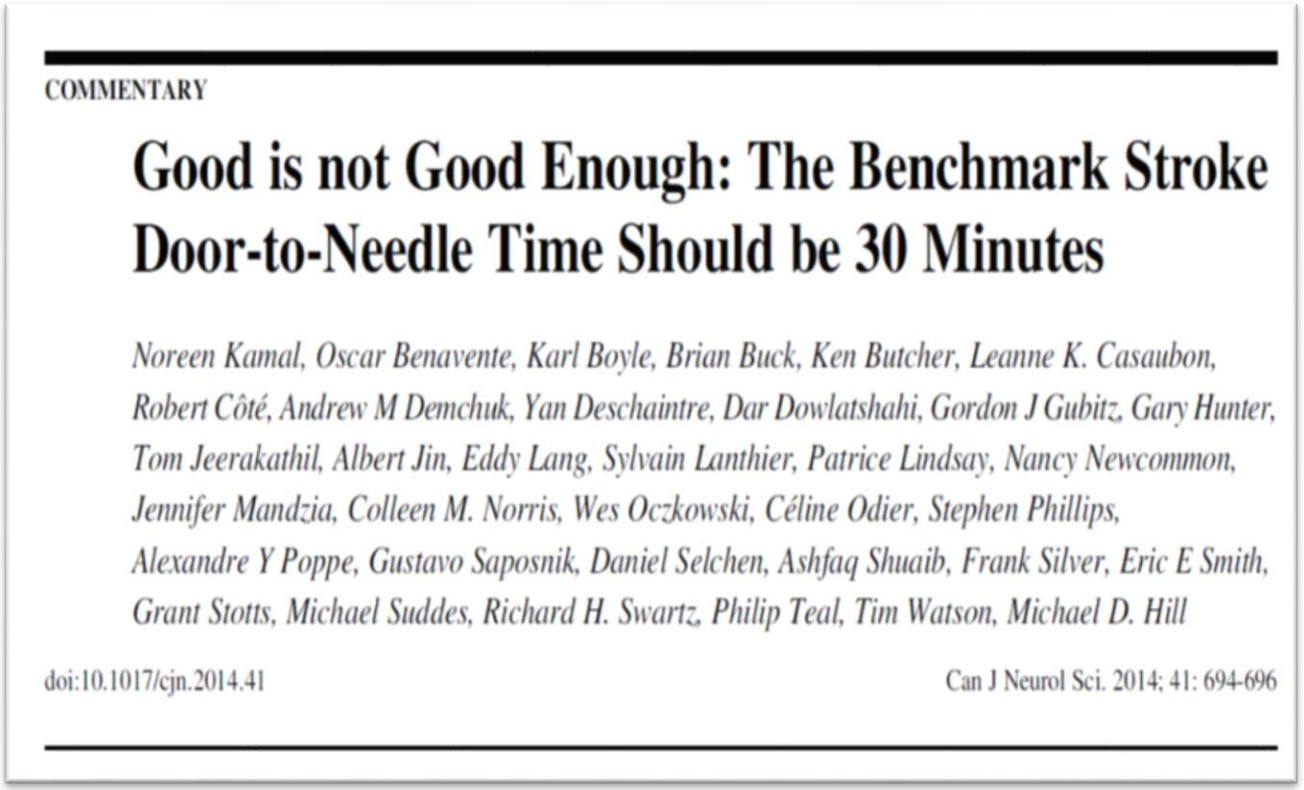


What is a reasonable DTN?



New target median < 30 minutes

- DTN of <30 minutes are achievable outside of tertiary centres
- takes innovative system level QI processes



COMMENTARY

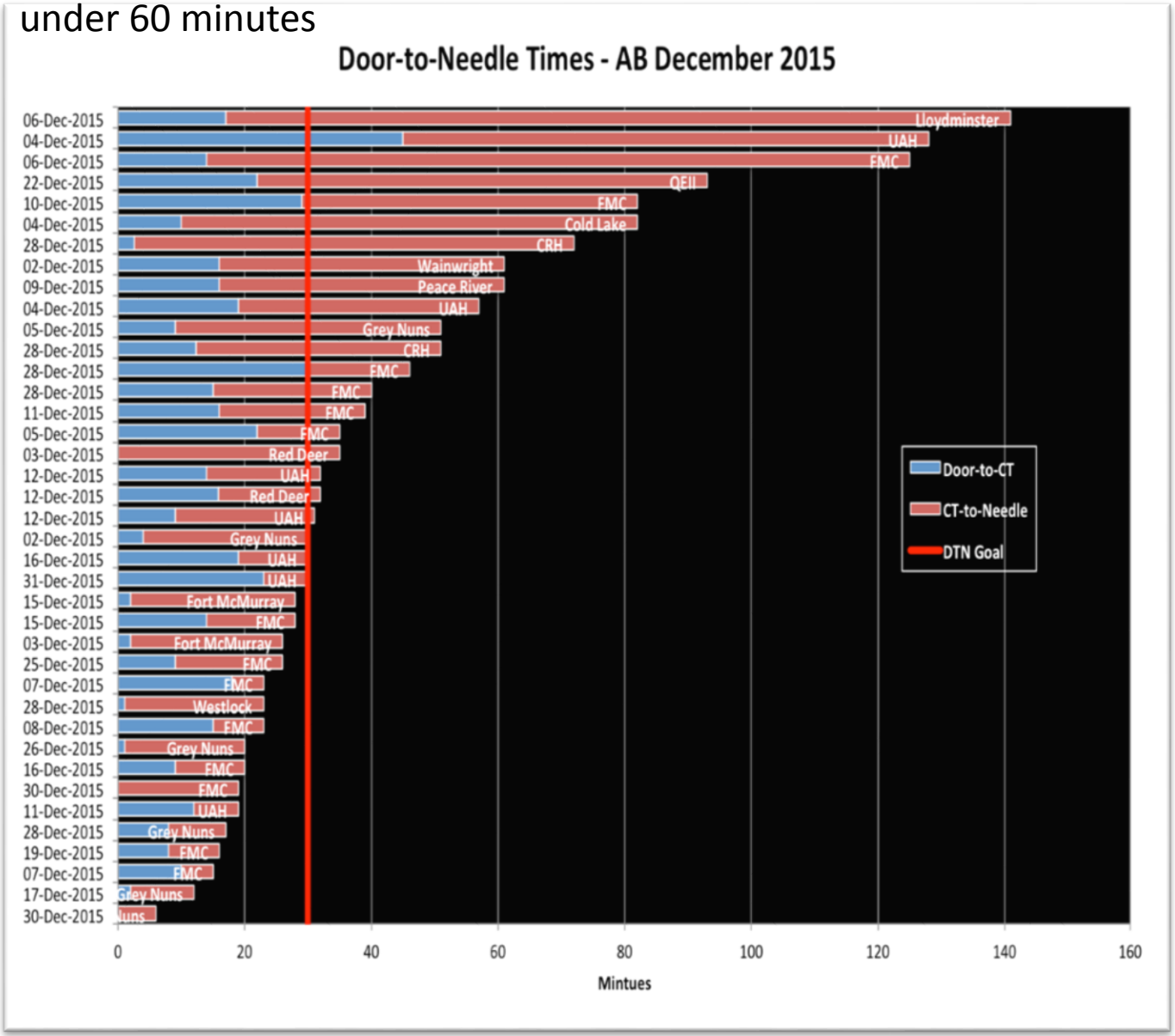
Good is not Good Enough: The Benchmark Stroke Door-to-Needle Time Should be 30 Minutes

Noreen Kamal, Oscar Benavente, Karl Boyle, Brian Buck, Ken Butcher, Leanne K. Casaubon, Robert Côté, Andrew M Demchuk, Yan Deschaintre, Dar Dowlatshahi, Gordon J Gubitz, Gary Hunter, Tom Jeerakathil, Albert Jin, Eddy Lang, Sylvain Lanthier, Patrice Lindsay, Nancy Newcommon, Jennifer Mandzia, Colleen M. Norris, Wes Oczkowski, Céline Odier, Stephen Phillips, Alexandre Y Poppe, Gustavo Saposnik, Daniel Selchen, Ashfaq Shuaib, Frank Silver, Eric E Smith, Grant Stotts, Michael Suddes, Richard H. Swartz, Philip Teal, Tim Watson, Michael D. Hill

doi:10.1017/cjn.2014.41

Can J Neurol Sci. 2014; 41: 694-696

In Dec 2015 Provincial median DTN 31 minutes; 78% treated under 60 minutes



From N Kar

Time is brain !!!

- Public awareness
- Setting up a fast triage and assessment system (from EMS pre-notification to activation of stroke team)
- Decision making (confirm diagnosis and rule out mimics)
  - Within window
  - Sudden onset
  - Focal symptoms
- Imaging

Clinical examination and imaging

- **Clinical examination**
  - Ischemic stroke: Cortical vs subcortical or posterior
  - Small or large deficit
  - Core vs prenumbra
- Imaging
  - No hemorrhage
  - Extent of cerebral tissue at risk
  - Is there a proximal occlusion

Clinical examination and imaging

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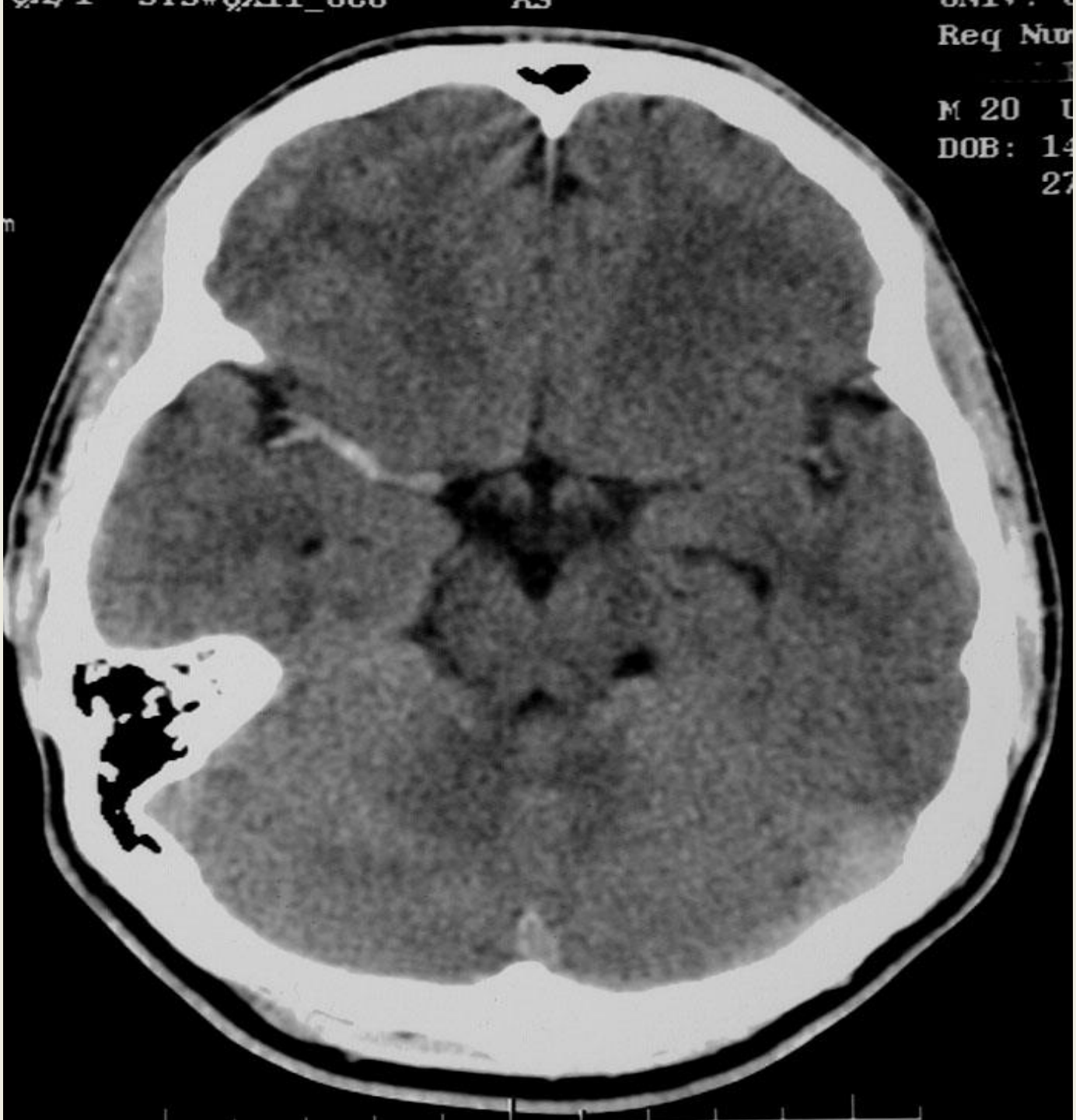
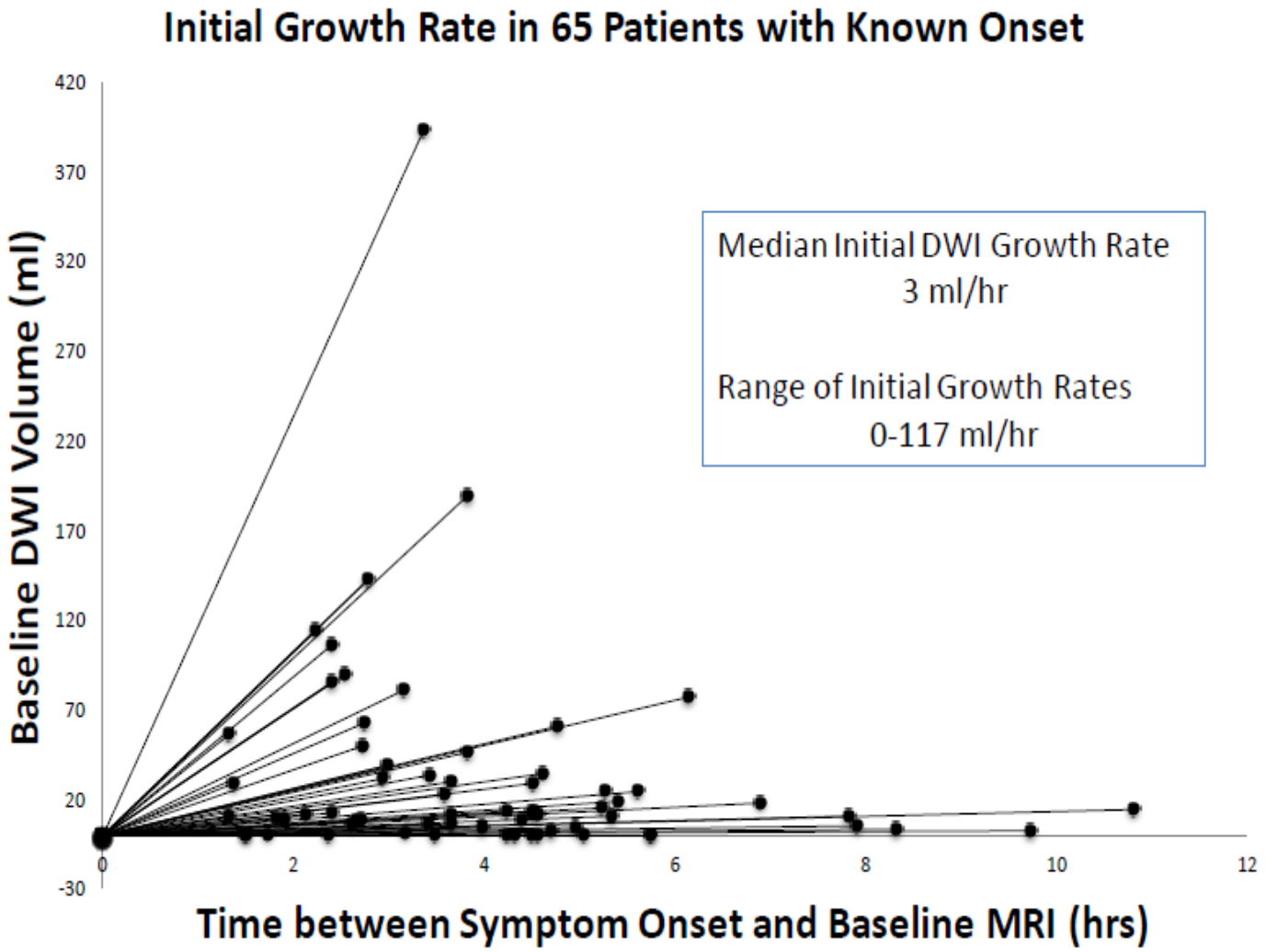

Req Nu
M 20
DOB: 14
27

DEFUSE 2: Speed of progression

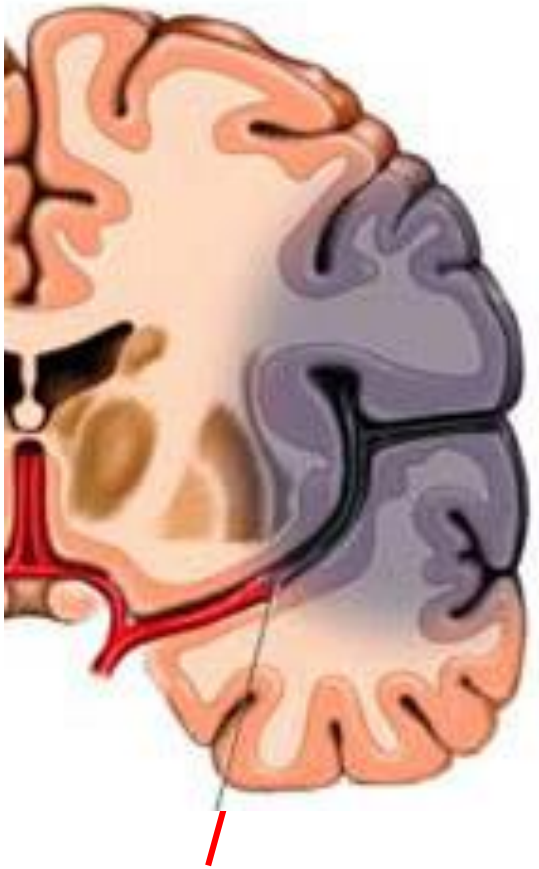
Part 1 Analysis



Acute Ischemic Stroke (classsic teaching)

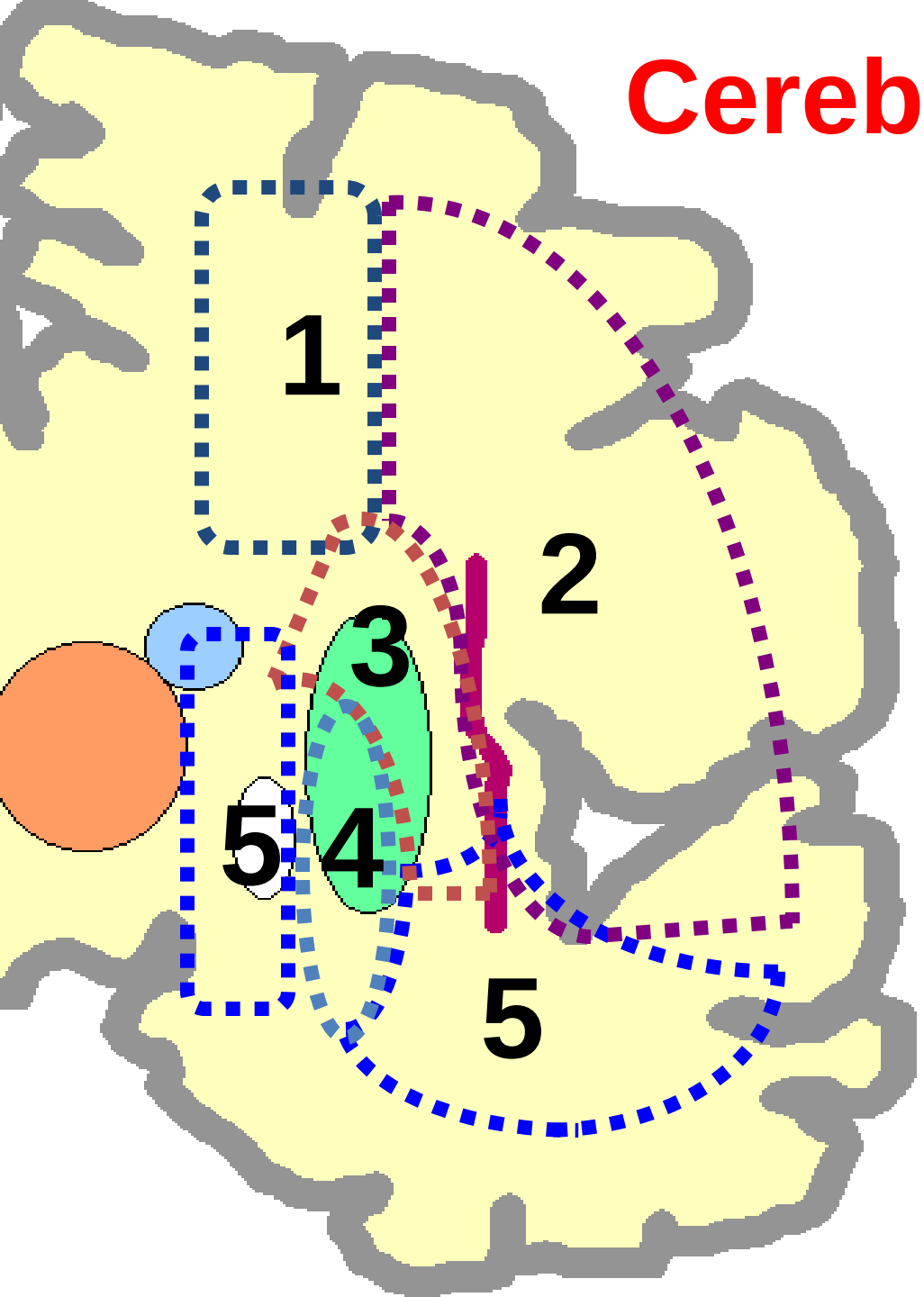
Thrombo-embolism

Ischemia (lack of blood flow)



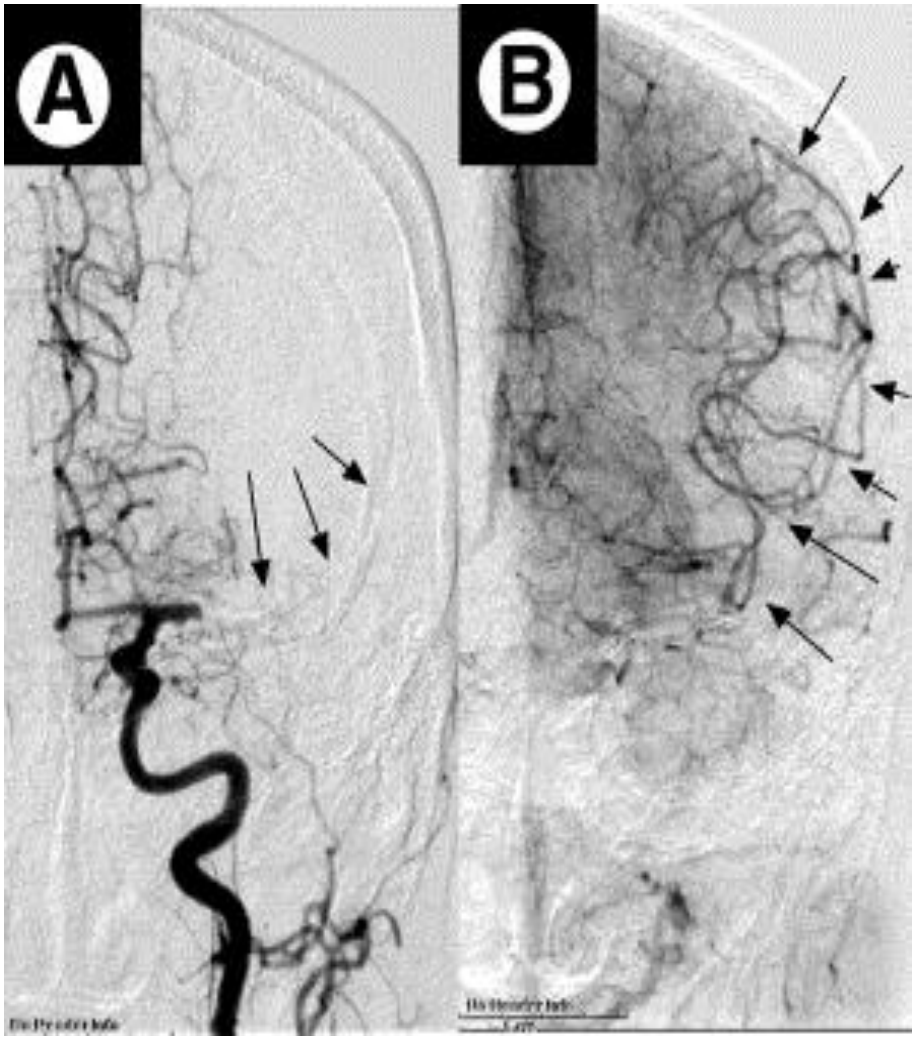
Thrombus (Clot)

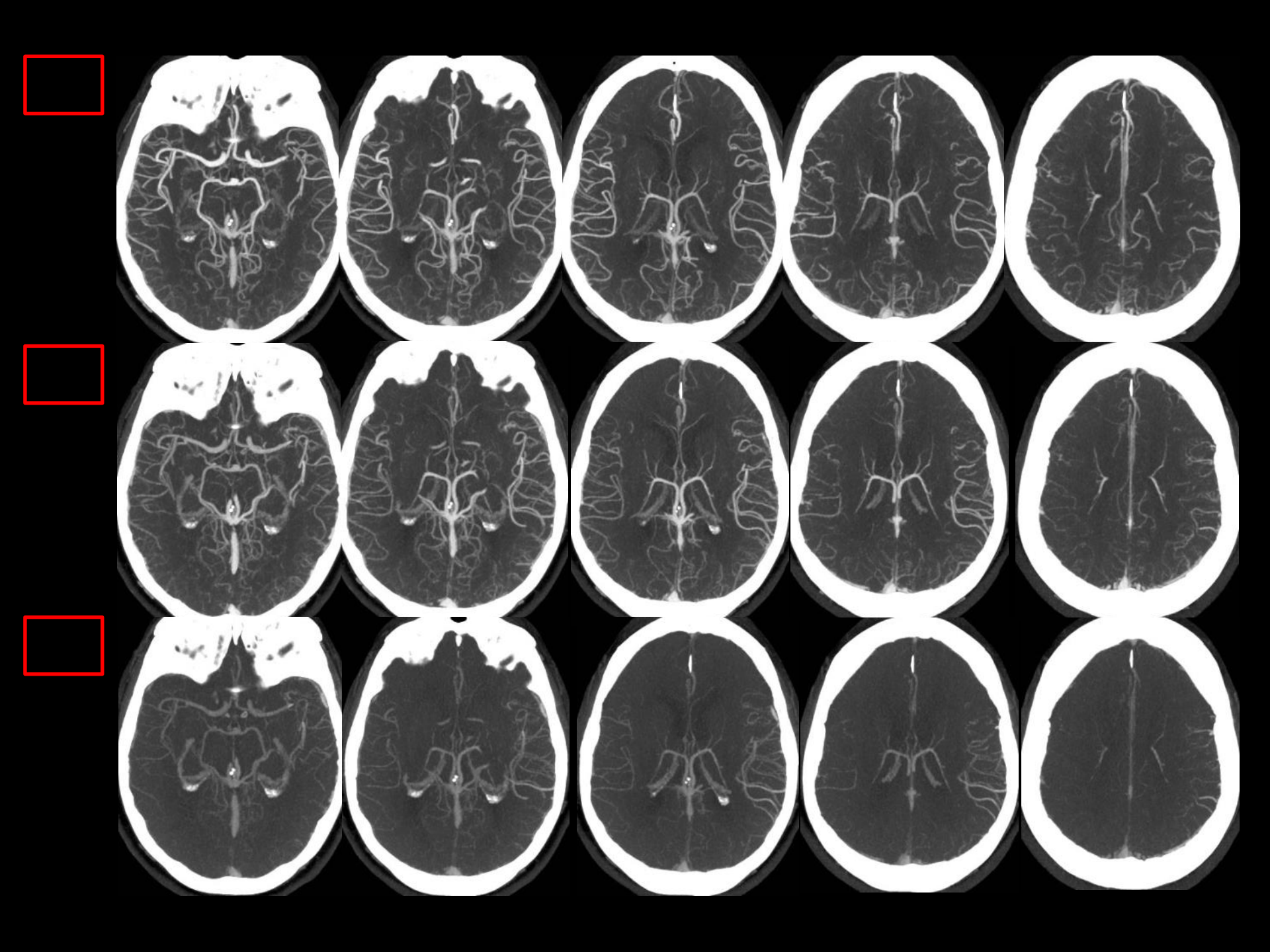
Cerebral Artery Areas

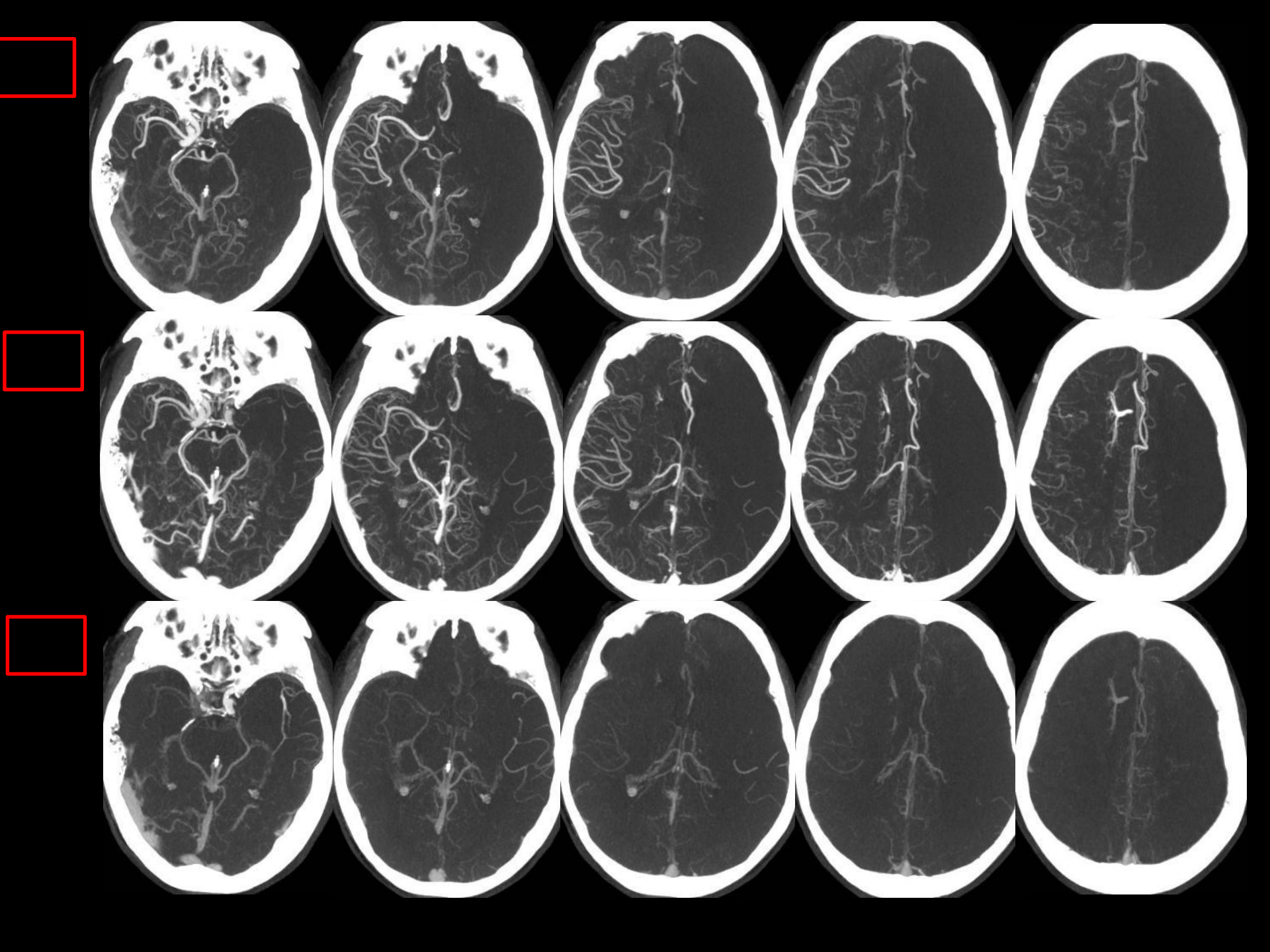


1. Anterior cerebral
2. Middle cerebral
3. Penetrating branches of middle cerebral
4. Anterior choroidal
5. Posterior cerebral

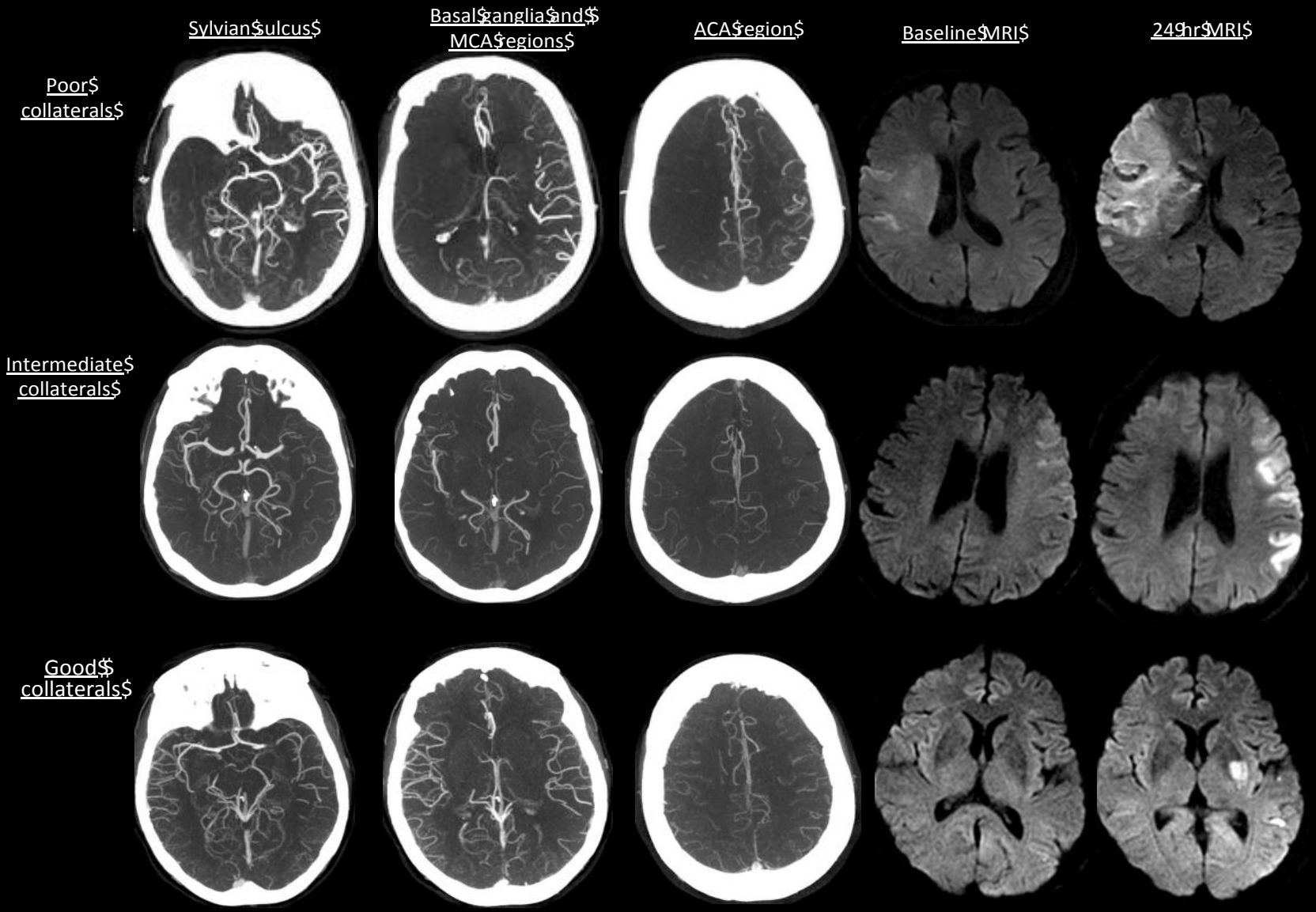
The role of collaterals in stroke progression







Collaterals Predict Imaging and Clinical Outcomes



Outline of presentation

- Rationale for reperfusion-treatment windows in acute stroke
- **Current recommendations and guidelines**
- Thrombolysis outside the time window

Who should get IV thrombolysis?

- Canadian Stroke Best Practice Recommendations:
  Hyperacute Stroke Care Guidelines, Update 2015

  - Eligible patients are those who can receive intravenous tPA within 4·5 h of the onset of stroke symptoms using criteria adapted from NINDS tPA Stroke Study

  - All eligible patients should receive intravenous tPA as soon as possible after hospital arrival using a dose of 0·9 mg/kg

http://www.strokebestpractices.ca/

AHA/ASA Scientific Statement

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

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

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Bart M. Demaerschalk, MD, MSc, FRCPC, FAHA, Chair;
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Yuko Y. Palesch, PhD; Shyam Prabhakaran, MD, MS, FAHA;
Gustavo Saposnik, MD, MSc, FAHA; Jeffrey L. Saver, MD, FAHA;
Eric E. Smith, MD, MPH, FAHA; on behalf of the American Heart Association Stroke Council and Council on Epidemiology and Prevention

Stroke **February 2016**

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*).**

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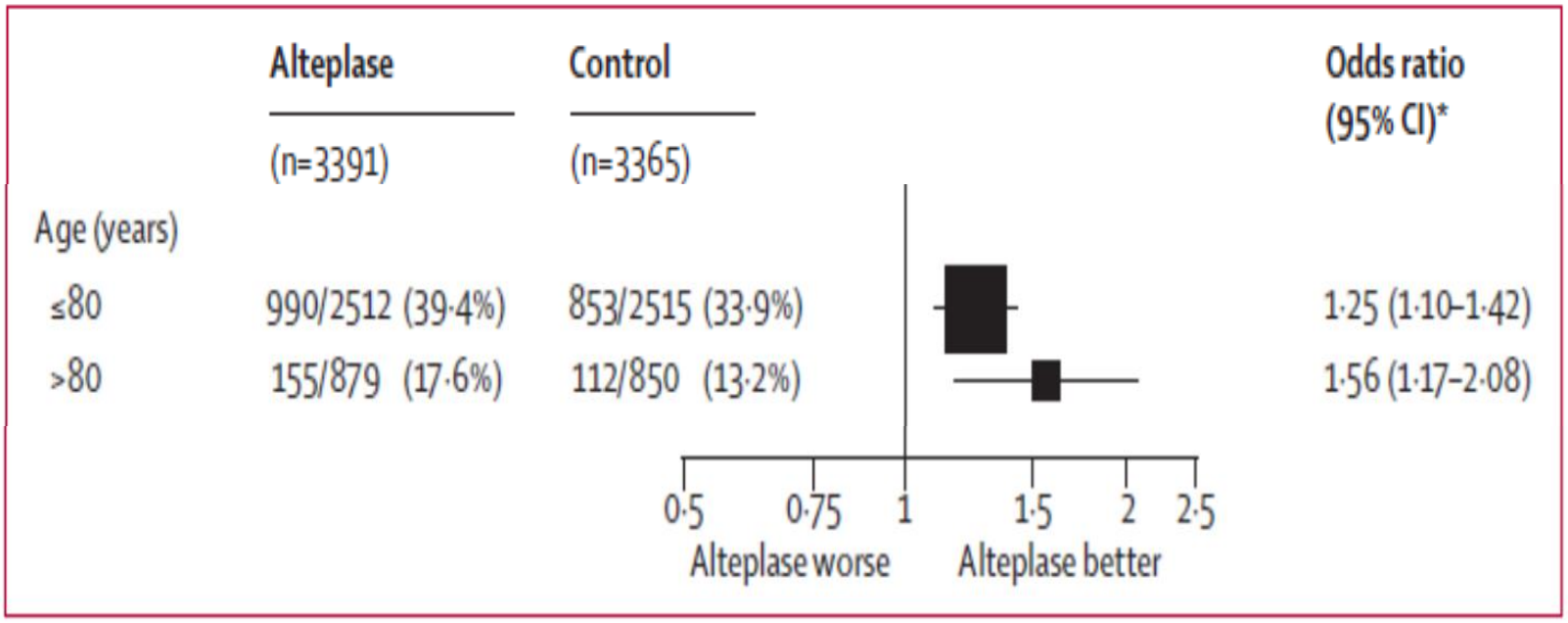
Age Issues: Recommendations

1. For otherwise medically eligible patients ≥18 years of age, intravenous alteplase administration within 3 hours is equally recommended for patients <80 and >80 years of age. Older age is an adverse prognostic factor in stroke but does not modify the treatment effect of thrombolysis. Although older patients have poorer outcomes, higher mortality, and higher rates of sICH than those <80 years of age, compared with control subjects, intravenous alteplase provides a better chance of being independent at 3 months across all age groups (*Class I; Level of Evidence A*).
2. The efficacy and risk of intravenous alteplase administration in the pediatric population (neonates, children, and adolescents <18 years of age) are not well established (*Class IIb; Level of Evidence B*).

Is thrombolysis beneficial in those >80 years?

Meta-analysis of patient data from 9 RCT

Age doesn't matter!

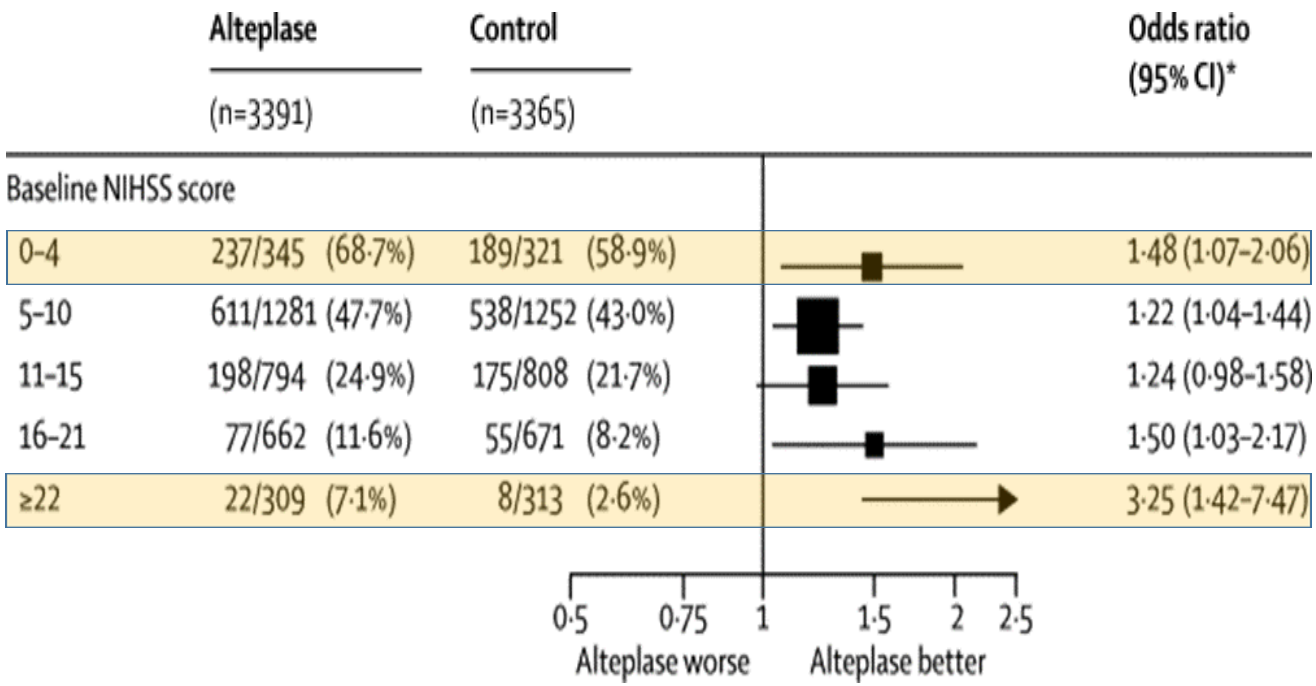


www.thelancet.com Vol 384 November 29, 2014

Stroke Severity: Recommendations

1. For severe stroke symptoms, intravenous alteplase is indicated within 3 hours from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms (*Class I; Level of Evidence A*).
2. For patients with mild but disabling stroke symptoms, intravenous alteplase is indicated within 3 hours from symptom onset of ischemic stroke. There should be no exclusion for patients with mild but nonetheless disabling stroke symptoms in the opinion of the treating physician from treatment with intravenous alteplase because there is proven clinical benefit for those patients (*Class I; Level of Evidence A*).

Effect of stroke severity on tPA outcomes?
Meta-analysis of individual patient data from 9 RCT

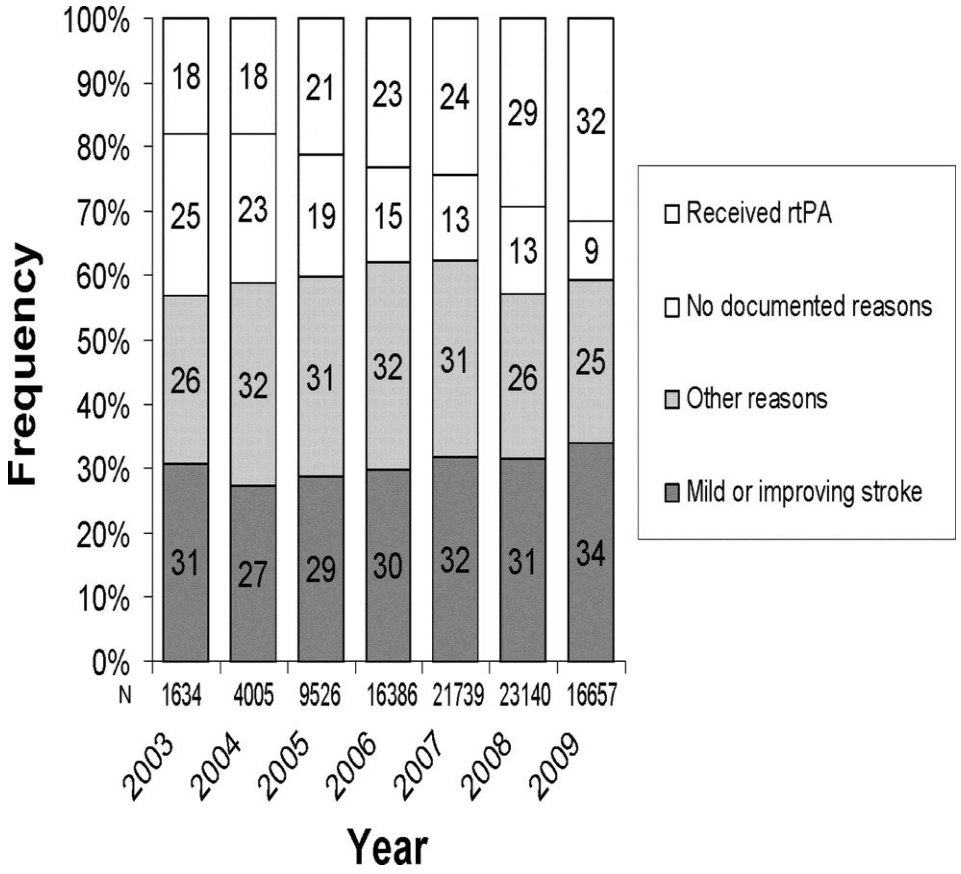


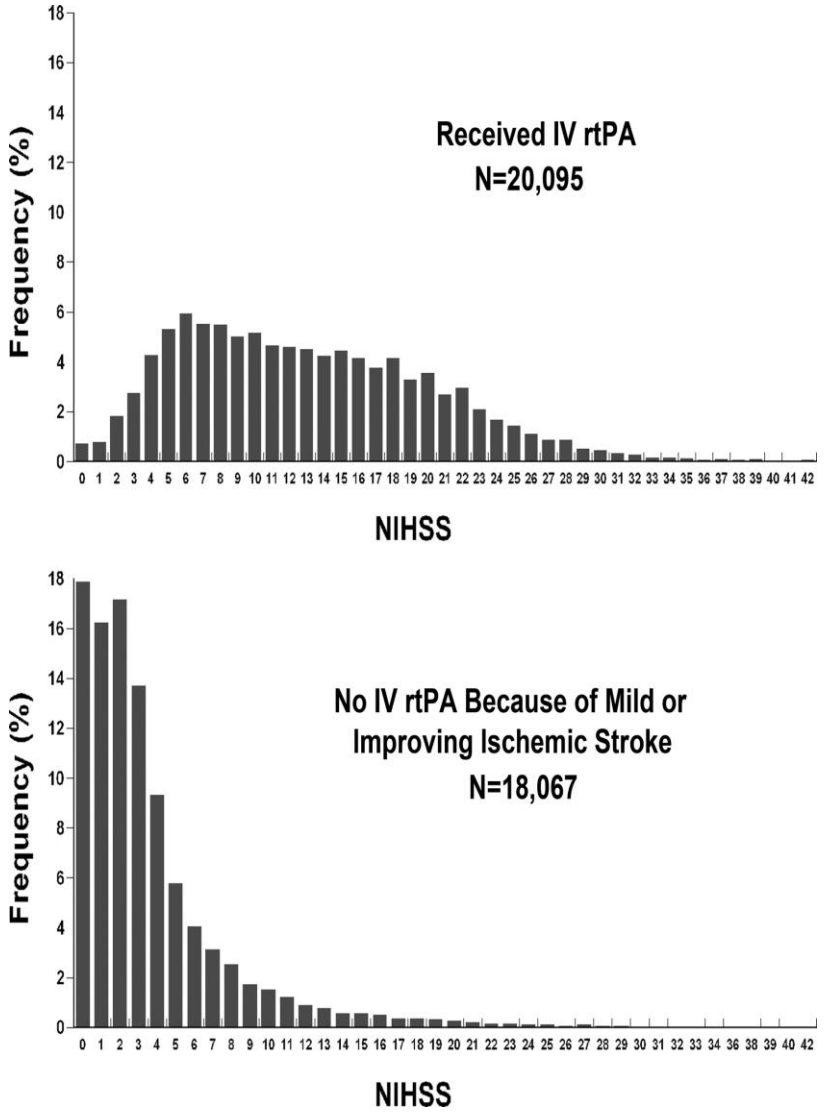
The Lancet, Volume 384, Issue 9958,

Rapidly Improving: Recommendations

1. Intravenous alteplase treatment is reasonable for patients who present with moderate to severe ischemic stroke and demonstrate early improvement but remain moderately impaired and potentially disabled in the judgment of the examiner (*Class IIa; Level of Evidence A*).
2. Because time from onset of symptoms to treatment has such a powerful impact on outcome, delaying treatment with intravenous alteplase to monitor for further improvement is not recommended (*Class III; Level of Evidence C*).

Mild improving stroke most common reason for non-treatment (GWTG data n=93,517)





Eric E. Smith et al. Stroke. 2011;42:3110-

Similar Canadian data

Proportion of patients who received thrombolysis during the study period

Type of stroke, hospital	% (95% CI)
Ischemic stroke (n=33561)	6.1 (5.8–6.4)
Comprehensive stroke center	11.0 (10.4–11.6)
Primary stroke centre	5.7 (5.2–6.2)
Other	1.0 (0.8–1.2)

Based on chart review of 33,561 cases of ischemic strokes admitted 2008-2009

Ganesh et al, CMAJ Open 2014. DOI:10.9778/cmajo.20140067

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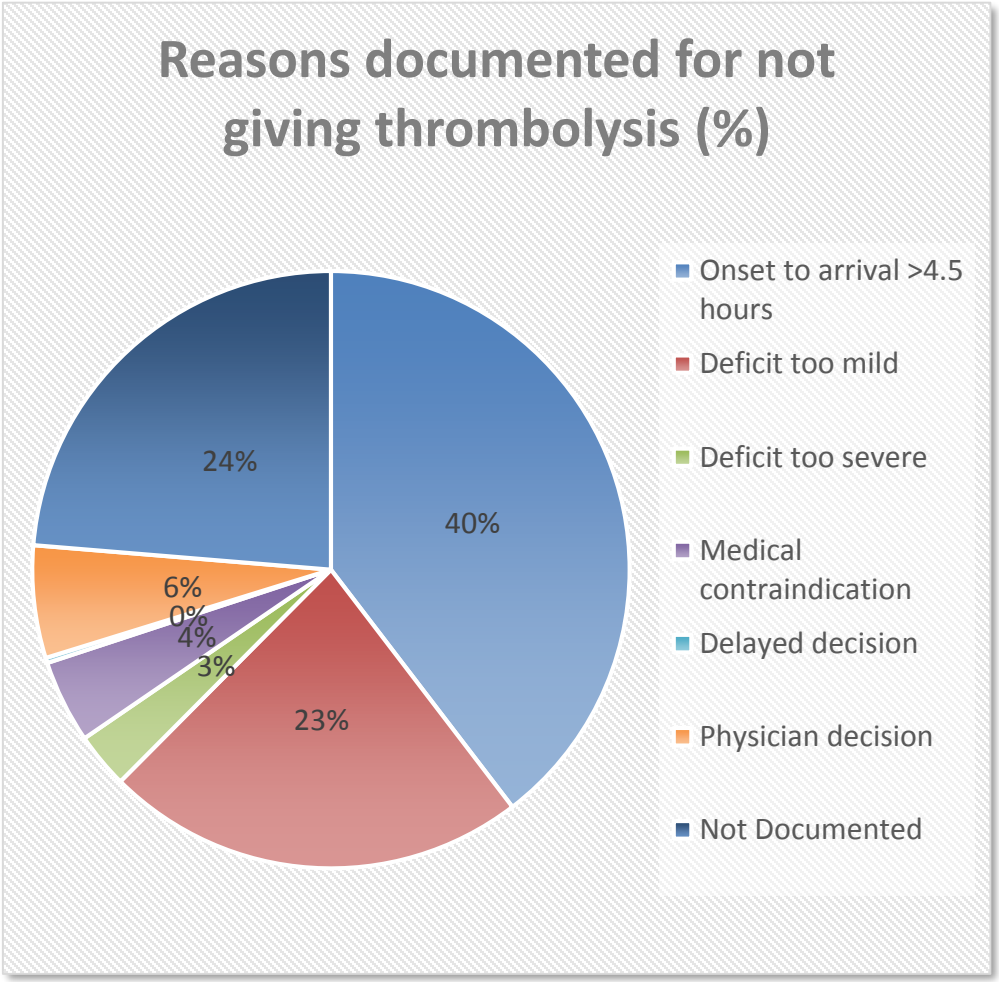

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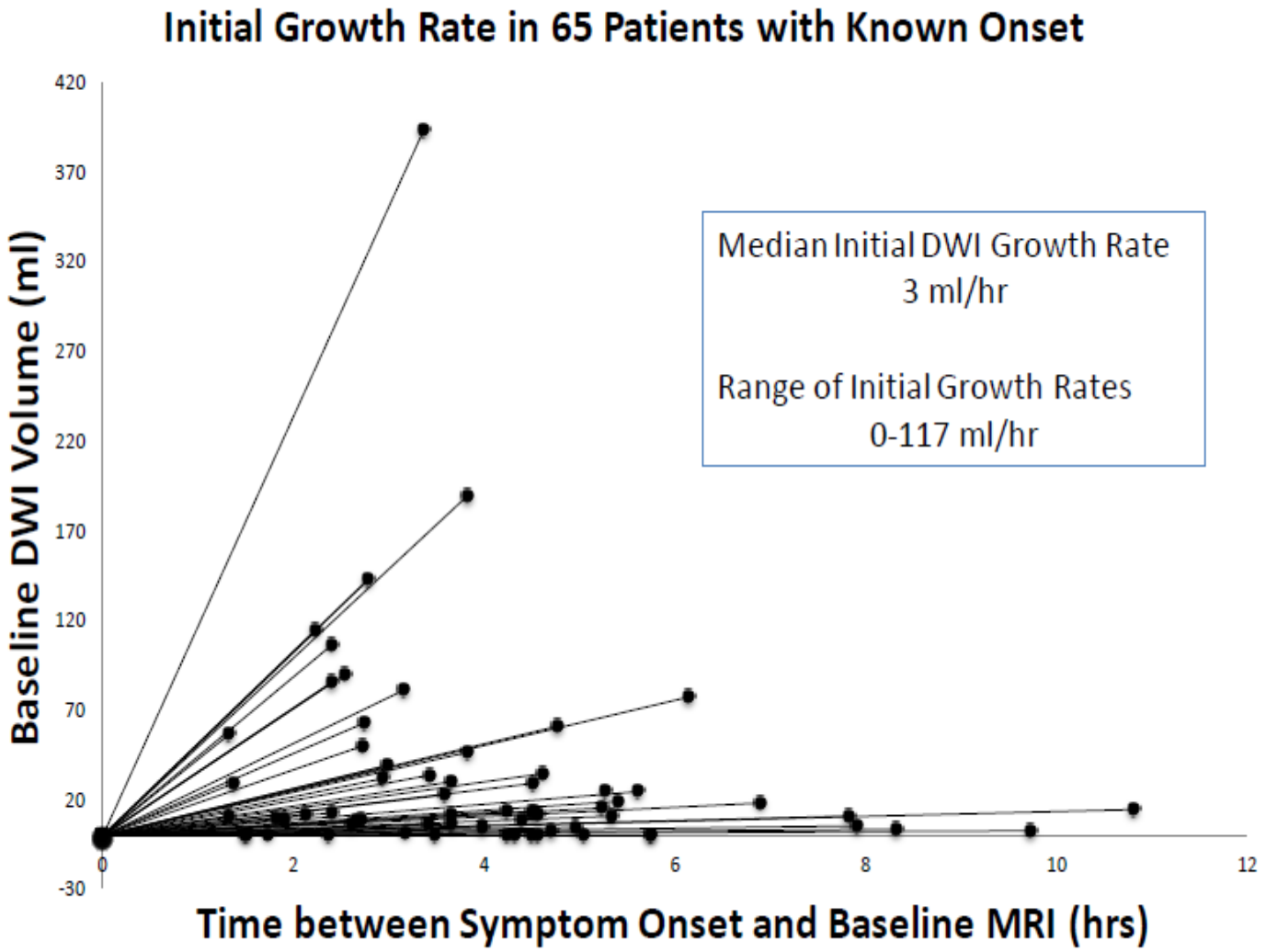
Outline of presentation

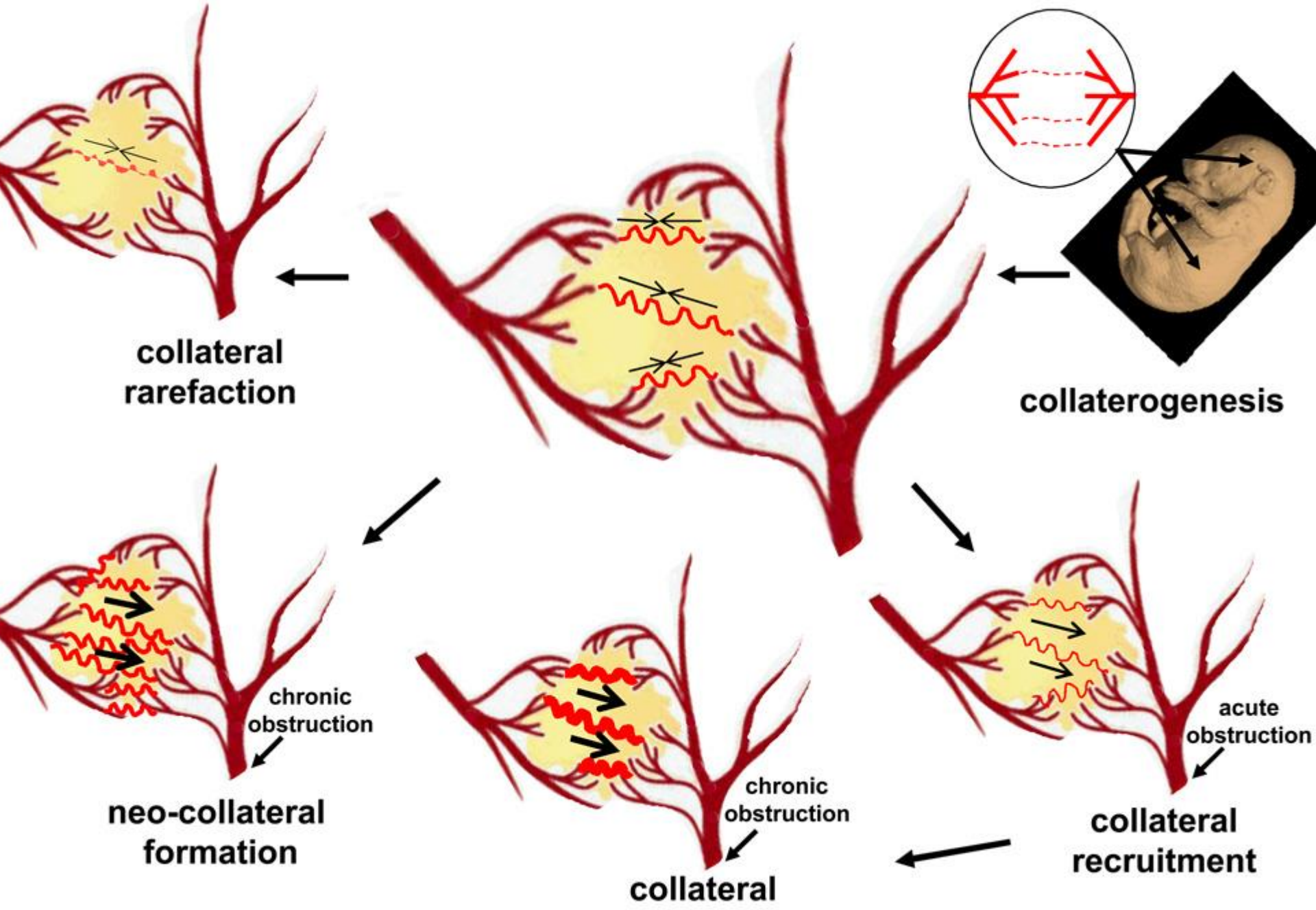
- Rationale for reperfusion-treatment windows in acute stroke
- Current recommendations and guidelines
- **Outside the time window**

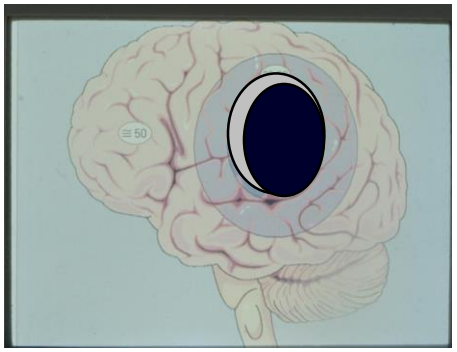
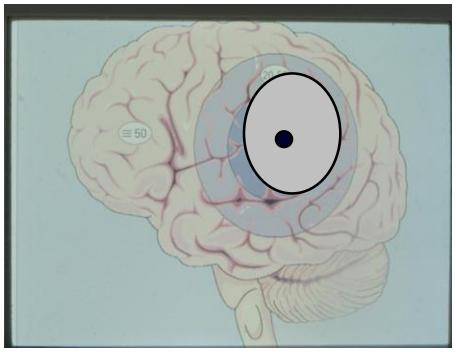
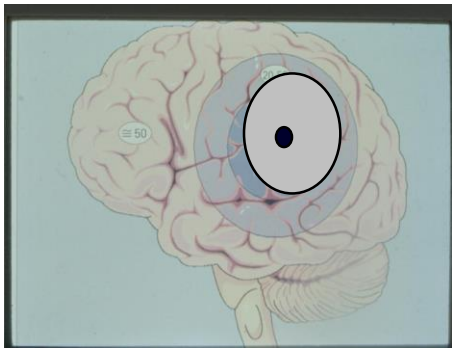
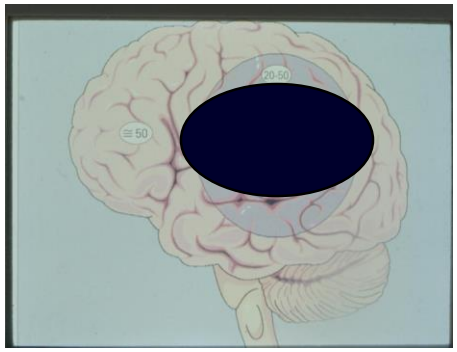
DEFUSE 2: Speed of progression

Part 1 Analysis

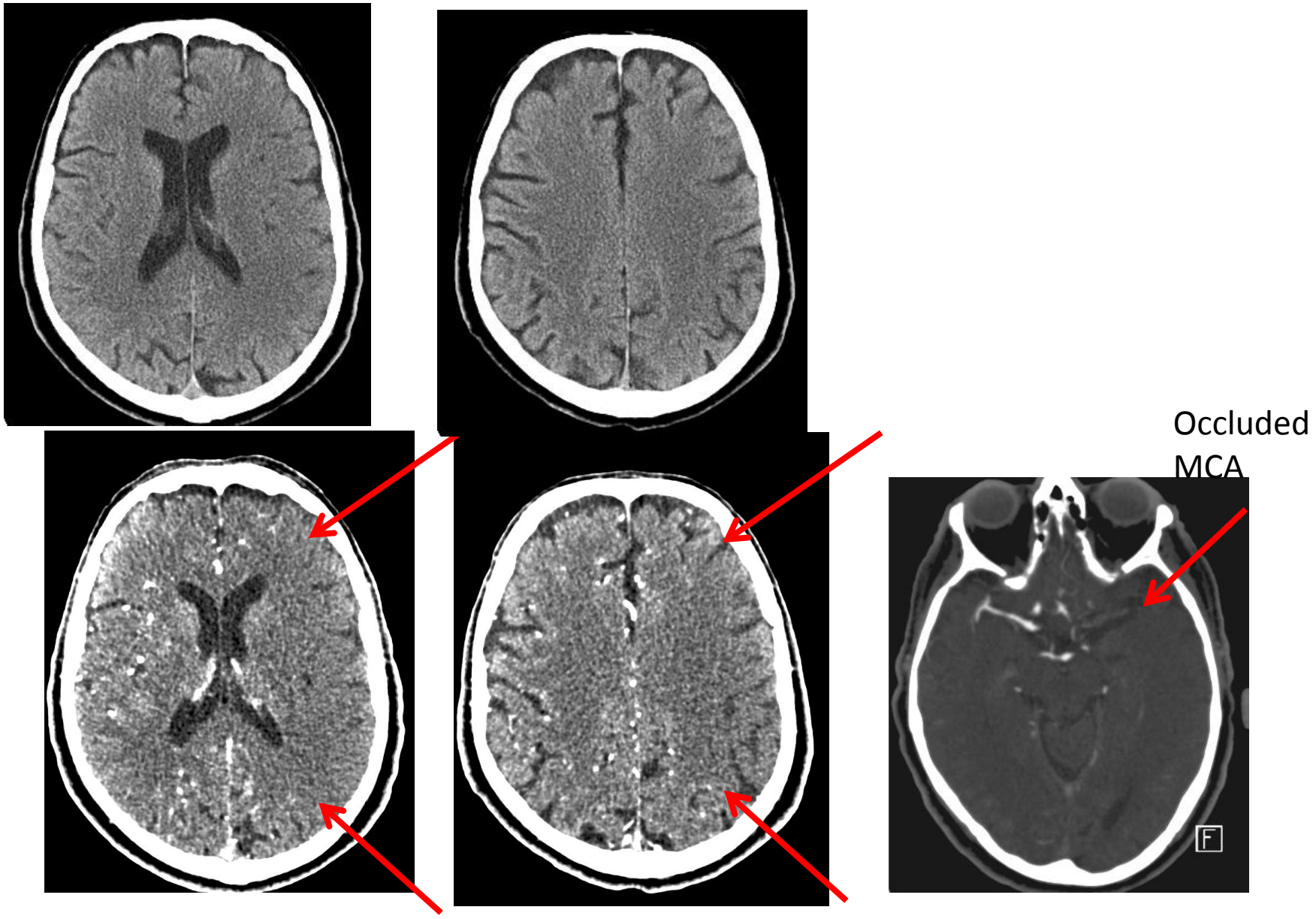


Lifecycle of the collateral circulation



	1 Hr	3 Hr	6 Hr
average			
slow			
fast			

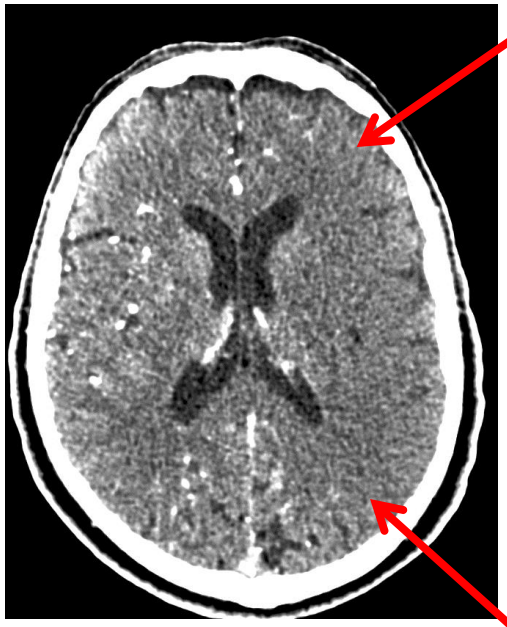
Identify Poor ‘Collaterals’ patients

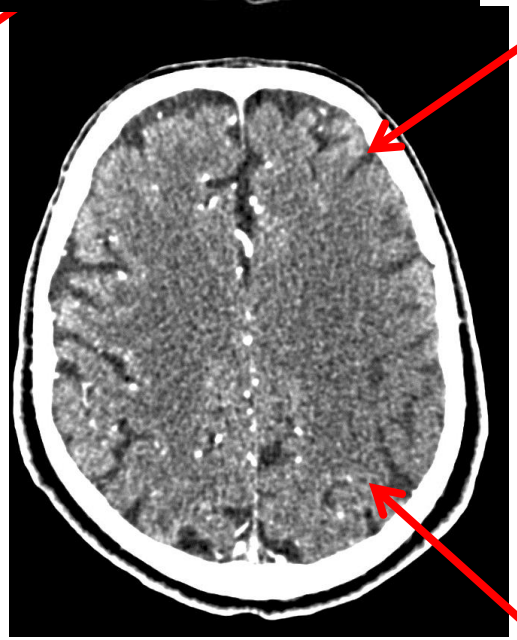


Iv rt-PA at 2 hours. Patient died in 5 days

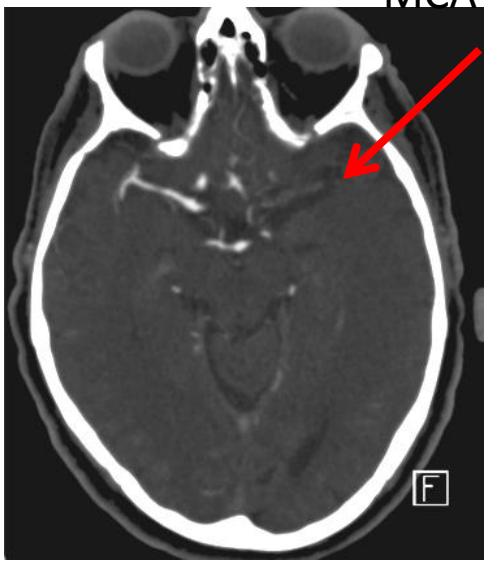
NCCT

CTA





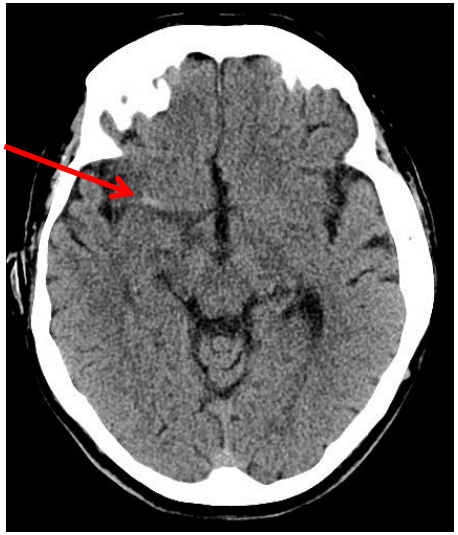
Occluded MCA

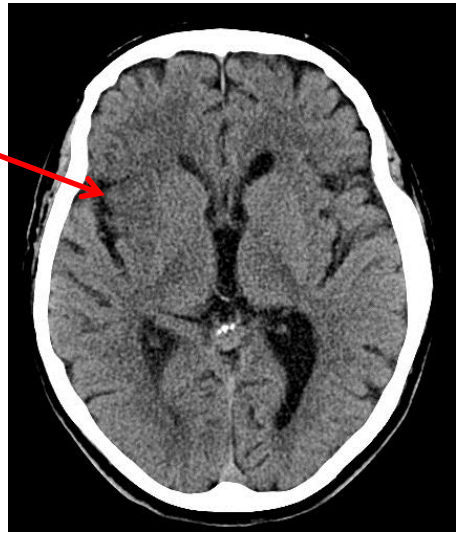


67 ♀ last well 8.5 h ago; NIHSS 13

Thrombus

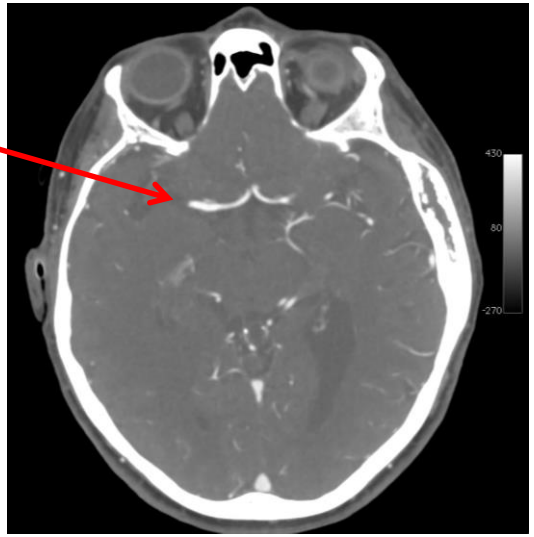
Ischemic Core

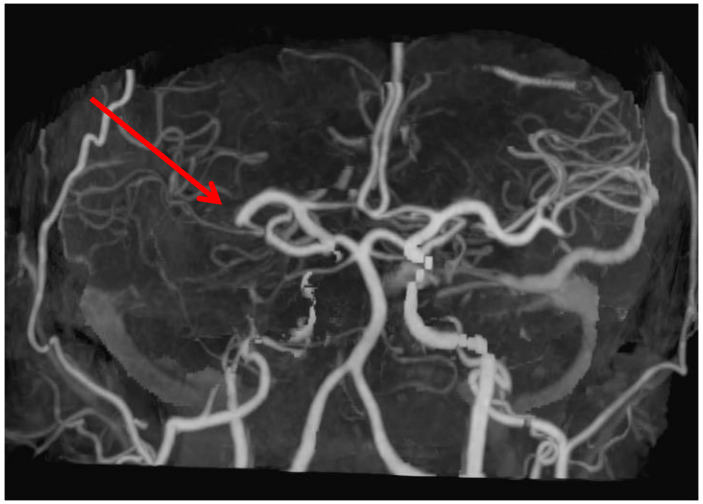




CT Angiogram

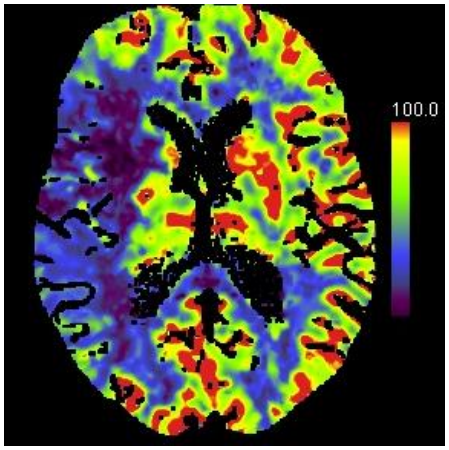
M1 Occlusion

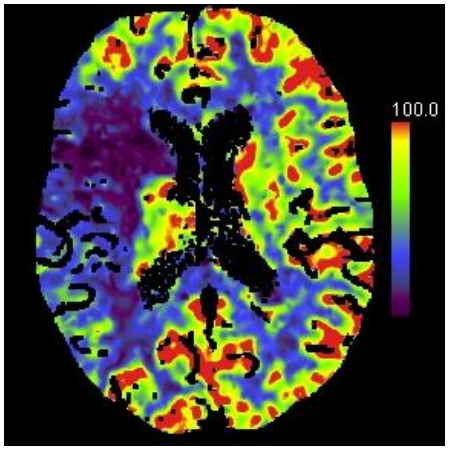


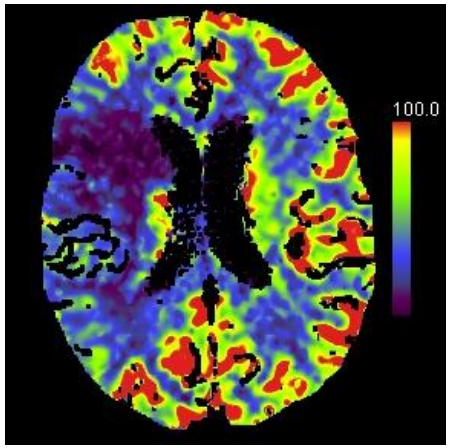


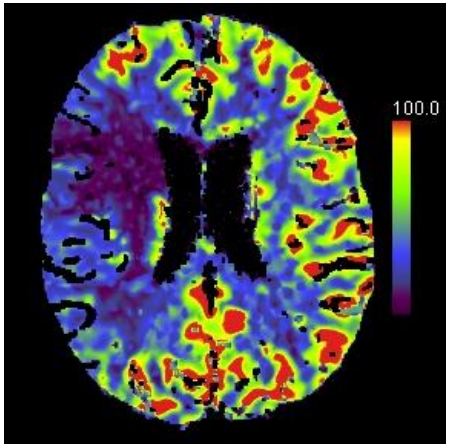
CBF (ml/100g/min)

Area at risk and core



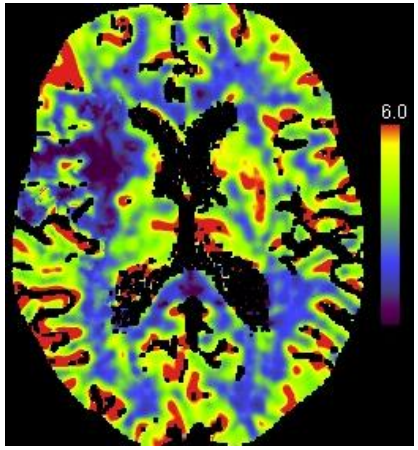


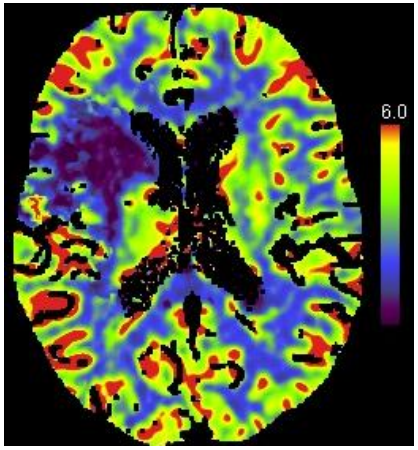


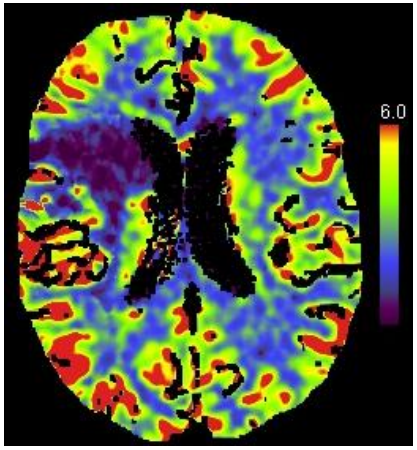


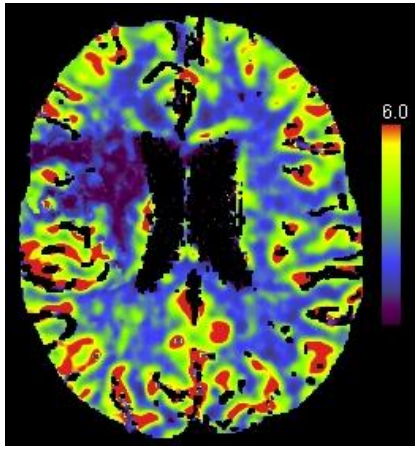
CBV (ml/100g)

Core (Irreversibly injured tissue)





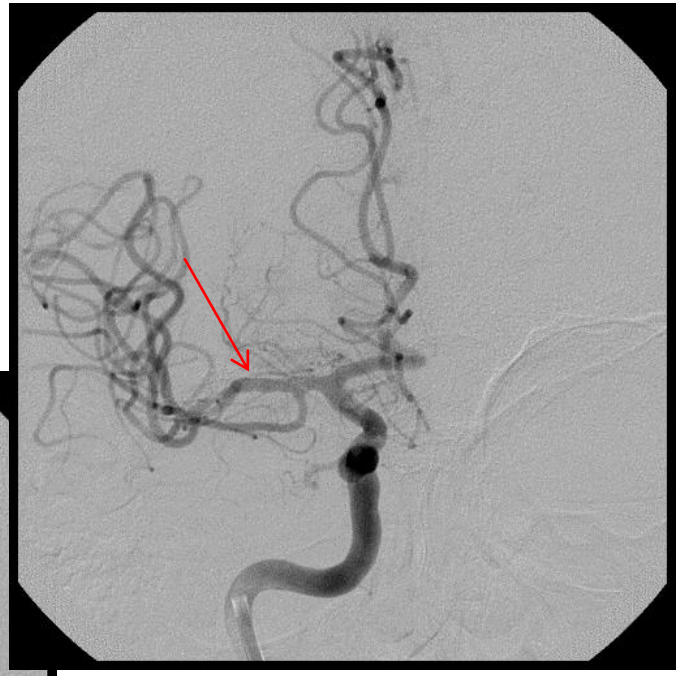




Pre-treatment

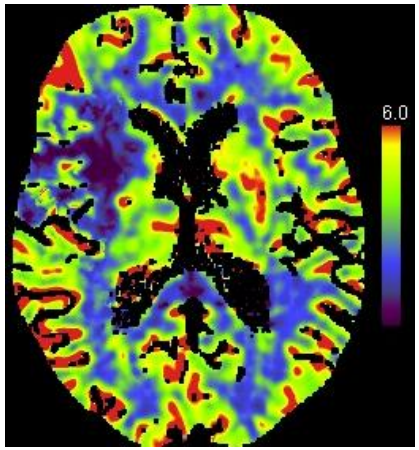
Penumbra-treatment

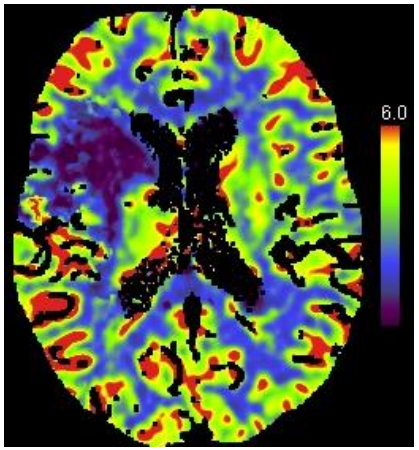
Post-treatment

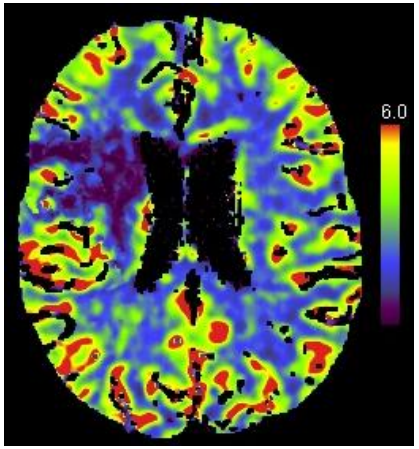


Patient made independent recovery (mRS=1)

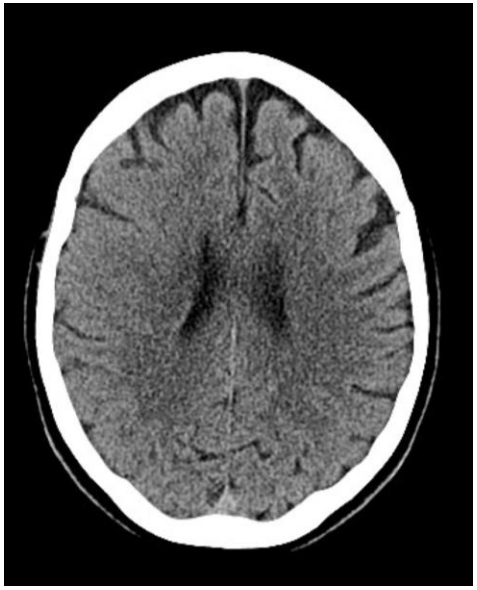
Acute CBV







24 H



Other factors effecting speed of neuronal injury

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

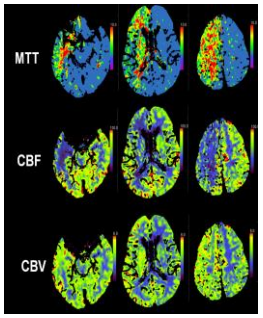
Outline of presentation

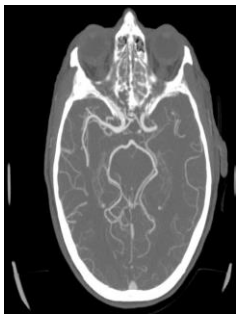
- Rationale for reperfusion-treatment windows in acute stroke
- Current recommendations and guidelines
- Outside thrombolysis window
- **What's new !!**

What's new in thrombolysis

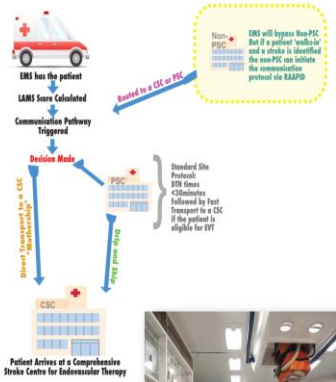
- Advances in multi-model imaging improving selection of patients
- Determination of collateral status allows for proper planning of treatment options and ICH risk, including activation of endovascular service
- Newer delivery methods and newer agents

Acute stroke 2017





2015



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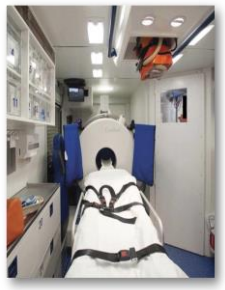

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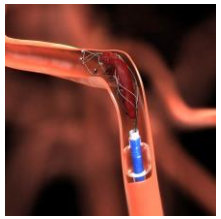
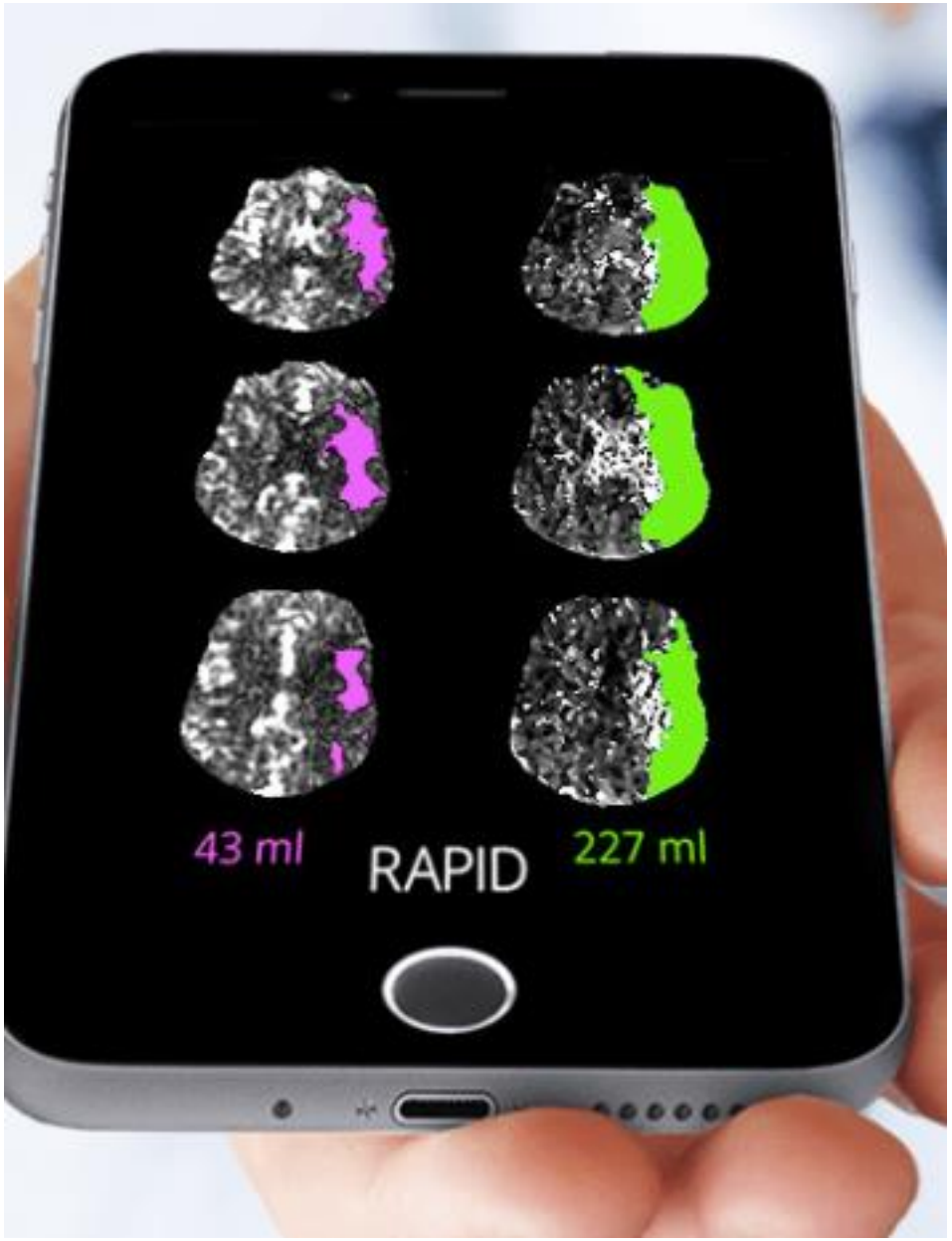
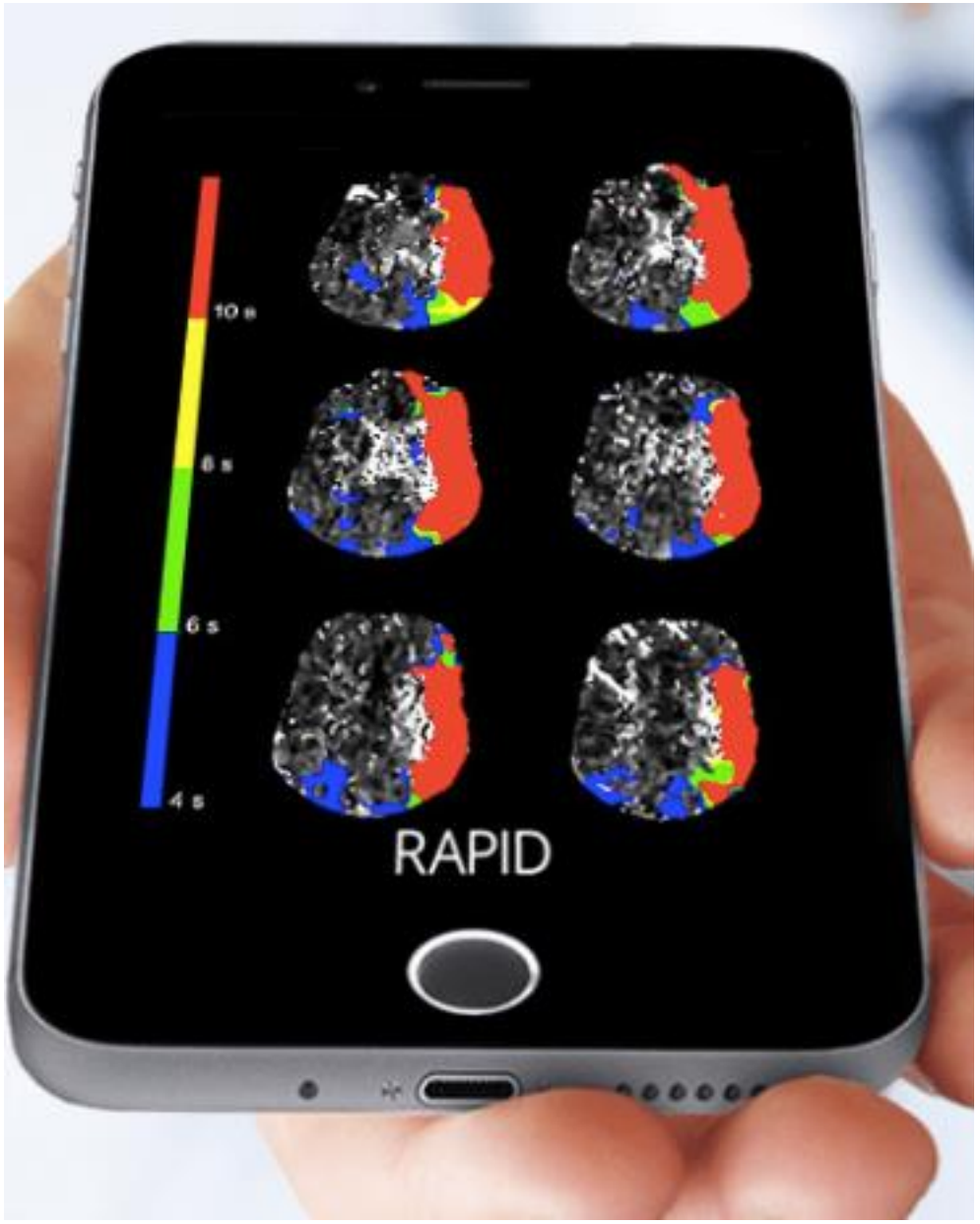
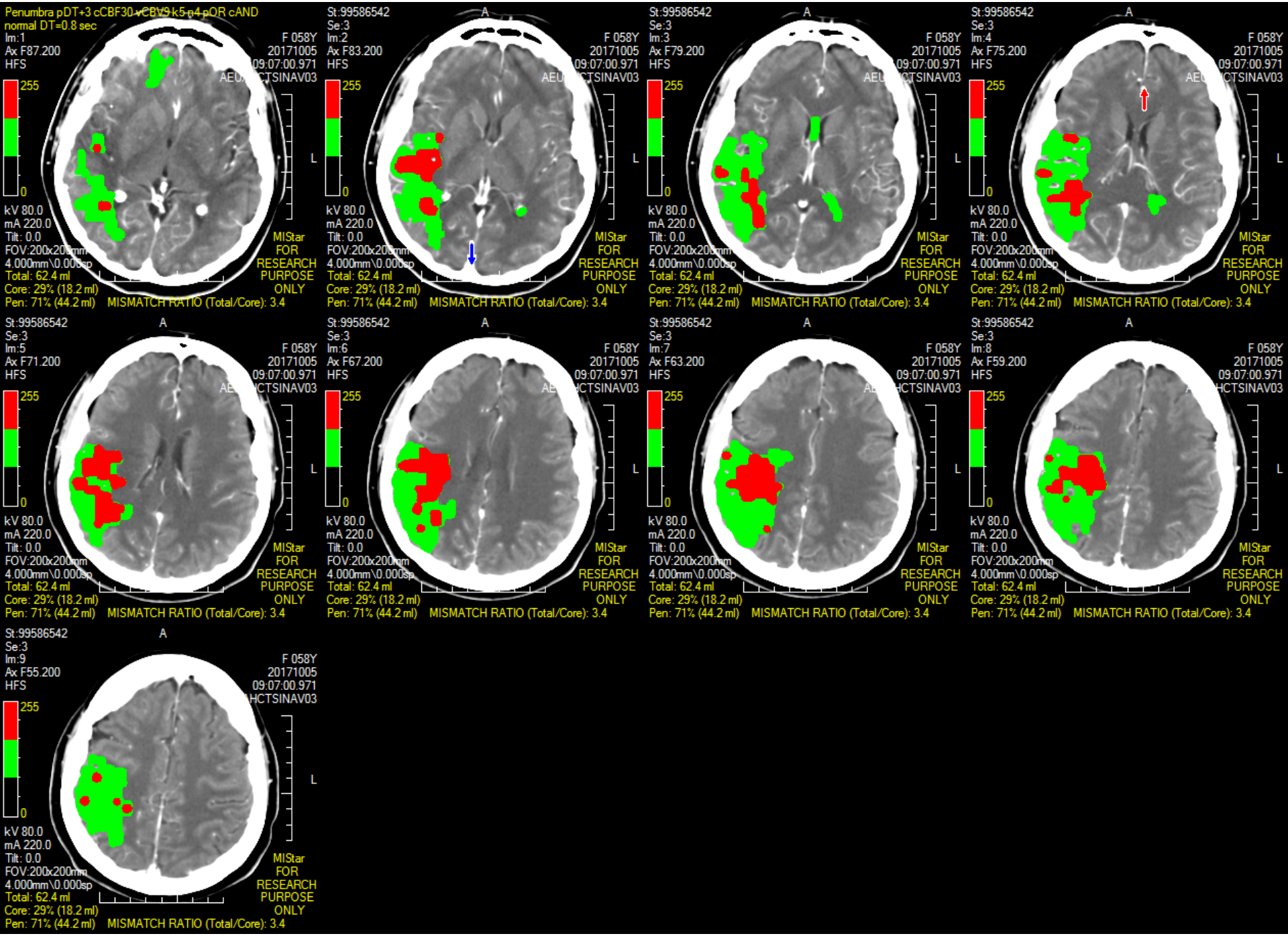
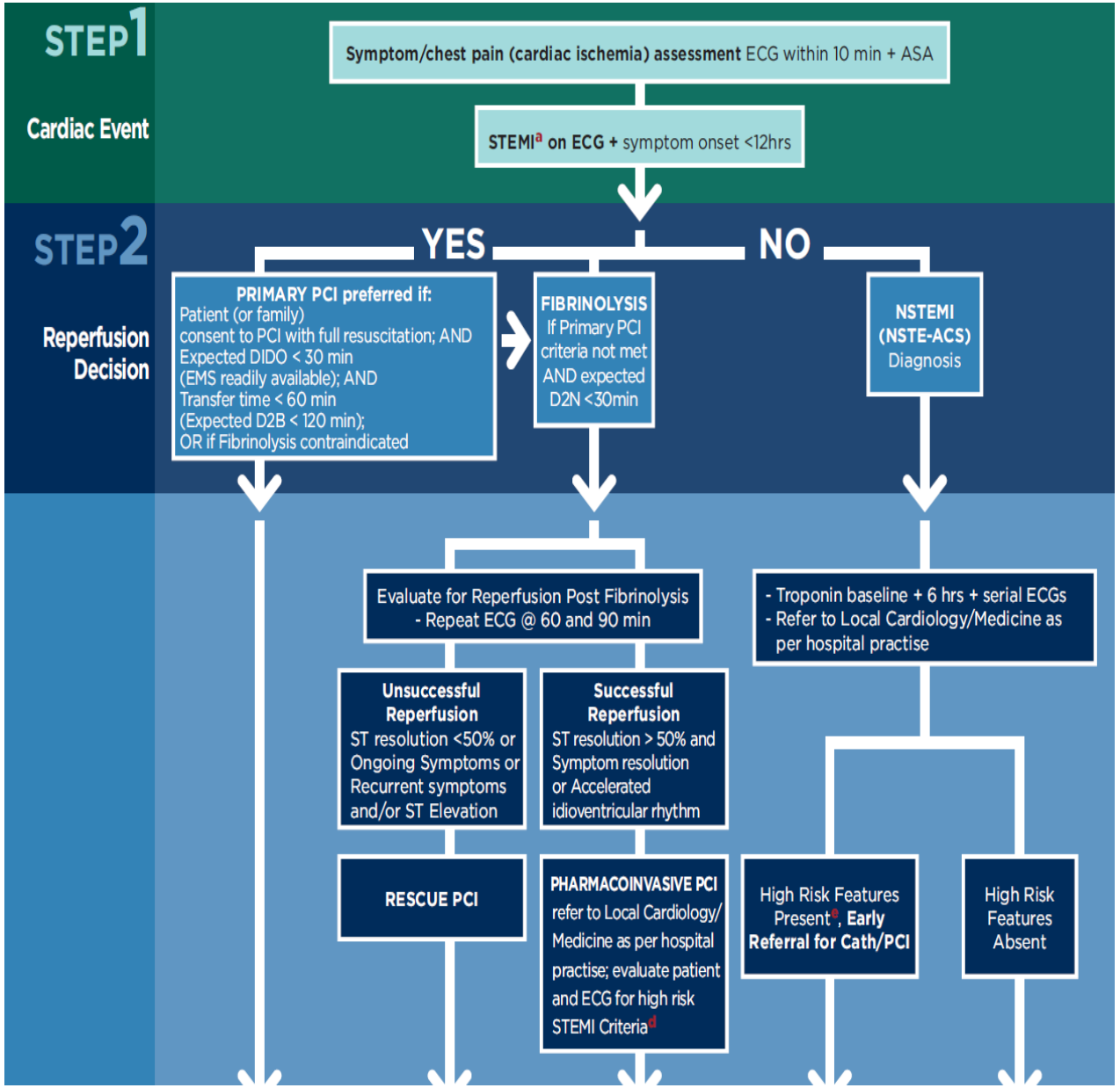



43 ml
RAPID
227 ml


10 s
8 s
6 s
4 s
RAPID


Penumbra pDT+3 cCBF30+cCBV9 k5=4 pOR cAND
normal DT=0.8 sec
Im:1
Ax F87.200
HFS
St:99586542
Se:3
Im:2
Ax F83.200
HFS
Im:3
Ax F79.200
HFS
Im:4
Ax F75.200
HFS
Im:5
Ax F71.200
HFS
Im:6
Ax F67.200
HFS
Im:7
Ax F63.200
HFS
Im:8
Ax F59.200
HFS
Im:9
Ax F55.200
HFS
F 058Y
20171005
09:07:00.971
HCTSINAV03
255
0
L
A
kV 80.0
mA 220.0
Tilt: 0.0
FOV:200x200mm
4.000mm\0.000sp
Total: 62.4 ml
Core: 29% (18.2 ml)
Pen: 71% (44.2 ml)
MISTAR FOR RESEARCH PURPOSE ONLY
MISMATCH RATIO (Total/Core): 3.4



In the future fibrinolysis for stroke may be reserved for a subset of patients with:

Longer transfer times
Distal occlusions
Contraindications to EVT

Need RCT (ongoing)

What are the goal of hyperacute stroke therapies?

Conclusions

- Guidelines recommend that iv-rt-PA be offered to eligible patients within 4.5 hours
- Advance imaging and experienced team essential to determine risk/benefits
- Thrombectomy may be offered to patients within and beyond 4.5 hours
- Patients qualifying for thrombectomy may be considered for iv-rt-PA (if no endovascular service)

Questions?

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