COMPLEX NAVIGATION MADE SIMPLE IN AIS

M.V.PADMA SRIVASTAVA MD, DM, FRCP (EDIN), FAMS, FNASC, FIAN, FNA

PROFESSOR, HEAD, DEPARTMENT OF NEUROLOGY

CHIEF, NEUROSCIENCES CENTER

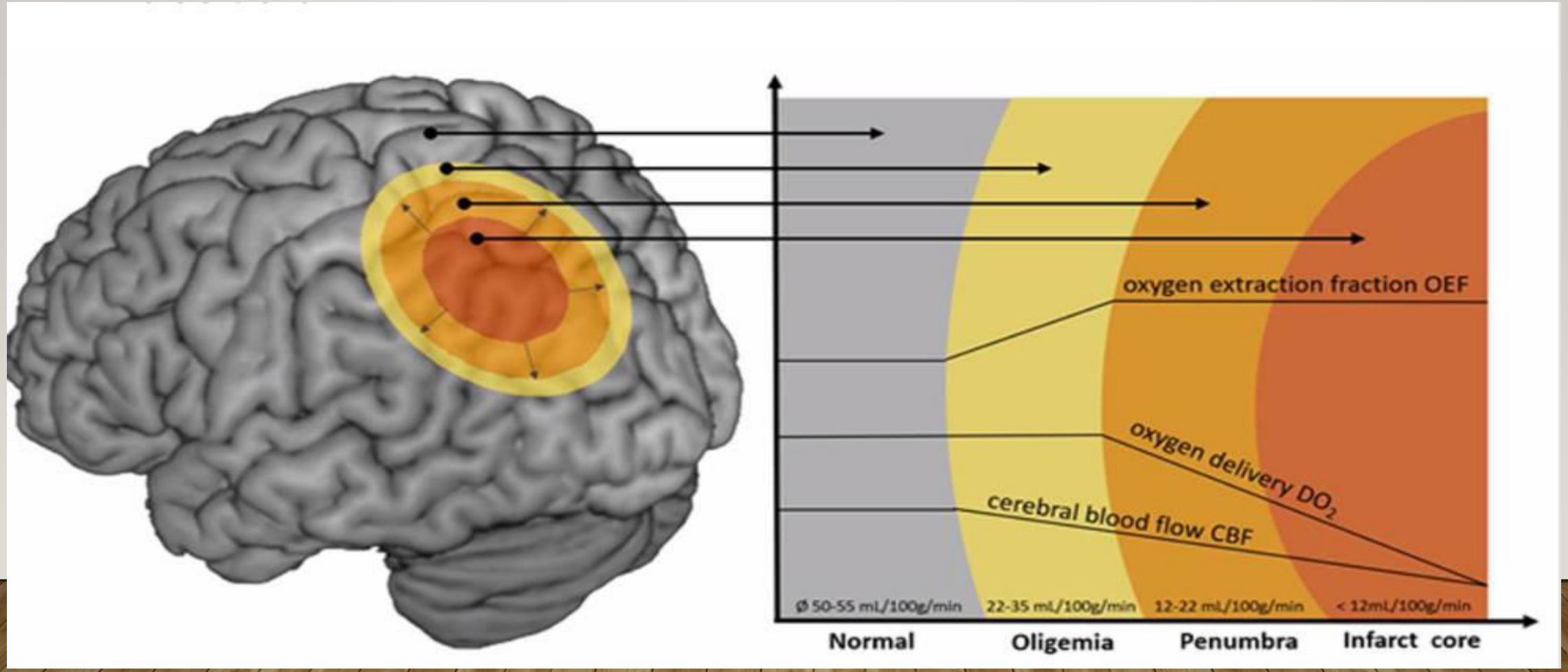
AIIMS, NEW DELHI

PAST PRESIDENT, INDIAN STROKE ASSOCIATION

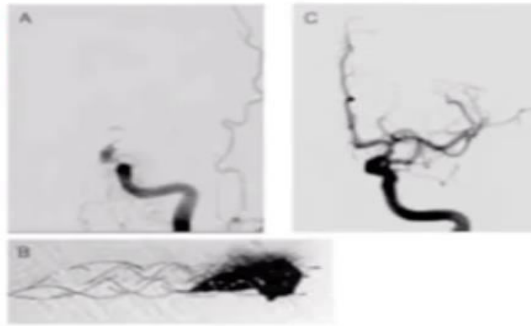
HON. PROFESSOR, UCLAN, UK.

INTRODUCTION

- "Time is brain"
- 1.9 million neurons die every minute of large artery occlusion



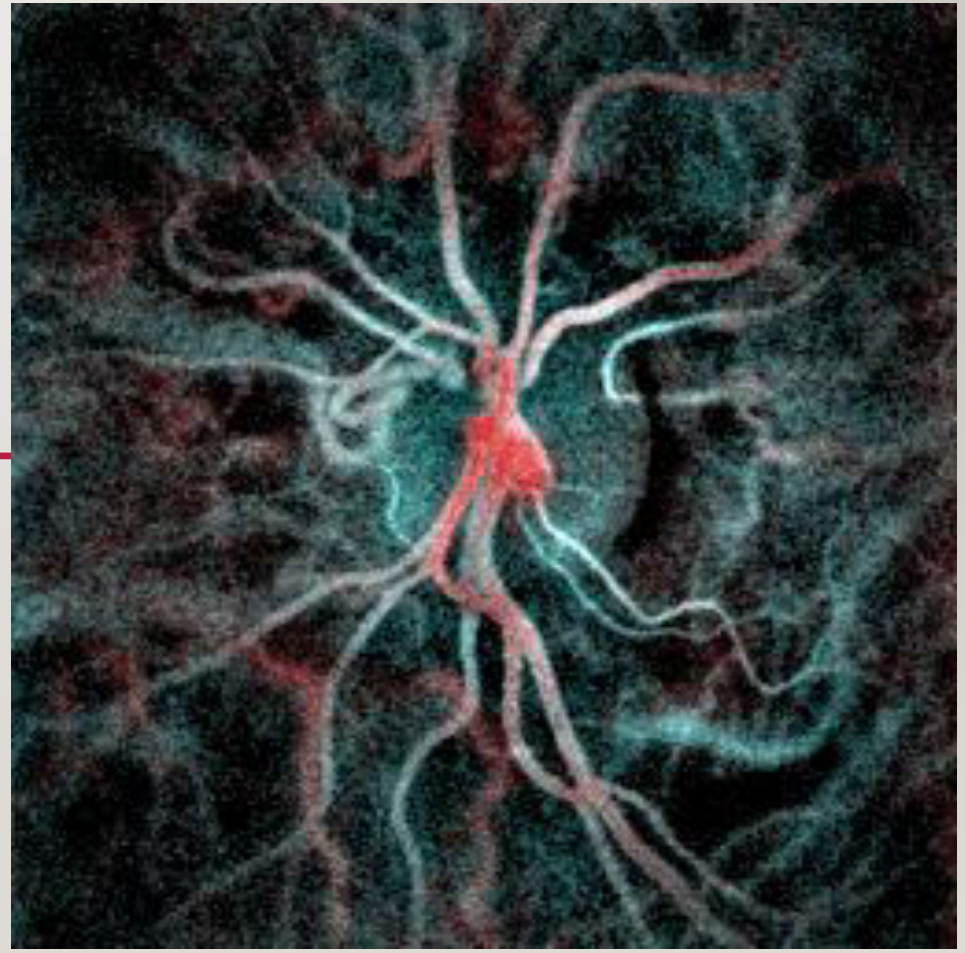
3 C of AIS- Clot, Core, Collaterals



Clots are the reason why we treat patients with acute ischemic stroke

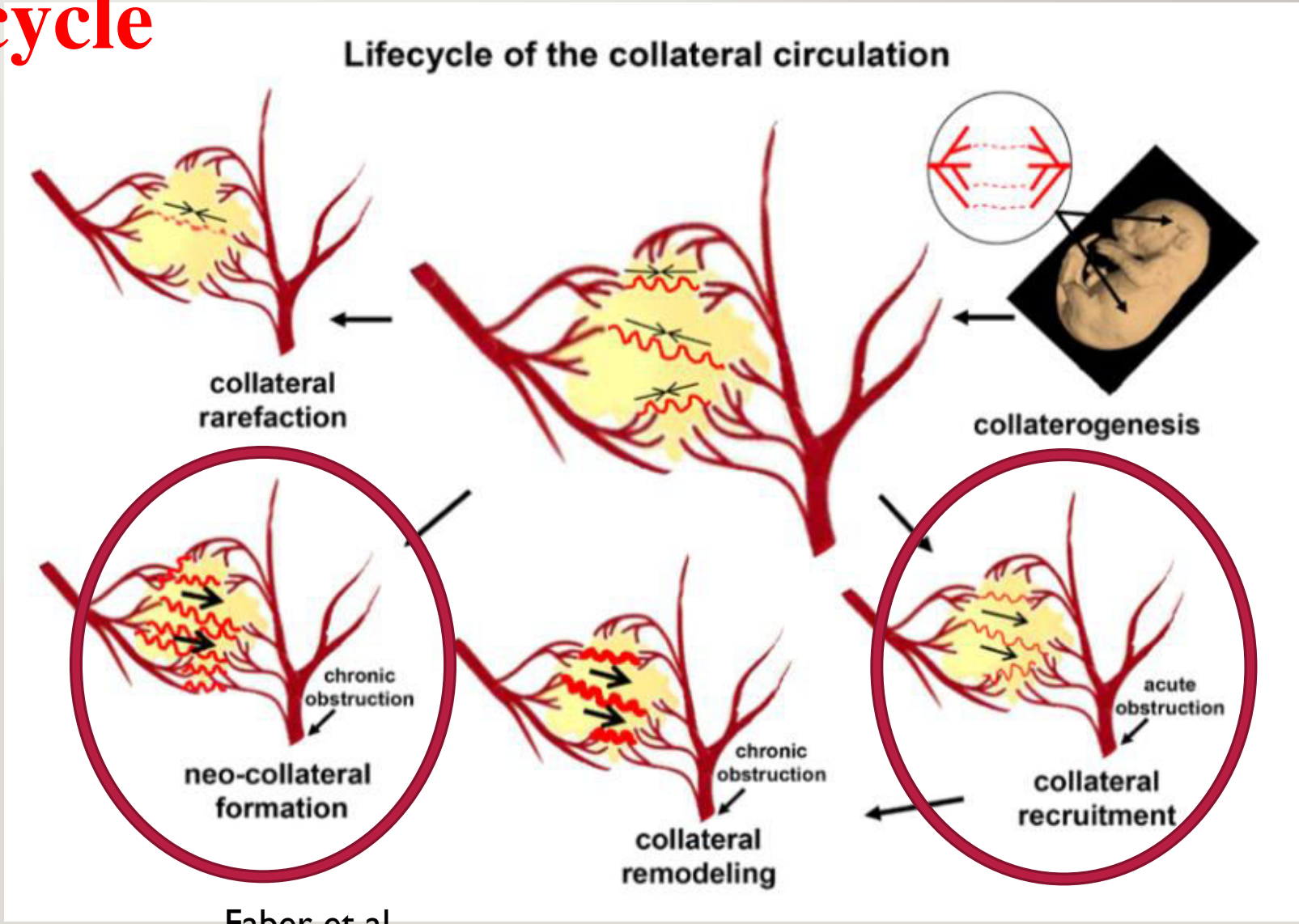
Collaterals are the reason why we are able to treat patients with acute ischemic stroke

UNDERSTANDING THE BASIC BIOLOGY OF THE COLLATERAL CIRCULATION



Collaterals - Lifecycle

- Embryonic formation of native collaterals (collaterogenesis)
- Acute obstruction induces flow across the collateral network (recruitment), followed by remodeling
- Chronic obstructive disease formation of additional collaterals in (neocollateral formation)
- Loss of native collaterals (rarefaction) can be caused by aging and other risk factors.



Faber et al
A Brief Etymology of the Collateral Circulation
Arterioscler Thromb Vasc Biol September 2014

TYPES OF COLLATERALS

Collateral Arteries/ Primary Collaterals

- artery-to-artery anastomoses- similar locations among human and other mammalian species.
- less anatomic lumen enlargement on a percentage basis (remodeling) in response to a chronic increase in shear stress in obstructive disease,
- anterior and posterior communicating arteries/collaterals of the circle of Willis.

Microvascular / Secondary Collaterals

- arteriole-to-arteriole anastomoses that cross-connect a small fraction
- significant tortuosity ,more remodeling of 5- to 10-fold in humans with occlusive disease
- pial (leptomenigeal) collaterals of the brain

Faber et al
A Brief Etymology of the Collateral Circulation *Arterioscler Thromb Vasc Biol* September 2014

PRIMARY COLLATERALS

- Collateral arteries- The circle of Willis constitutes the main cerebral collateral network
- Willisian Collaterals

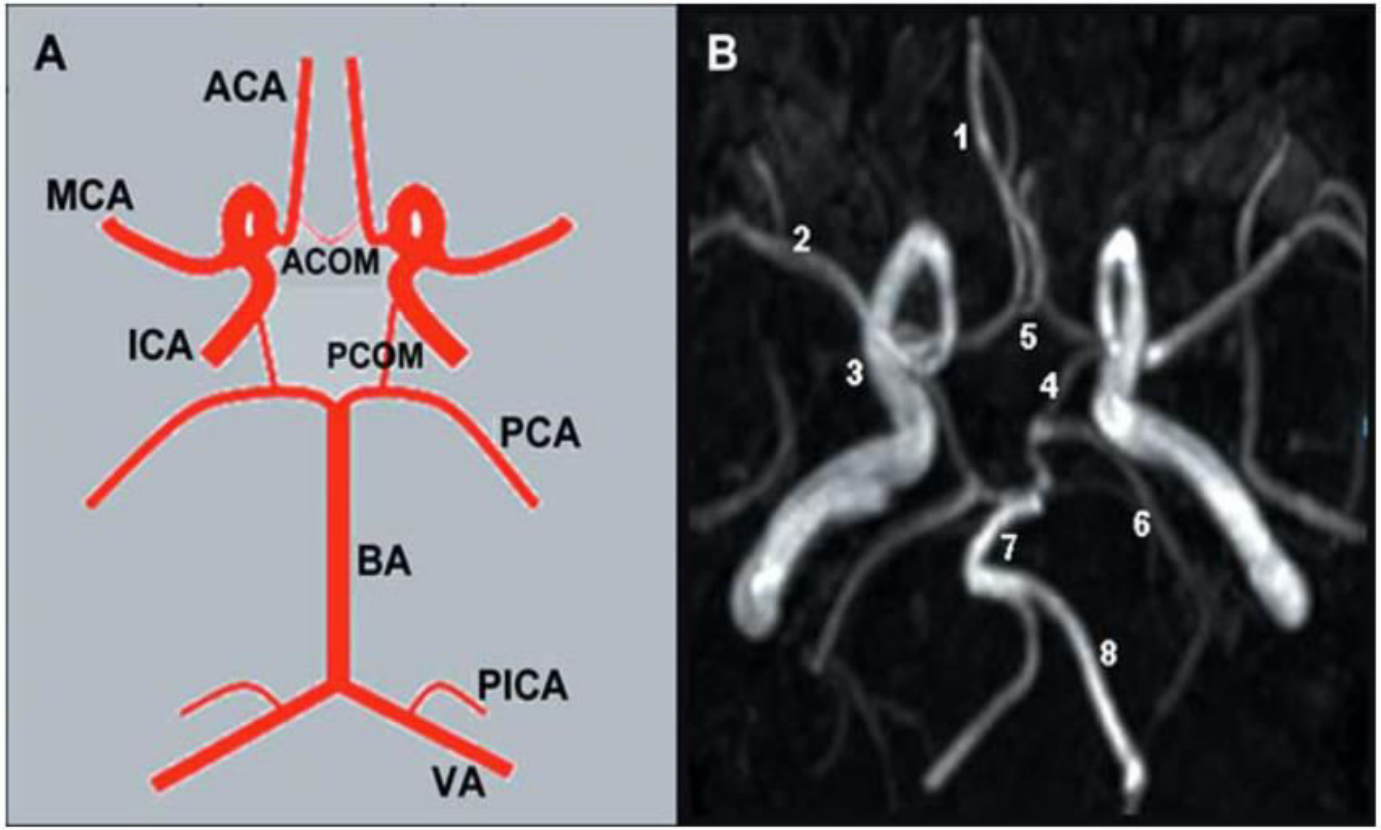
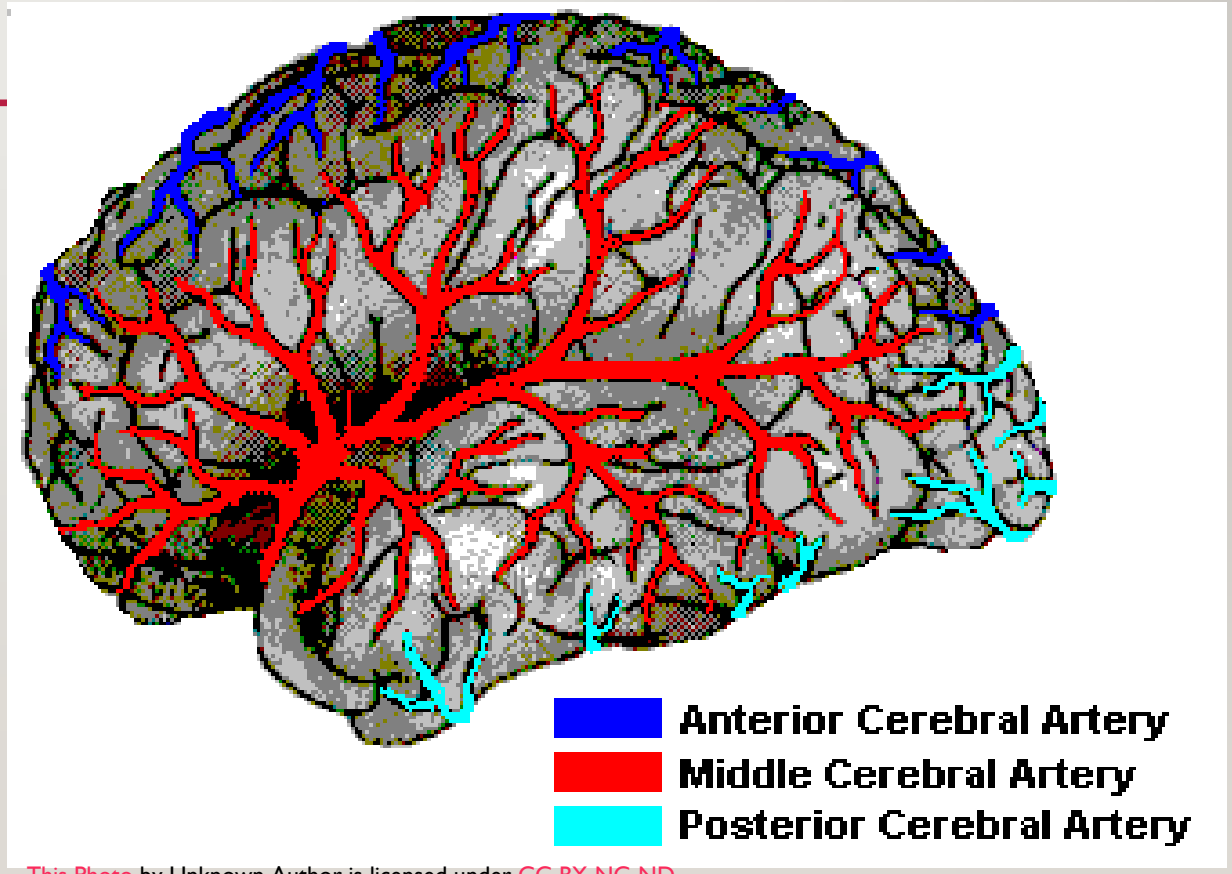


Fig. (1). Cerebral Collateral Circulation.
Panel A. Schematic representation of a complete circle of Willis. Panel B. Magnetic Resonance Angiography of the circle of Willis. 1= Anterior Cerebral Artery (ACA). 2= Middle Cerebral Artery (MCA). 3= Internal Carotid Artery (ICA). 4= Posterior Communicating Artery (PCOM). 5= Anterior Communicating Artery (ACOM). 6= Posterior Cerebral Artery (PCA). 7= Basilar Artery (BA). 8= Vertebral Artery (VA).

Bang et al Collateral Circulation in Ischemic Stroke
Stroke November 2015

SECONDARY COLLATERALS

- Lepto-meningeal collaterals
- Dural arteriolar anastomoses
- Tectal plexus
- Rete mirabilis caroticus
- Main A-A collaterals



Liebeskind
Collateral Circulation *Stroke* September 2003

LEPTOMENINGEAL COLLATERALS -LMC

- ACA-MCA
- MCA-PCA
- SCA-PICA

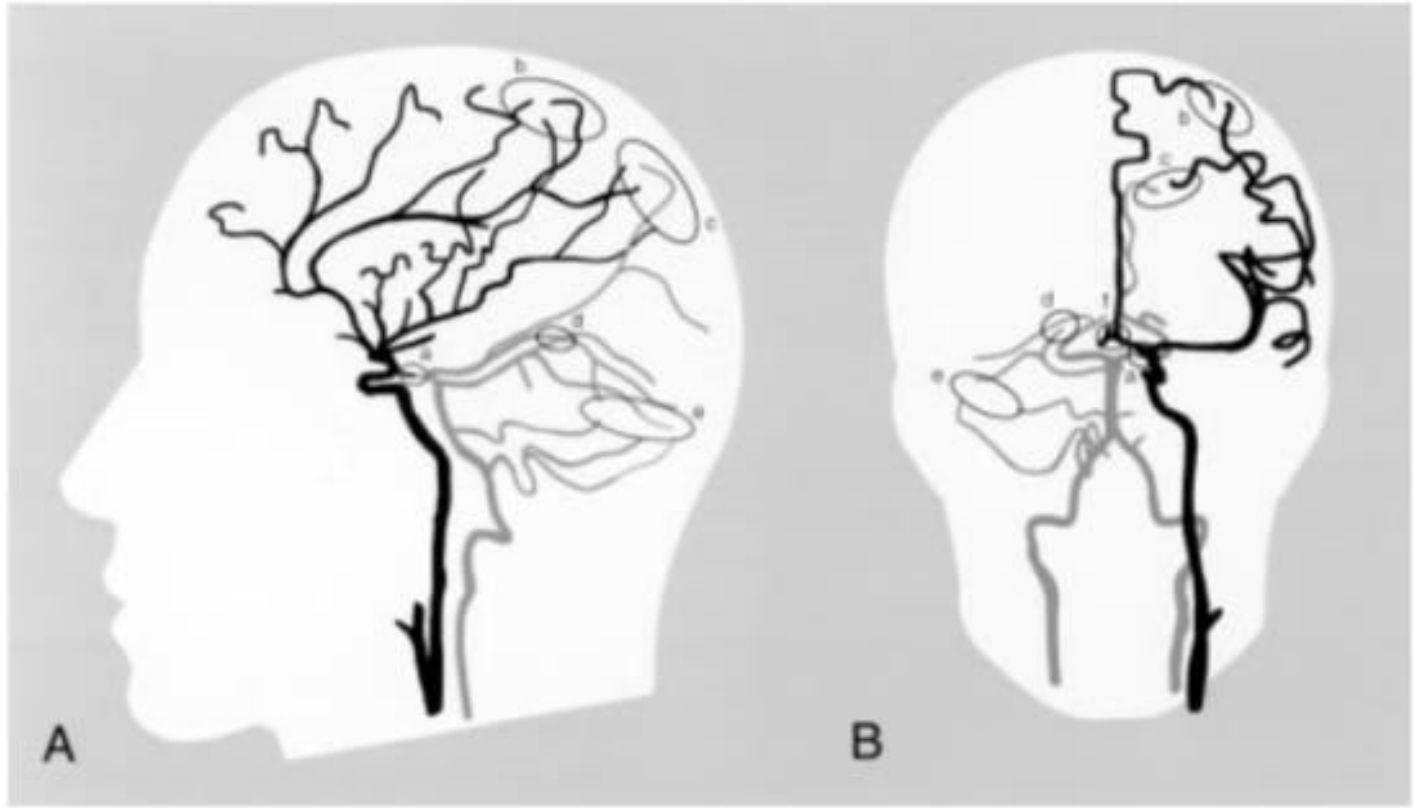
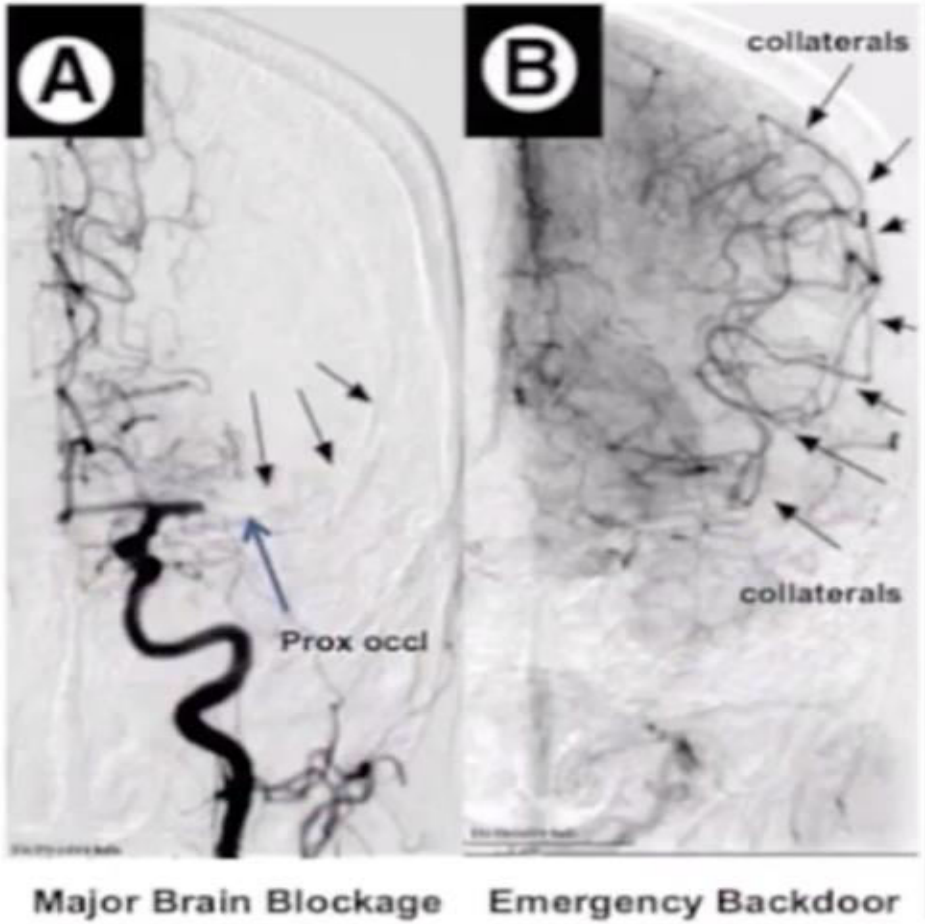


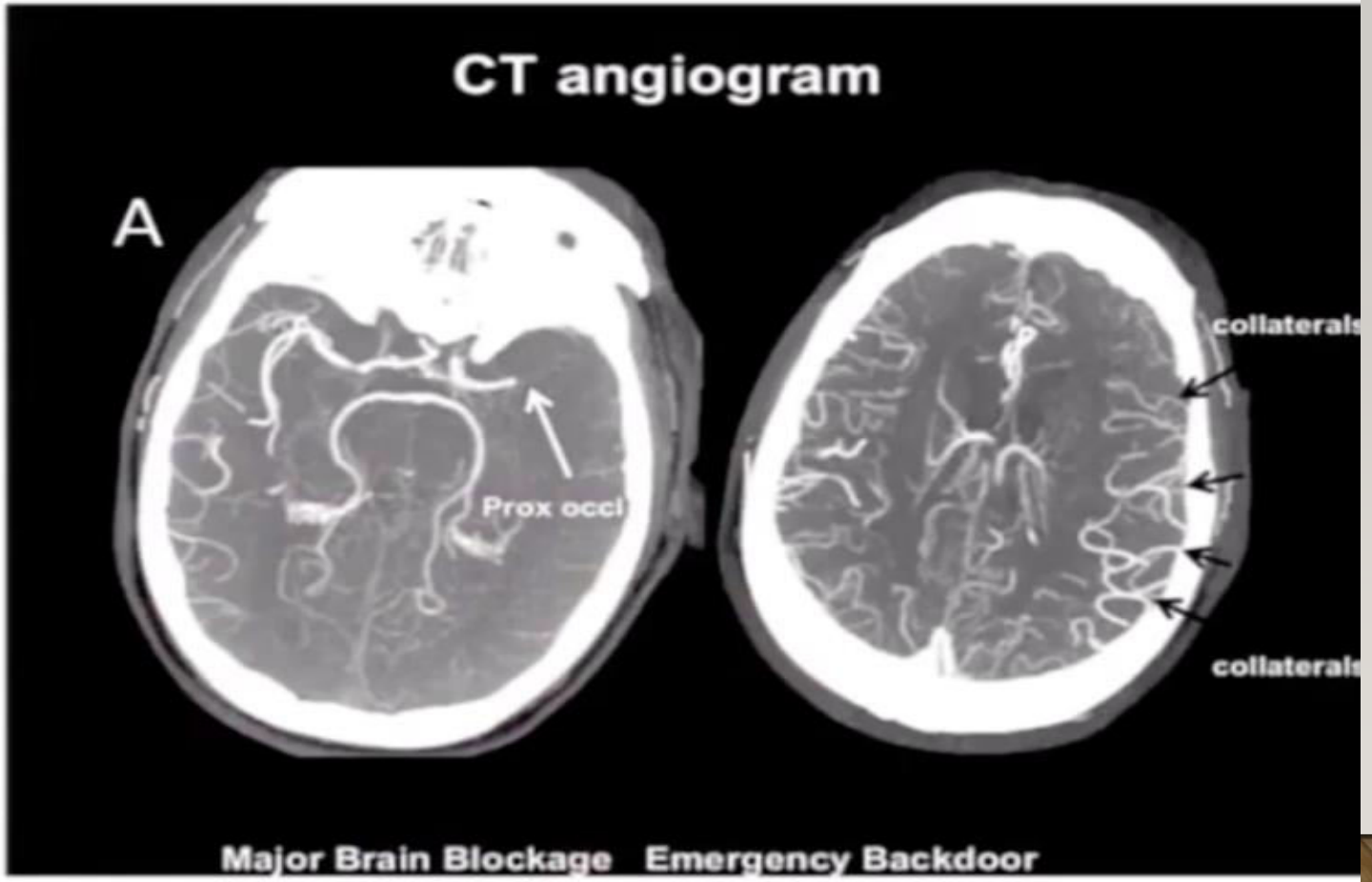
Figure 2. Intracranial arterial collateral circulation in lateral (A) and frontal (B) views. Shown are posterior communicating artery (a); leptomeningeal anastomoses between anterior and middle cerebral arteries (b) and between posterior and middle cerebral arteries (c); tectal plexus between posterior cerebral and superior cerebellar arteries (d); anastomoses of distal cerebellar arteries (e); and anterior communicating artery (f).

Liebeskind
Collateral Circulation *Stroke* September 2003

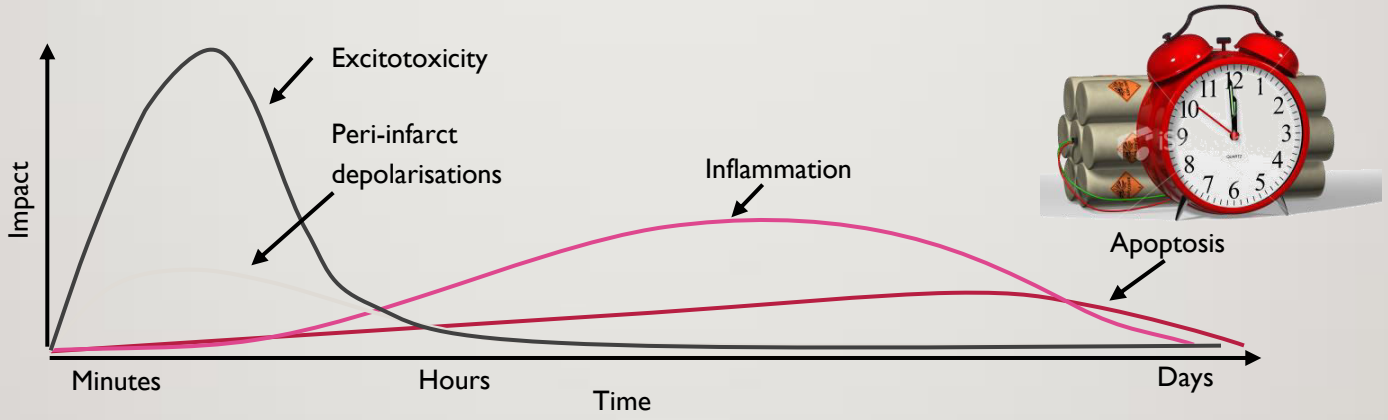
WHY COLLATERAL IMAGING IS NECESSARY IN ACUTE ISCHEMIC STROKE ?

Clots Block Blood flow; Collaterals are the Backdoor





"TIME IS BRAIN"



Estimated Pace of Neural Circuitry Loss In Typical Large-Vessel Supratentorial Acute Ischaemic Stroke				
	Neurons Lost	Synapses Lost	Myelinated Fibres Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km	36 y
Per Hour	120 million	830 billion	714 km	3.6 y
Per Minute	1.9 million	14 billion	12 km	3.1 wk
Per Second	32,000	230 million	200 m	8.7 h

Saver. *Stroke* 2006;37:263-266.

Penumbra- A Very Individual Feature

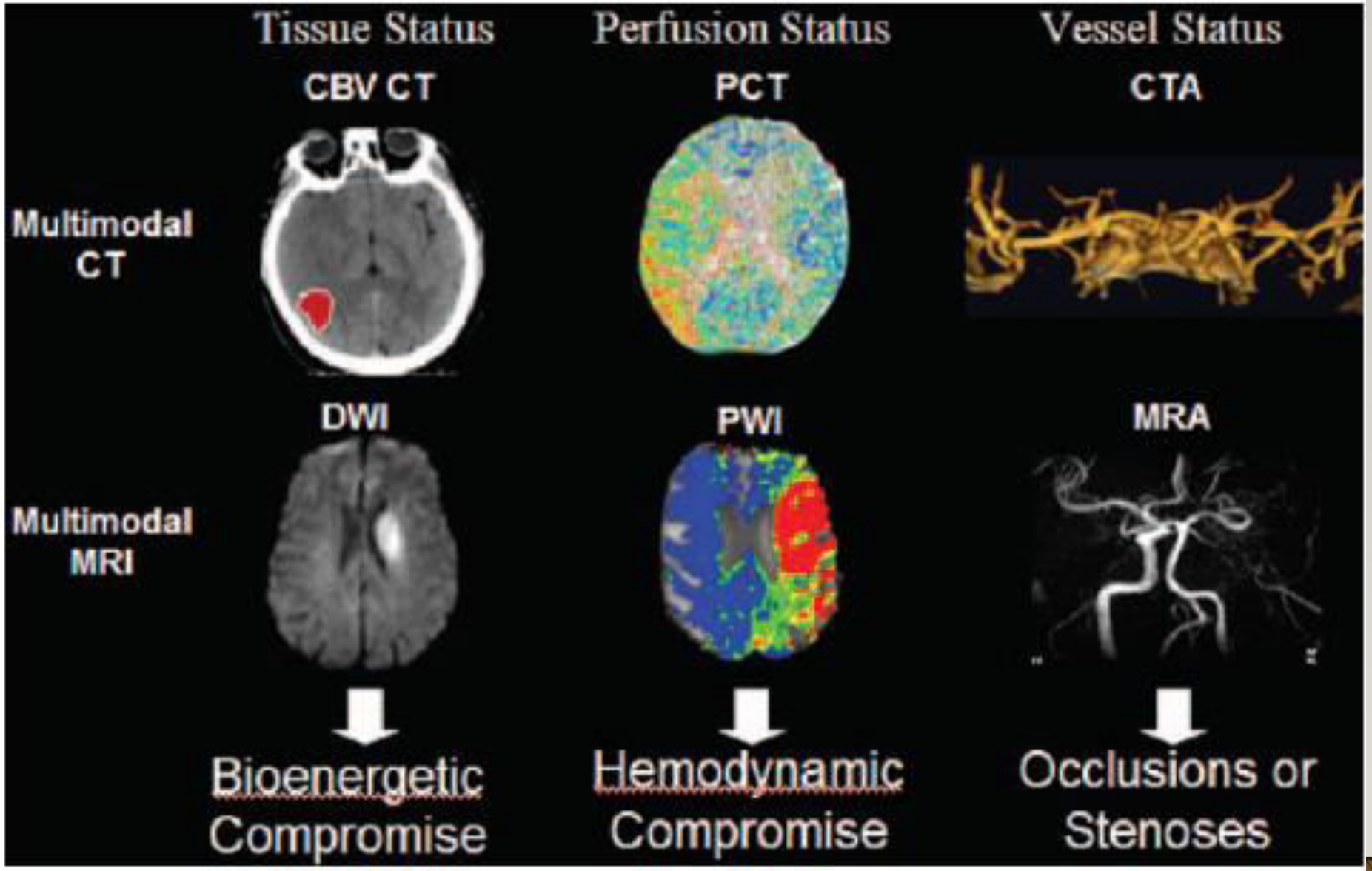
There are no precise data on the percentage of patients at a given time point who still have a reasonable amount of penumbral tissue and vessel occlusion

It is reasonable to believe that:

- At 60 min, about 90%
- At 2 h about 80 %
- At 3 h about 60% and
- At 4.5 h about 40% of patients have penumbral tissue

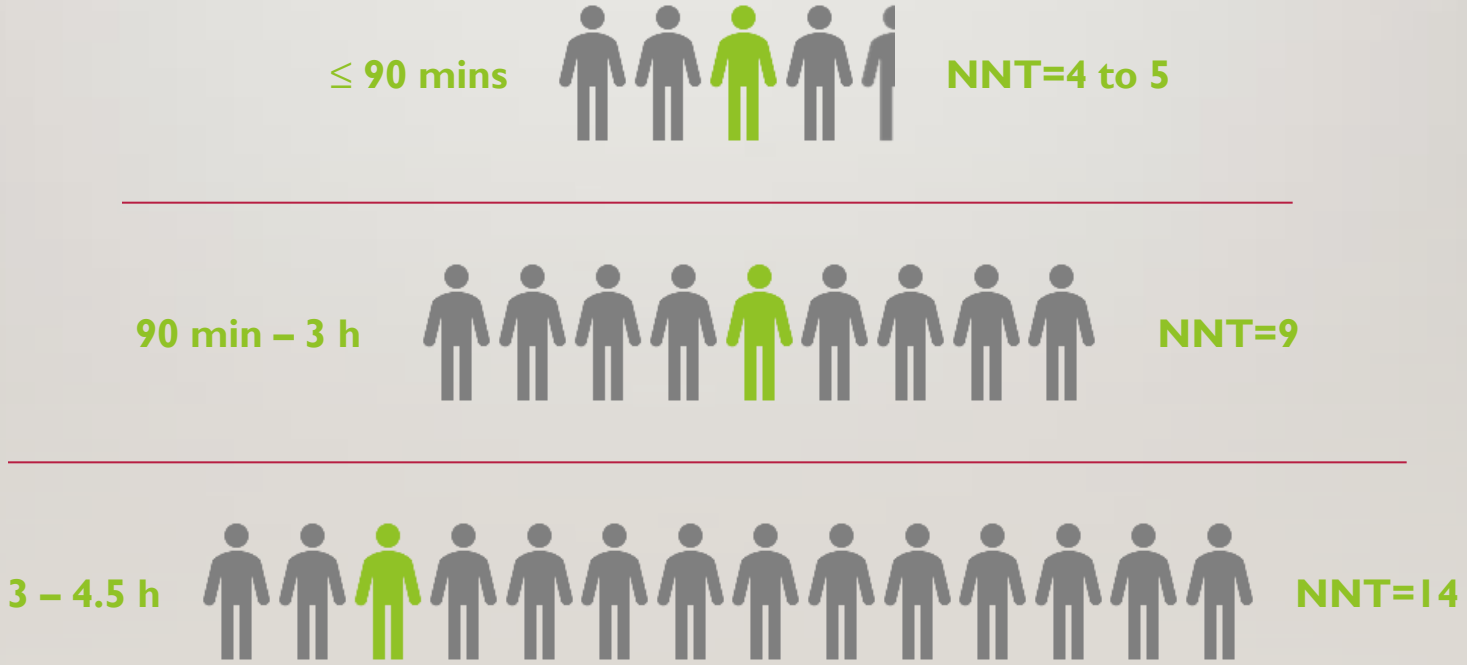
Thereafter, one can only guess:

- Maybe 30% at 9 h
- And less than 20% beyond 12 h


Tissue Status
Perfusion Status
Vessel Status
CBV CT
PCT
CTA
Multimodal CT
DWI
PWI
MRA
Multimodal MRI
Bioenergetic Compromise
Hemodynamic Compromise
Occlusions or Stenoses

mRS, modified Rankin Scale
NNT, number needed to treat to achieve one additional patient with mRS 0-1
Lees et al. *Lancet* 2010;375:1695-1703.

THROMBOLYSIS: NNT TO ACHIEVE EXCELLENT RECOVERY (MRS 0-1)

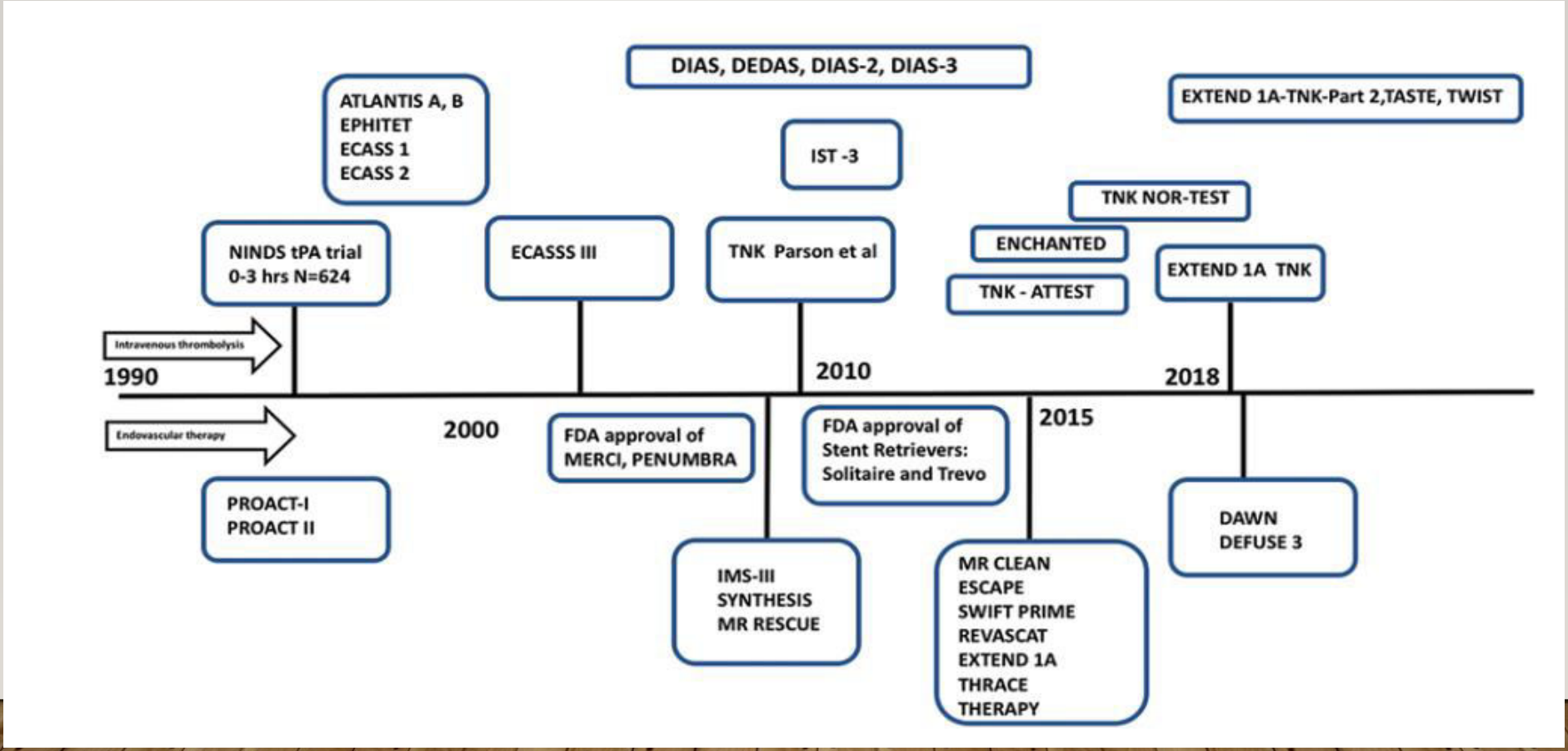


CURRENT STATUS OF SPECIFIC TREATMENT FOR ACUTE ISCHEMIC STROKE

- Yes
- 1. Tissue plasminogen activator within 4.5 hrs. Alteplase/tenecteplase
- 2. Endovascular treatment in selected pts. Within 6/8/12/24hours……
- 2. Aspirin within 48 hrs.
- 3. Management in SCU
- May Be
- 1. Neuroprotection

ALTEPLASE IN ACUTE ISCHEMIC STROKE

Two decades passed since NINDS study



Vishnu VY, MVP Srivastava. Innovations in Acute Stroke Reperfusion Strategies. AIAN 2019; 22:6-12.

INTERVENTIONS PROVEN TO IMPROVE STROKE OUTCOMES

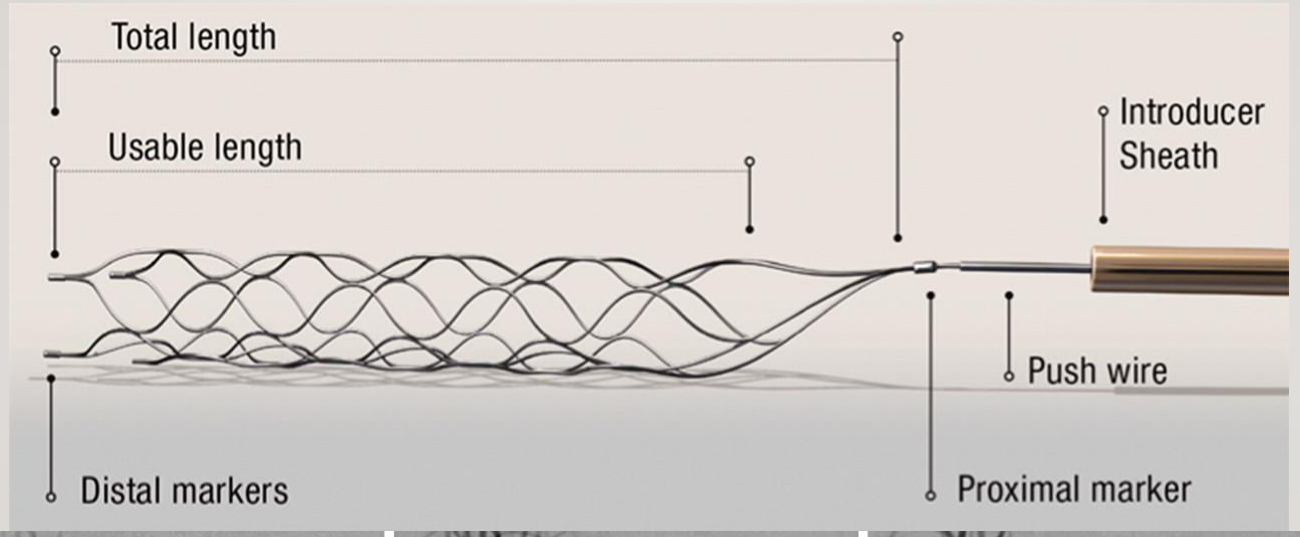
- Management of patient in Stroke Unit.
- Use of Aspirin within 48 hours of stroke onset.
- Hemicraniectomy
- IV thrombolysis within 4.5 hours of stroke onset

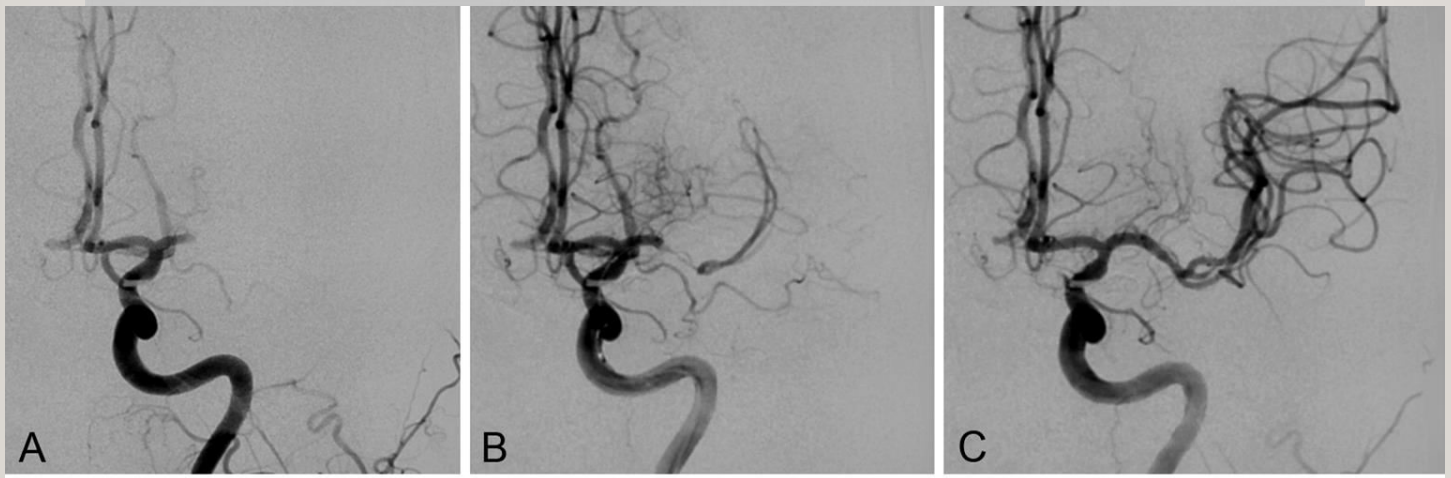
TIME HAS COME!

- MR CLEAN
- ESCAPE
- EXTEND-A
- SWIFT-PRIME
- REVASCAT
- THRACE
- THERAPY
- DAWN
- Endovascular equipoise no longer exists!

MR. CLEAN

- New Mantra: Time is Clot!
- Outcome revolves around: Core and Collaterals
- Cleaner and Faster identification of patients and expertise in recanalization (faster and safer).





http://stroke.ahajournals.org/content/43/1/280/F3.expansion.html

WHY THIS SEA CHANGE?

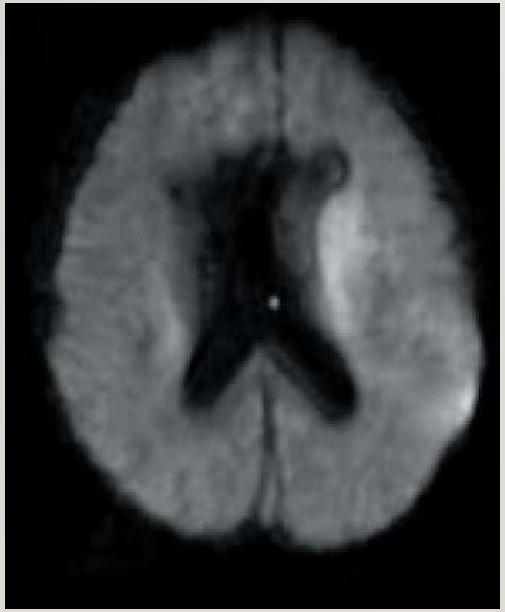
- Devices with faster and more complete recanalization
- Heightened awareness of importance of time; efficiency of stroke care pathways and workflow efficiencies
- Neuroimaging criteria for selection of patients for intervention

- What is happening in real world?
- Most aggressive stroke centers across the world are routinely practicing bridging therapy.
- This is the best approach in all centres acting as “hubs”for the Telestroke services.

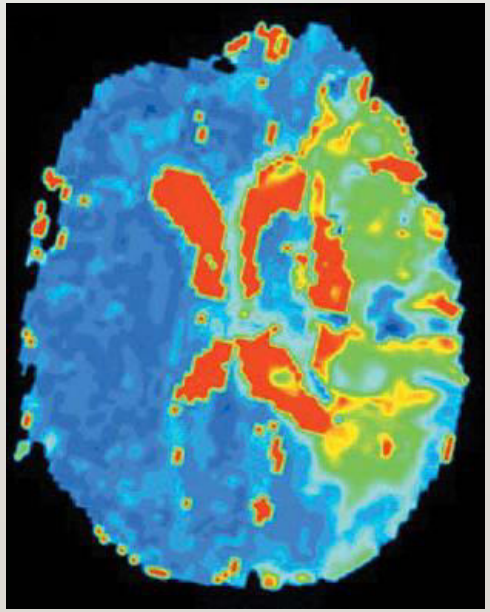
OVER A DECADE, ESPECIALLY IN THE PAST 3 YEARS, ACUTE STROKE DECISION-MAKING HAS BECOME COMPLEX AND INCREASINGLY INDIVIDUALIZED

- First thrombolytic agent and time window defined across a population
  - → Alteplase, 4.5 hours
- Then endovascular device and time window defined across a population
  - → Stent-retrievers/suction catheters, 6 hours
- Finally, imaging selection criteria defined who would benefit for extended time windows out to 24 hours from stroke onset
  - → CTA-CTP for endovascular therapy
  - → MRI FLAIR-DWI mismatch for thrombolysis

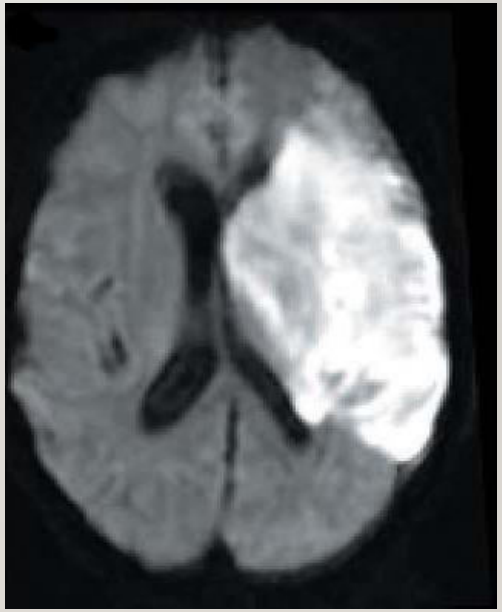
DIFFUSION-PERFUSION MISMATCH IN SUB-SIX HOUR STROKE



DWI



PWI- MTT

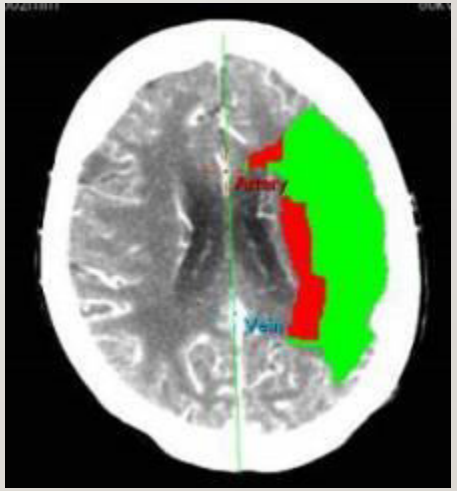


DWI- 3 days later

UNKNOWN ONSET/LATE REVASCULARISATION

>4.5 H BASED ON ADVANCED « MISMATCH – IMAGING »

« Time is brain »



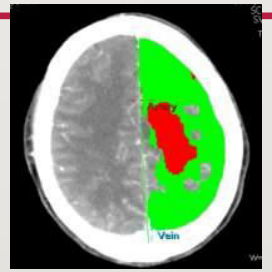
CTP

« Little core & large penumbra is brain »

Michel Ann Neurol 2005

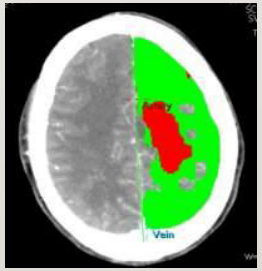
THREE CLINICALLY USEFUL MISMATCH DEFINITIONS

1) Core – penumbra mismatch > 1.8



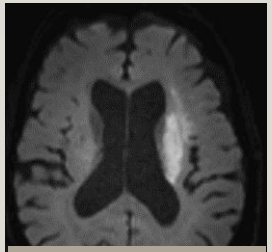
Red: core
Green: penumbra

2) Core – clinical mismatch

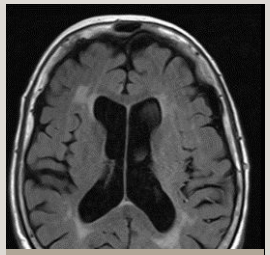


Small core
High NIHSS

3) DWI – FLAIR mismatch

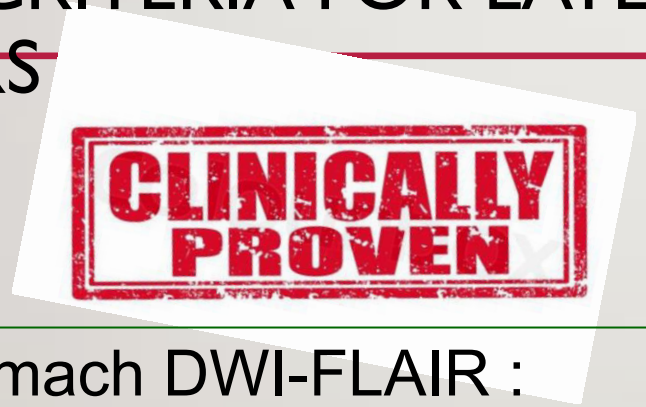


DWI +



FLAIR -

OUR CRITERIA FOR LATE IV THROMBOLYSIS > 4.5 HOURS



Mismach DWI-FLAIR :

✓ Mismatch DWI – FLAIR

or

Mismatch CTP or MR-PWI :

✓ Mismatch ratio > 1.8

AND IF I DO NOT HAVE MRI OR CT-PERFUSION

FOR UNKNOWN ONSET/LATE REVASCULARISATION DECISIONS ?

Core – clinical mismatch

Small core
High NIHSS

→ For example using a high ASPECTS score as evidence for « small core »

Nannoni AJNR 2021

OUR CRITERIA FOR LATE IV THROMBOLYSIS > 4.5 HOURS

Mismach DWI-FLAIR :

✓ Mismatch DWI – FLAIR

or

Mismatch CTP or MR-PWI :

✓ Mismatch ratio > 1.8

or: Plain CT (ASPECTS)

Mismatch ASPECTS-clinical :

✓NIHSS 4-10
and CT-ASPECTS ≥ 8

or

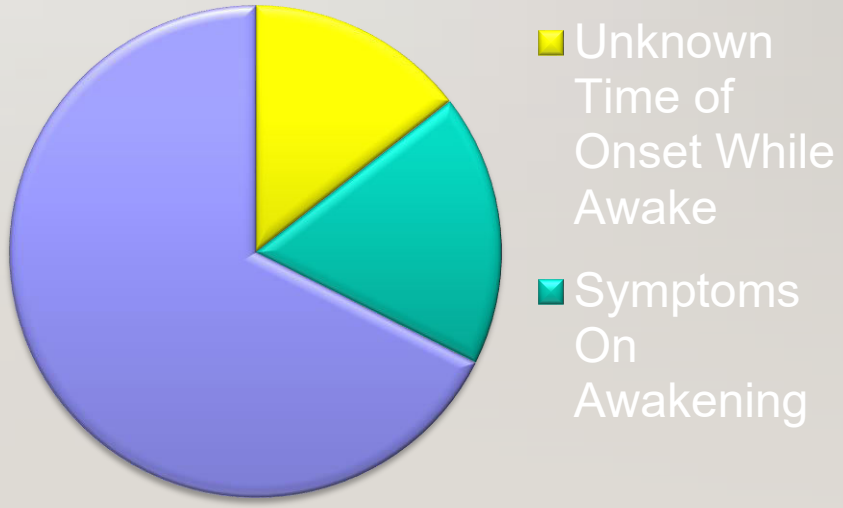
✓NIHSS ≥ 10
and CT-ASPECTS ≥ 7

Based on: Nannoni AJNR 2021; Nannoni Int J Stroke 2021

EXPANDING THE THERAPEUTIC WINDOW FOR ACUTE ISCHEMIC STROKE: *WAKE-UP OR UNWITNESSED STROKE ONSET*

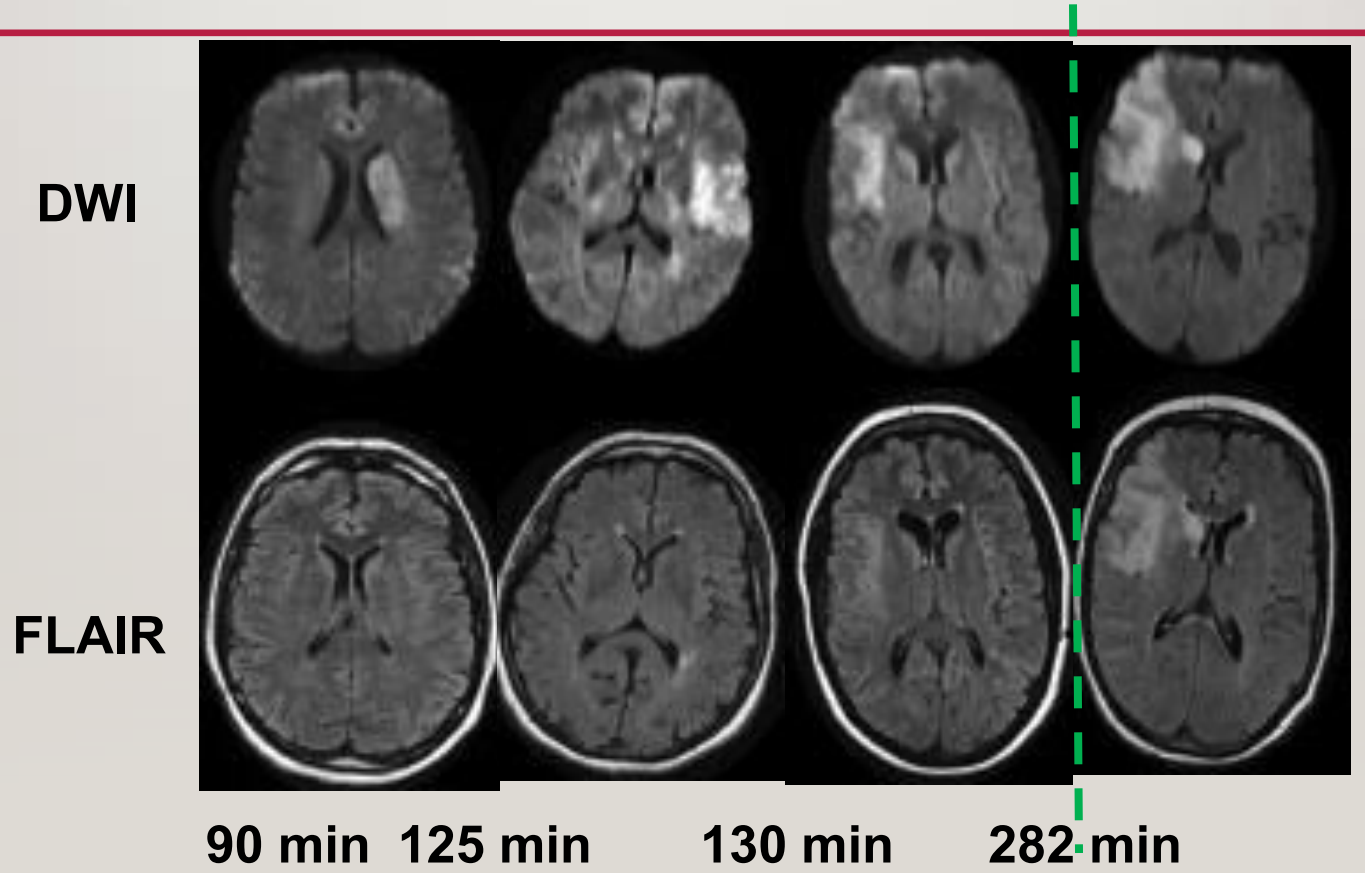
- ~10% of stroke patients arrive within 4.5 hours of symptom onset and can be treated with IV tPA
- Up to 1/3 of stroke patients wake-up with stroke symptoms or have unwitnessed onset
- Historically, they are disqualified from acute treatments

Unclear Onset Strokes ~ 30% of all Strokes



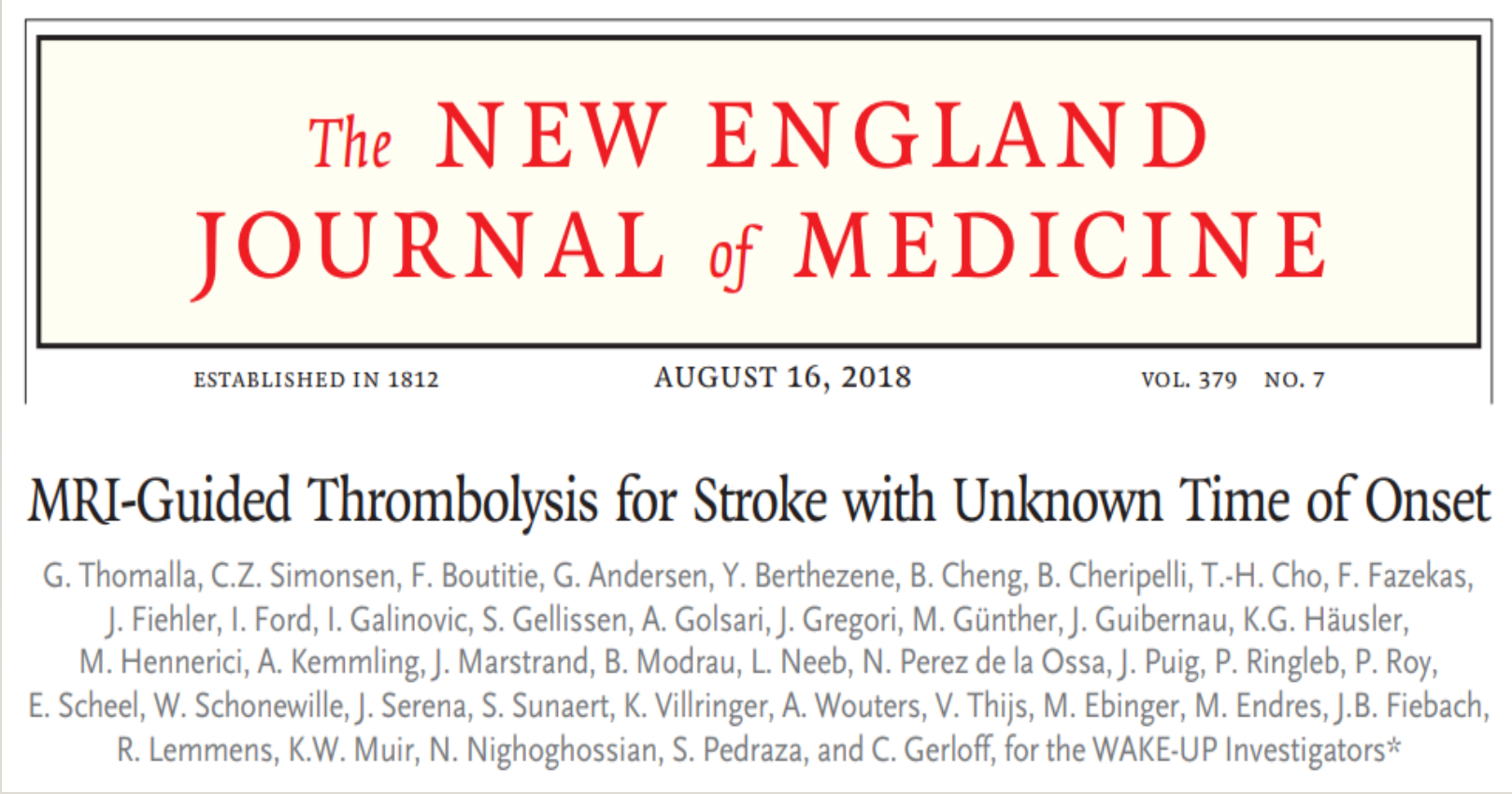
J Stroke Cerebrovasc. Dis. 2011.

POSITIVE DWI, NEGATIVE FLAIR MAY IDENTIFY STROKES < 4.5 HOURS OLD



Thomalla et al. Ann Neurol. 2009.

THROMBOLYSIS IN WAKE-UP STROKE



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 16, 2018 VOL. 379 NO. 7

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

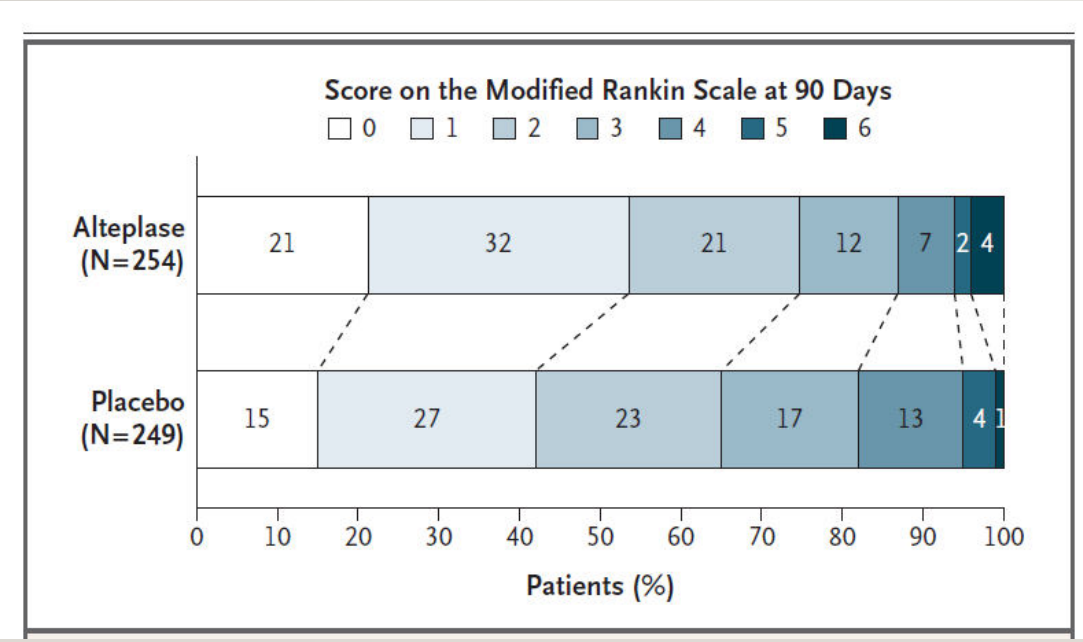
G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas, J. Fiehler, I. Ford, I. Galinovic, S. Gellissen, A. Golsari, J. Gregori, M. Günther, J. Guibernau, K.G. Häusler, M. Hennerici, A. Kemmling, J. Marstrand, B. Modrau, L. Neeb, N. Perez de la Ossa, J. Puig, P. Ringleb, P. Roy, E. Scheel, W. Schonewille, J. Serena, S. Sunaert, K. Villringer, A. Wouters, V. Thijs, M. Ebinger, M. Endres, J.B. Fiebach, R. Lemmens, K.W. Muir, N. Nighoghossian, S. Pedraza, and C. Gerloff, for the WAKE-UP Investigators*

WAKE-UP Stroke Trial

- Acute stroke with “last known normal” time > 4.5 hrs (no upper time limit)
- Met standard eligibility criteria for the use of alteplase
- Had DWI-FLAIR mismatch (abnormal signal on DWI and no marked signal change on FLAIR in the region of the acute stroke).
- Excluded:
  - Large strokes > 1/3 of MCA or NIHSS > 25
  - Planned thrombectomy
- The primary endpoint was favorable outcome, defined as mRS = 0-1 at 90 days
- Randomized to Alteplase vs. Placebo within 4.5 hrs of awakening or “symptom discovery”

Thomalla et al. NEJM 2018.

WAKE-UP STROKE TRIAL



Primary Outcome

Alteplase: 53.3% mRS 0-1

Placebo: 41.8% mRS 0-1

P=0.02

NNT = 8

Shift in distribution of mRS scores of 90 day functional disability

P = 0.003

Thomalla et al. NEJM 2018.

THROMBOLYSIS IN WAKE-UP STROKE

Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Alteplase Group (N=254)	Placebo Group (N=249)	Effect Variable	Adjusted Value (95% CI)†	P Value
Primary efficacy end point					
Favorable outcome at 90 days — no./total no. (%)‡	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02
Secondary efficacy end points					
Median score on modified Rankin scale at 90 days (IQR)§	1 (1–3)	2 (1–3)	Common odds ratio	1.62 (1.17 to 2.23)	0.003¶
Correlation between treatment response at 90 days and deficit level at baseline — no./total no. (%)‖	72/246 (29.3)	44/244 (18.0)	Odds ratio	1.88 (1.22 to 2.89)	0.004¶
Global Outcome Score at 90 days**			Odds ratio	1.47 (1.07 to 2.04)	0.02¶
Median score on Beck Depression Inventory at 90 days (IQR)††	6.0 (2.0–11.0)	7.0 (2.0–14.0)	Mean difference ($\log_e$)	−0.04 (−0.22 to 0.15)	0.69¶
Total score on EQ-5D at 90 days‡‡	1.9±2.1	2.4±2.4	Mean difference	−0.52 (−0.88 to −0.16)	0.004¶
Score on visual analog scale on EQ-5D at 90 days§§	72.6±19.7)	64.9±23.8	Mean difference	7.64 (3.75 to 11.51)	<0.001¶
Median infarct volume at 22–36 hr (IQR) — ml ¶¶	3.0 (0.8–17.7)	3.3 (1.1–16.6)	Mean difference ($\log_e$)	−0.16 (−0.47 to 0.15)	0.32¶

NNT 9

IMPLICATIONS OF WAKE UP TRIAL

- ≈1 out of every 6 patients wakes up with stroke symptoms and has an unclear time of symptom onset
- Landmark trial- Showed the utility of alteplase in imaging selected patients with extended window period
- **Maintained Screening log** unlike many other BIG trials
- Useful to estimate the additional % of patients -potentially eligible
- 503 of 1362 screened (36.9%) patients were enrolled
- Increase overall treatment rates with alteplase by ≈9%
- *In centers which administer alteplase to 20% of patients, this would increase treatment rates by 50%. For those that treat a lesser percent of patients, the relative increase will be even higher.*

Mackey J et al. Population-based study of wake-up strokes. *Neurology.* 2011;76:1662–1667
Silver B et al. Stroke. 2018;49:00-00

IMPLICATIONS OF WAKE UP TRIAL - CONCERNS

- Rate of a good clinical outcome in both the alteplase and placebo arms (53.3% and 41.8% with an mRS of 0 to 1 at 90 days) are less than what would be expected for those with lower severity strokes (median NIHSS 6)

- *Single Centre study – some may argue for a confirmatory trial*

- ≈20% of the patients in the study had an occlusion of a large intracranial artery and would have qualified for treatment with thrombectomy in DAWN/DEFUSE trial
- No data are available for octogenarians and nonagenarians
- Requirement of having an MRI for emergent brain imaging – 24X7
- *Is TNK better than Alteplase in >4.5 hrs with mismatch ?*

  TWIST Trial

Silver B et al. Stroke. 2018;49:00-00

EXTENDING WINDOW PERIOD FOR THROMBOLYSIS

Extending the time for thrombolysis (ECASS-4: ExTEND)

Randomized double-blind placebo-controlled study

Hypothesis: AIS patients with significant penumbral mismatch at 4.5–9 h after onset of stroke or wake upstroke, will have better clinical outcome compared to placebo

Primary outcome was day 90 categorical shift in MRS

Planned sample size was 264

Trial was stopped early after recruiting 120 patients due to **slow recruitment and many patients were eligible for mechanical thrombectomy**

Results of this study were presented in ESO conference, 2018

Failed to demonstrate efficacy and the primary endpoint was mRS shift

OR 1.23 (95% CI 0.66–2.32)

Secondary outcome of mRS 0–1 was 35% vs. 28.6%

OR 1.38 (95% CI 0.63–3.01)

Trial was underpowered and hence strong conclusions cannot be made out of these results.

THROMBOLYSIS IN THE ERA OF TISSUE CLOCK

Should we go to tissue clock irrespective of time in thrombolysis within 4.5 hrs also ?

Should we thrombolyze a patient with poor ASPECTS and poor collaterals with window period < 4.5 hrs or infarct < 1 hr also ?

TENECTEPLASE

Table 1: Comparison of pharmacokinetic and pharmacodynamic properties of alteplase and tenecteplase

Properties	TPA	TNK
Fibrin specificity	++	+++
Thrombolytic potency	+	+++
PAI-1 resistance	–	++
Fibrinogen depletion	++	+
PRT activity	++	+++
Clearance (ml/kg/min)	16.1	1.9

TPA=Tissue plasminogen activator, TNK=Tenecteplase, PRT=Platelet-rich thrombus, PAI-1=Plasminogen activator inhibitor-1, - No action, + Activity present, ++ and +++ Indicates higher grades of activity

Vishnu VY, MVP Srivastava. Innovations in Acute Stroke Reperfusion Strategies. AIAN 2019; 22:6-12.

Penumbral Imaging–Based Thrombolysis with Tenecteplase Is Feasible up to 24 Hours after Symptom Onset

Mahesh Kate,[a] Robert Wannamaker,[a] Harsha Kamble,[a] Parnian Riaz,[a] Laura C. Gioia,[a] Brian Buck,[a] Thomas Jeerakathil,[a] Penelope Smyth,[a] Ashfaq Shuaib,[a] Derek Emery,[b] Kenneth Butcher[a]

Table 2. Outcome variables in three groups

Variable	Treated with tenecteplase	Mismatch pattern not treated	Non-mismatch pattern	*P*
Infarct growth (mL)	6.7 (–3.0 to 28.5)	15.9 (2.5–34.8)	74.5 (32.3–113.2)	<0.001
Penumbral salvage (mL)	48.3 (24.9–80.4)	17.4 (–12.5 to 33.8)	–90.8 (–197.3 to 19.8)	<0.001
Final infarct (mL)	31.3 (15.9–55.6)	38.6 (26.0–51.0)	121.6 (74.9–221.9)	<0.001
Symptomatic hemorrhage*	1 (6.3)	0	1 (4.3)	0.6
Any hemorrhagic transformation†	6 (37.5)	2 (11.1)	8 (34.8)	0.09
Parenchymal hematoma‡	4 (25.0)	1 (5.6)	1 (4.3)	0.6
Hemorrhagic infarction	2 (12.5)	1 (5.6)	7 (30.4)	0.2
Mortality	0	0	10 (43.5)	
mRS 90 days	2 (2–2.5)	3 (3–4)	5 (4–6)	<0.001
mRS 0–2	11 (73.3)	4 (22.2)	1 (4.3)	<0.001

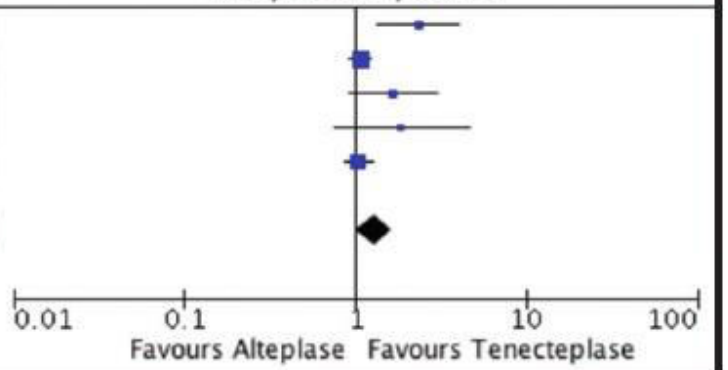
Journal of Stroke 2018;20(1):122-130

Tenecteplase

Study or Subgroup	Tenecteplase Events	Total	Alteplase Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Parsons 2012	21	25	9	25	13.1%	2.33 [1.35, 4.04]
Logallo 2017	229	549	214	551	36.0%	1.07 [0.93, 1.24]
Huang 2015	19	47	12	49	11.5%	1.65 [0.90, 3.01]
Haley 2010	15	50	5	31	6.0%	1.86 [0.75, 4.61]
Campbell 2018	72	101	69	101	33.4%	1.04 [0.87, 1.25]
Total (95% CI)		**772**		**757**	**100.0%**	**1.28 [1.01, 1.63]**
Total events	356		309			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 10.67$, df = 4 (P = 0.03); $I^2 = 63\%$

Test for overall effect: Z = 2.00 (P = 0.05)



Vishnu VY, MVP Srivastava. Innovations in Acute Stroke Reperfusion Strategies. AIAN 2019; 22:6-12.

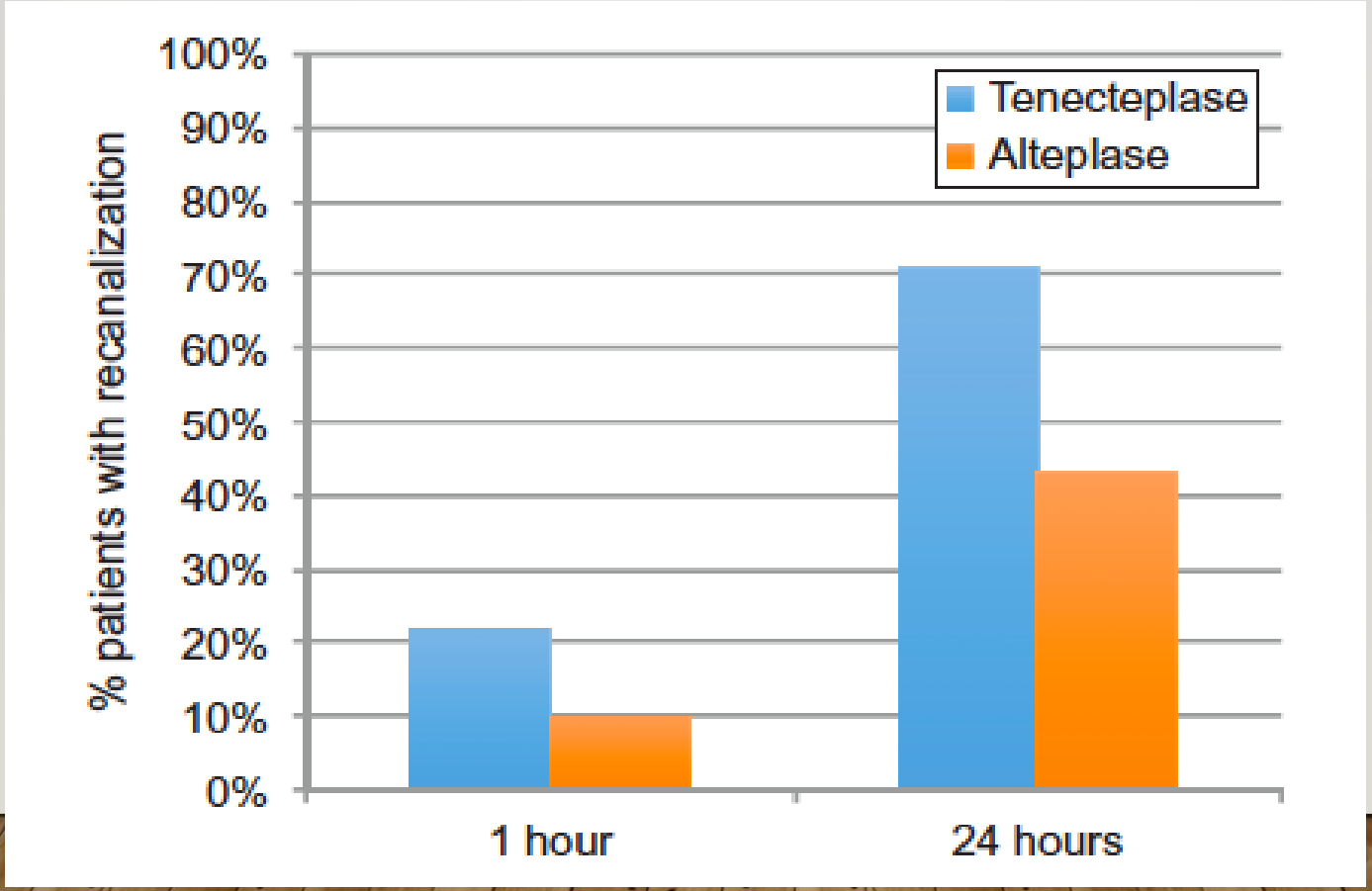
COMPLETED TRIALS IN TNK

Trial	Year	Study design	TNK dose groups (mg/kg)	Non-TNK thrombolytic comparator group	N
Haley[30]	2005	RCT	0.1 vs. 0.2 vs. 0.4 vs. 0.5	No	88
Parsons[31]	2009	Obs	0.1	No	15
Haley[38]	2010	Obs	0.1 vs 0.25 vs 0.4	Alteplase 0.9 mg/kg	112
Parsons[28]	2012	RCT	0.1 vs. 0.25	Alteplase 0.9 mg/kg	75
ATTEST[27]	2015	RCT	0.25	Alteplase 0.9 mg/kg	104
TEMPO-1[33]	2015	Obs	0.1 vs. 0.25	No	50
NOR-TEST[35]	2017	RCT	0.4	Alteplase 0.9 mg/kg	1100
EXTEND-IA TNK[36]	2018	RCT	0.25	Alteplase 0.9 mg/kg	202
Kate[39]	2018	Obs	0.25	No	16

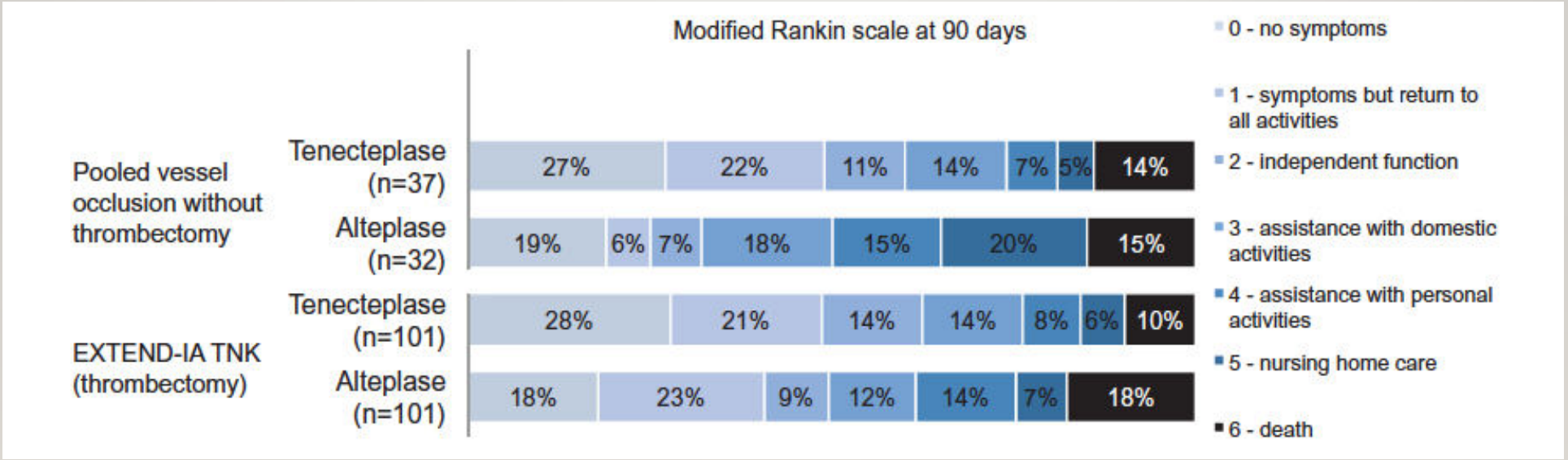
TRIALS IN TNK

Trial	TNK dose groups (mg/kg)	Non-TNK thrombolytic comparator group	Timing	N
ATTEST-2 (NCT02814409)	0.25	Alteplase 0.9 mg/Kg	<4.5 h	1870
TASTE-2 (ACTRN12613000243718)	0.25	Alteplase 0.9 mg/Kg	<4.5 h	Up to 1024[a]
EXTEND-IA TNK II (NCT03340493)	0.25 vs. 0.4	No		Up to 656[a]
TWIST (NCT03181360)	0.25	No (non-thrombolytic standard of care)	<4.5 h from awakening	500
TEMPO-2 (NCT02398656)	0.25	No (non-thrombolytic standard of care)	<12 h	1274

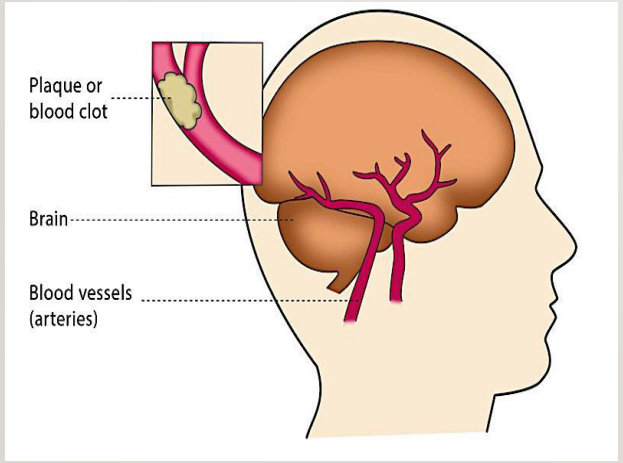
RECANALIZATION WITH TENECTEPLASE VERSUS ALTEPLASE IN PATIENTS WITH BASELINE VESSEL OCCLUSION AT APPROXIMATELY 1 H POST-TREATMENT (22% VS. 10% P.0.023, EXTEND-IA TNK) AND AT 24 H POST-TREATMENT (71% VS. 43%, P<0.001, POOLED ANALYSIS OF ATTEST AND AUSTRALIAN TNK TRIAL).



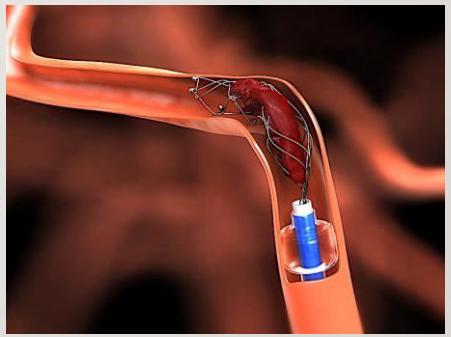
DISTRIBUTION OF MODIFIED RANKIN SCALE SCORES AT 90 DAYS IN PATIENTS WITH BASELINE VESSEL OCCLUSION TREATED WITH (A) THROMBOLYSIS AND THROMBECTOMY IN EXTEND-IA TNK AND (B) THROMBOLYSIS ONLY IN POOLED ANALYSIS OF ATTEST AND AUSTRALIAN TNK TRIAL.



ENDOVASCULAR THERAPY: GAME CHANGER



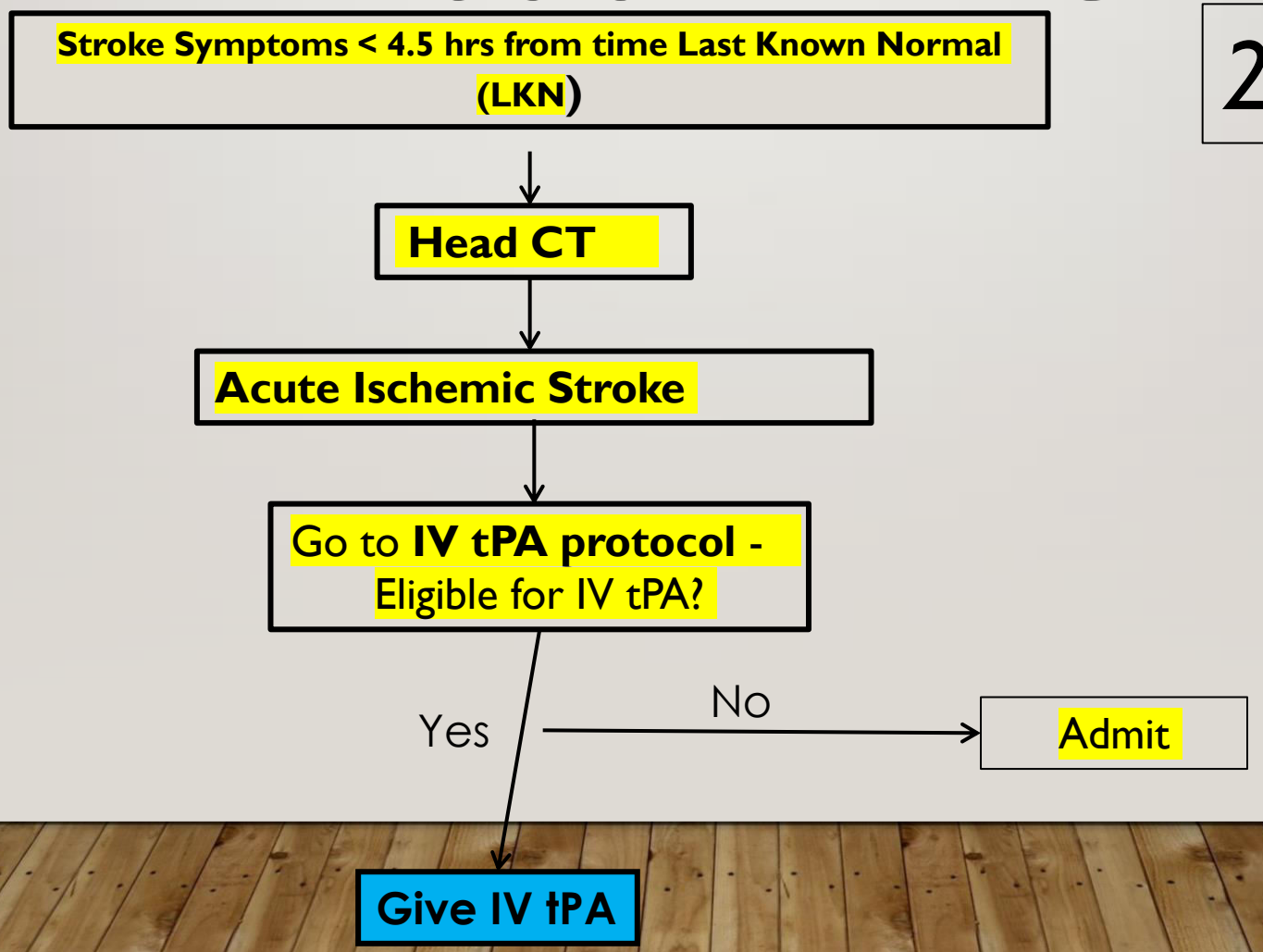
Trial
MR CLEAN[35]
REVASCAT[36]
EXTEND 1A[37]
SWIFT-prime[38]
ESCAPE[39]
THRACE[40]
THERAPY[41]
PISTE[42]
EASI[43]



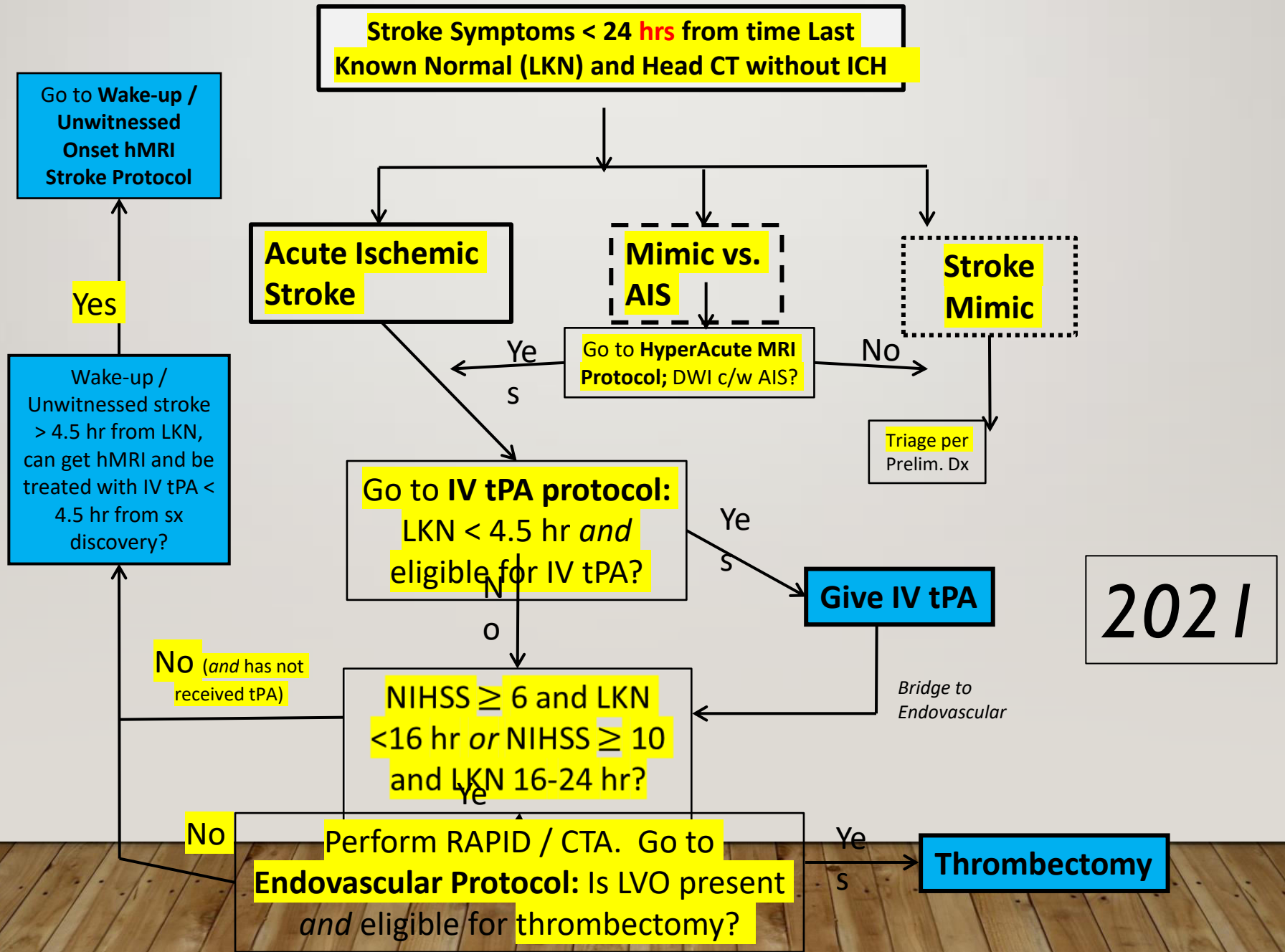
Evans MRB, et al. Pract Neurol 2017;0:252–265. doi:10.1136/practneurol-2017-001685

ACUTE ISCHEMIC STROKE DECISION-MAKING

2008



Acute ischemic stroke decision-making



2021

LATE TIME WINDOW:: ???

DON'T WE NEED TO LOOK AT TISSUE

- Time
- Recanalisation
- Reperfusion
- Tissue

TISSUE VERSUS TIME

- 2 big studies IV:
- WAKE UP
- EXTEND

- 2 big studies IA:
- DAWN
- DEFUSE 3

DWI/PWI. CTP

- Look for a **mismatch**
- Look for tissue still potentially **underperfused**
- **Recanalisation** will lead to **better outcome**

DEFUSE- 3 TRIAL

Infarct volume<70 ml with ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of >=1.8

ORIGINAL ARTICLE

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

G.W. Albers, M.P. Marks, S. Kemp, S. Christensen, J.P. Tsai, S. Ortega-Gutierrez, R.A. McTaggart, M.T. Torbey, M. Kim-Tenser, T. Leslie-Mazwi, A. Sarraj, S.E. Kasner, S.A. Ansari, S.D. Yeatts, S. Hamilton, M. Mlynash, J.J. Heit, G. Zaharchuk, S. Kim, J. Carrozzella, Y.Y. Palesch, A.M. Demchuk, R. Bammer, P.W. Lavori, J.P. Broderick, and M.G. Lansberg, for the DEFUSE 3 Investigators*

DAWN TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 4, 2018 VOL. 378 NO. 1

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel, V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim, J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith, D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*

- Infarct volume-DWI or CTP Assessment/Clinical Mismatch

OTHERS

- REVASCAT : Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior circulation Stroke Within 8 hours
- ESCAPE: Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke: Recruited subjects upto 12 hours.
- POSITIVE: Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy: Halted

IMAGING CRITERIA: DAWN

- Stratification by age and NIHSS:
- Maximum infarct core cut off volumes measured by specific imaging software in an automated fashion:
- > 80 years (core upto 20 ml; < 80 years, NIHSS 10-19, core up to 30 ml; NIHSS >20, core up to 51 ml).

DEFUSE-3:

- Allowed a larger core volume up to 70 ml but required a mismatch measured by perfusion CT or MRI of > 1.8 (ratio) and 15 ml (penumbra volume), measured by a specific imaging software in an automated fashion.
- Both require post processing soft ware.
- Approx., number of patients who can get IVT: 25%
- EVT < 6 hours: 10%
- With DAWN & DEFUSE 3 criteria: 2.7%

ESCAPE TRIAL

ORIGINAL ARTICLE

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

M. Goyal, A.M. Demchuk, B.K. Menon, M. Eesa, J.L. Rempel, J. Thornton, D. Roy, T.G. Jovin, R.A. Willinsky, B.L. Sapkota, D. Dowlatshahi, D.F. Frei, N.R. Kamal, W.J. Montanera, A.Y. Poppe, K.J. Ryckborst, F.L. Silver, A. Shuaib, D. Tampieri, D. Williams, O.Y. Bang, B.W. Baxter, P.A. Burns, H. Choe, J.-H. Heo, C.A. Holmstedt, B. Jankowitz, M. Kelly, G. Linares, J.L. Mandzia, J. Shankar, S.-I. Sohn, R.H. Swartz, P.A. Barber, S.B. Coutts, E.E. Smith, W.F. Morrish, A. Weill, S. Subramaniam, A.P. Mitha, J.H. Wong, M.W. Lowerison, T.T. Sajobi, and M.D. Hill for the ESCAPE Trial Investigators*

ABSTRACT

BACKGROUND

Among patients with a proximal vessel occlusion in the anterior circulation, 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment. We evaluated rapid endovascular treatment in addition to standard care in patients with acute ischemic stroke with a small infarct core, a proximal intracranial arterial occlusion, and moderate-to-good collateral circulation.

ESCAPE

- Criteria with CT and CT multiphase angiography and volumetry of CT angiography-based lesion core as a substitute for DWI.

META-ANALYSIS : AURORA

- Analysis of pooled data for 4 trials
- Significant treatment benefit of endovascular therapy versus standard treatment increasing the odds for an improved outcome at day 90 by 2.77 (95% CI, 1.95-3.94) (NNT, 2.5).
- Similar to HERMES Collaboration analysis for EVT < 6 hours.
- Late Time Window Paradox: Treatment effect was stronger from 12 – 24 hours vs 6-12 hours.

EXTEND -IA

- CT perfusion imaging, which was processed with the use of fully automated software (RAPID)
- Ischemic core- relative cerebral blood flow (CBF) < 30% of that in normal tissue.
- Ischemic penumbra -time to maximum (Tmax) delay > 6 seconds.

ORIGINAL ARTICLE

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

B.C.V. Campbell, P.J. Mitchell, T.J. Kleinig, H.M. Dewey, L. Churilov, N. Yassi, B. Yan, R.J. Dowling, M.W. Parsons, T.J. Oxley, T.Y. Wu, M. Brooks, M.A. Simpson, F. Miteff, C.R. Levi, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, M. Priglinger, T. Ang, R. Scroop, P.A. Barber, B. McGuinness, T. Wijeratne, T.G. Phan, W. Chong, R.V. Chandra, C.F. Bladin, M. Badve, H. Rice, L. de Villiers, H. Ma, P.M. Desmond, G.A. Donnan, and S.M. Davis, for the EXTEND-IA Investigators*

ABSTRACT

BACKGROUND

Trials of endovascular therapy for ischemic stroke have produced variable results. We conducted this study to test whether more advanced imaging selection, recently developed devices, and earlier intervention improve outcomes.

Impact of Collaterals on Successful Revascularization in Solitaire FR With the Intention for Thrombectomy

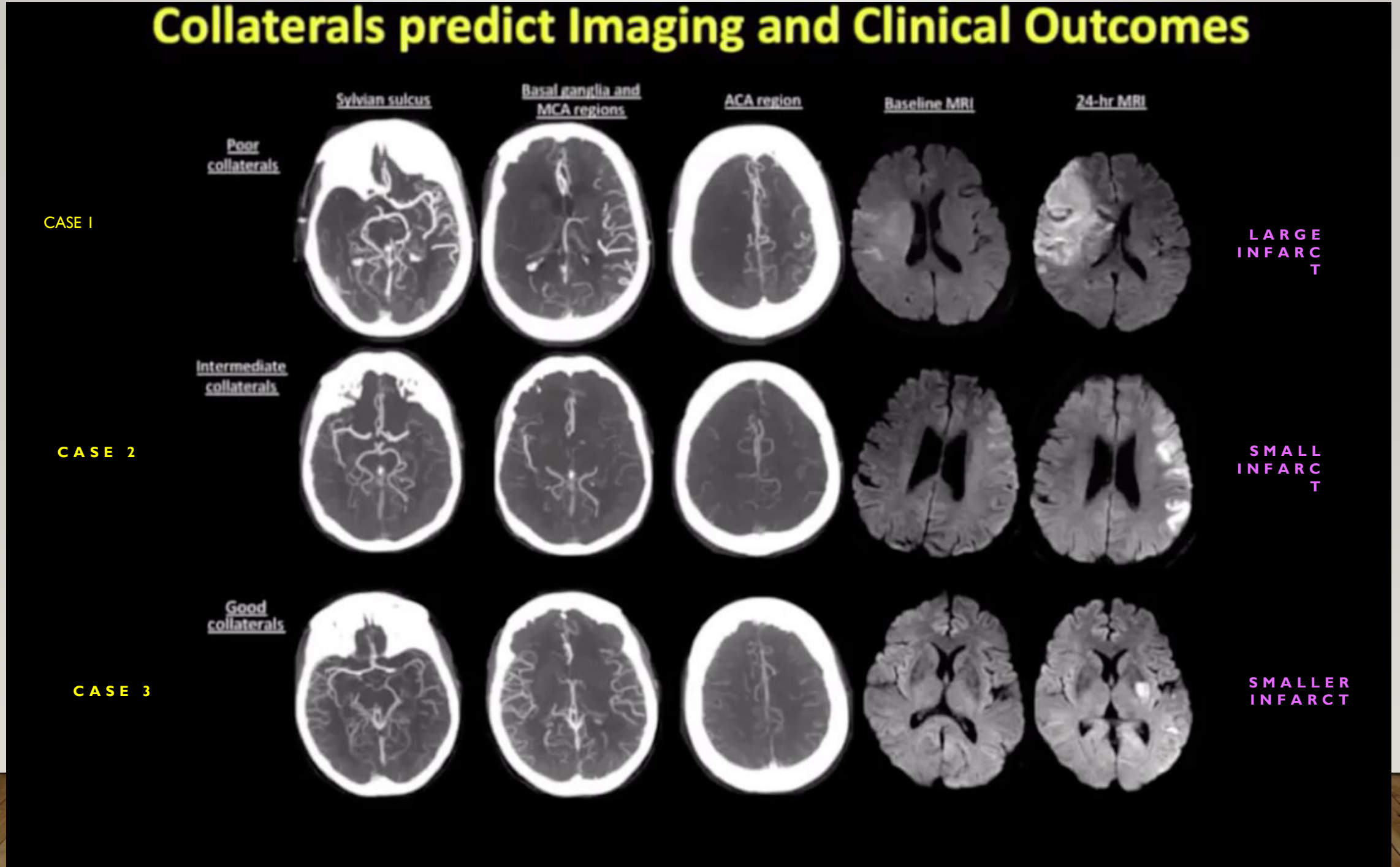
David S. Liebeskind, MD; Reza Jahan, MD; Raul G. Nogueira, MD; Osama O. Zaidat, MD; Jeffrey L. Saver, MD; for the SWIFT Investigators

Background and Purpose—Collaterals at angiography before endovascular therapy were analyzed to ascertain the effect on a novel end point of successful revascularization without symptomatic hemorrhage in the Solitaire FR With the Intention for Thrombectomy (SWIFT) study.

Methods—Collateral grade (American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology) on baseline angiography was independently assessed, blind to other data, with statistical analyses delineating the relationship with clinical, laboratory, and imaging parameters.

Conclusions—Better collaterals were associated with lower glucose, lower blood pressure, smaller baseline infarcts in SWIFT, and greater likelihood of successful revascularization without hemorrhage and good clinical outcomes.

Collaterals predict Imaging and Clinical Outcomes



CASE 1

LARGE INFARCT

CASE 2

SMALL INFARCT

CASE 3

SMALLER INFARCT

IMAGING IN COLLATERAL CIRCULATION

- Collateral circulation- Characterized with angiography or described in terms of resultant perfusion or patterns of infarction
- Imaging correlates of collaterals parallel the basic four Ps of stroke imaging—

1. Pipes
2. Perfusion
3. Penumbra
4. Parenchyma

- Delay and dispersion - the most accurate measures of collateral function

-determinants of tissue outcome in the absence of revascularization

Bang et al Collateral Circulation in Ischemic Stroke
Stroke November 2015

DIAGNOSTIC TECHNIQUES FOR COLLATERAL ASSESSMENT

ASSESSMENT

ANATOMICAL

- ✓ Computed tomography angiography (CTA)
- ✓ Digital subtraction angiography (DSA)
- ✓ Magnetic resonance angiography (MRA)
- ✓ Transcranial doppler (TCD) ultrasound

FUNCTIONAL

- ✓ CT Perfusion
- ✓ Positron emission tomography (PET)
- ✓ Single-photon emission computed tomography (SPECT)
- ✓ Magnetic resonance perfusion (MRP)
- ✓ ASL

CLINICAL SIGNIFICANCE OF COLLATERALS

META-ANALYSIS

Liu L, et al. Stroke and Vascular Neurology. 2018.

- Two recent systematic reviews and meta-analyses investigated the effects of pretreatment collateral circulation

➢clinical outcomes

➢Imaging outcomes of patients

- with stroke receiving endovascular treatment.

Leng et al Cerebrovasc Dis 2016;

Impact of Collateral Status on Successful Revascularization in Endovascular Treatment: A Systematic Review and Meta-Analysis

Xinyi Leng[a] Hui Fang[a, b] Thomas W.H. Leung[a] Chen Mao[a] Yuming Xu[b]
Zhongrong Miao[c] Liping Liu[c] K.S. Lawrence Wong[a] David S. Liebeskind[d]

RESULTS: 27 STUDIES (2,366 SUBJECTS) WERE INCLUDED IN QUALITATIVE ANALYSIS, AMONG WHICH 24 STUDIES (2,239 SUBJECTS) WERE QUANTITATIVELY ANALYZED.

GOOD PRE-TREATMENT COLLATERALS SIGNIFICANTLY INCREASED THE RATE OF BOTH SUCCESSFUL REPERFUSION (RR 1.28, 95% CI 1.17–1.40; $P < 0.001$) AND RECANALIZATION (RR 1.23, 95% CI 1.06–1.42; $P = 0.006$), AS COMPARED WITH POOR COLLATERALS.

Impact of collaterals on the efficacy and safety of endovascular treatment in acute ischaemic stroke: a systematic review and meta-analysis

Xinyi Leng,[1] Hui Fang,[1,2] Thomas W H Leung,[1] Chen Mao,[3] Zhongrong Miao,[4] Liping Liu,[4] Ka Sing Wong,[1] David S Liebeskind[5]

Liebeskind 2014 IMS-III	50	96	54	180	10.4%	1.74 [1.29, 2.33]
Liebeskind 2014 SWIFT	20	35	14	71	6.3%	2.90 [1.67, 5.02]
Mangiafico 2014	22	65	4	37	2.8%	3.13 [1.17, 8.39]
Marks 2014 DEFUSE 2	13	25	8	25	4.8%	1.63 [0.82, 3.22]
Nambiar 2014	23	53	7	31	4.5%	1.92 [0.93, 3.95]
Rai 2012	38	62	6	27	4.4%	2.76 [1.33, 5.74]
Seet 2012	1	1	2	10	1.7%	3.30 [0.85, 12.75]
Seeta Ramaiah 2014	24	34	23	53	8.9%	1.63 [1.12, 2.37]
Sheth 2014	17	34	13	49	6.0%	1.88 [1.06, 3.35]
Shin 2014	23	33	0	10	0.5%	15.21 [1.00, 230.23]
Singer 2015-1 ENDOSTROKE	20	41	25	83	7.6%	1.62 [1.03, 2.55]
Singer 2015-2 ENDOSTROKE	38	78	24	82	8.4%	1.66 [1.11, 2.50]
Sung 2015	9	19	0	11	0.4%	11.40 [0.73, 178.73]
Total (95% CI)		**1096**		**908**	**100.0%**	**1.98 [1.64, 2.38]**
Total events	596		256			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 33.60$, df = 18 (P = 0.01); $I^2 = 46\%$

Test for overall effect: Z = 7.17 (P < 0.00001)

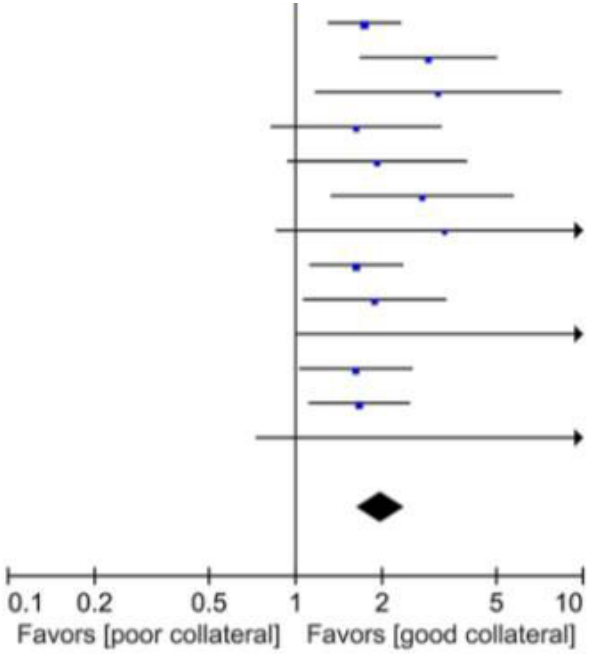


Figure 1 Forest plot showing individual and overall risk ratios of good versus poor pretreatment collateral status for favourable functional outcome (modified Rankin Scale 0–2) at 3 months, in patients with acute ischaemic stroke receiving endovascular treatment, with or without prior intravenous thrombolysis.

Liu L, et al. Stroke and Vascular Neurology 2018;

EVT AND COLLATERAL CIRCULATION IN AIS

- Data from over 20 studies of >2000patients with stroke treated with IAT and/or MT, with or without prior IVT shows better pretreatment collateral circulation is associated with

1. Higher rates of successful recanalisation
2. Significantly lower risk of symptomatic intracranial haemorrhage within 7 days or before discharge
3. Doubled chance of achieving a favourable functional outcome at 3 months
4. Halved risk of death at 3 months

- Inferences -compensates cerebral blood flow adjacent to the ischaemic area -> better access of the clot to intrinsic and extrinsic thrombolytic agents
- possibly a back pressure that facilitates dislodgement of the clot
- mitigate the ischaemia-reperfusion injuries.

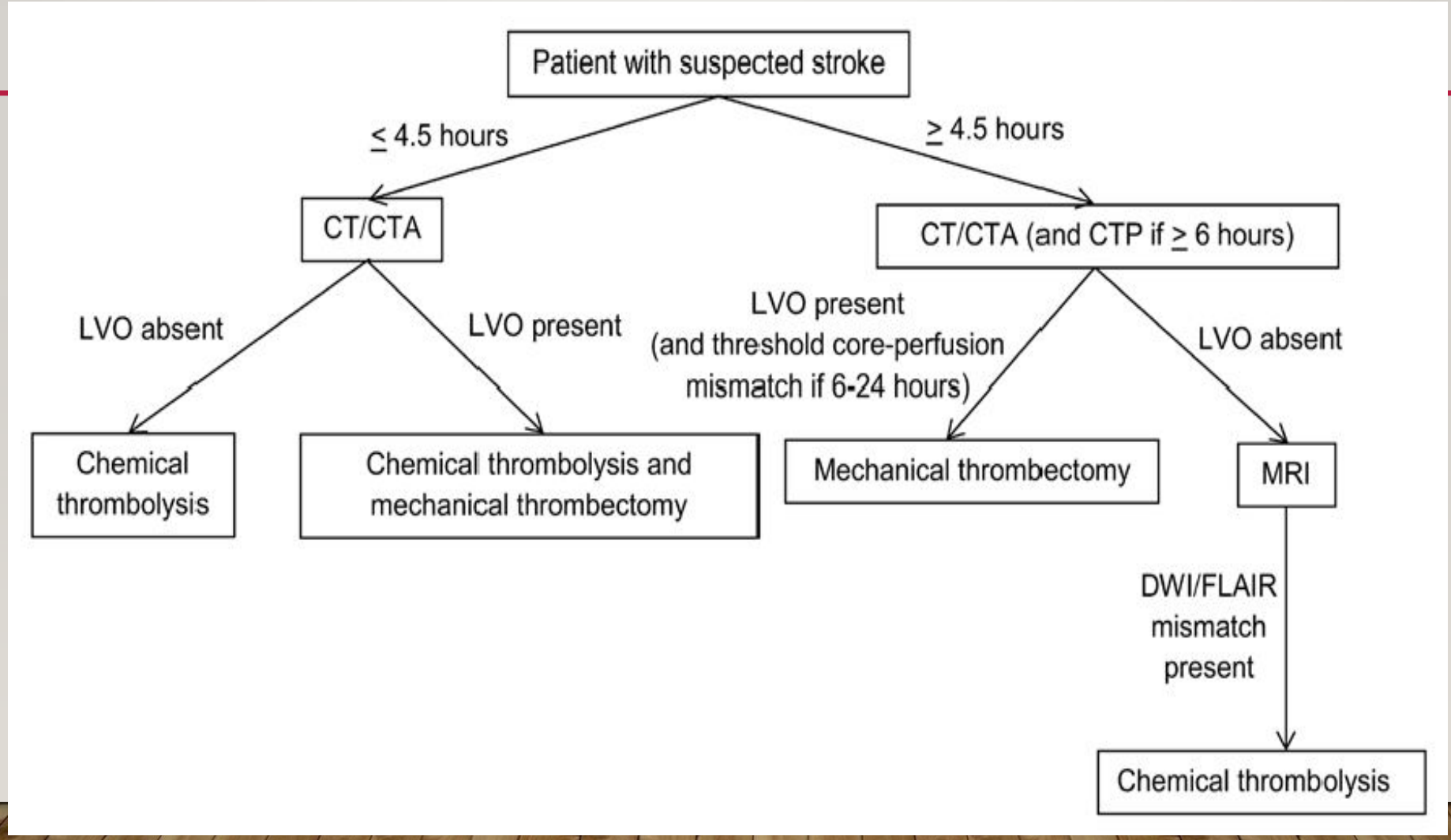
AHA GUIDELINES

2.2.3. Mechanical Thrombectomy Eligibility–Vessel Imaging (Continued)	COR	LOE
5. It may be reasonable to incorporate collateral flow status into clinical decision-making in some candidates to determine eligibility for mechanical thrombectomy.	IIb	C-LD

Several studies, including secondary analyses from MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands) and IMS (Interventional Management of Stroke) III, provide data supporting the role of collateral assessments in identifying patients likely or unlikely to benefit from mechanical thrombectomy.[103,104] The ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times), using multiphase CTA to select patients with moderate to good collateral circulation for mechanical thrombectomy up to 12 hours from onset, was stopped early for efficacy.[105] Acquisition of advanced imaging should not delay door–to–groin puncture times.

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

ALGORITHM FOR PATIENTS WITH AIS



Silver B et al. Stroke. 2018;49:00-00

- Time from symptom onset can no longer serve as the sole emergency treatment criterion for IVT /EVT.
- The idiom “Time is brain” should NOT be abandoned!
- Patients suspected to have a acute stroke syndrome must have pre-hospital, hospital, inter hospital and intra hospital pathways running ASAP.

CONCLUSIONS

- Change to physiological (imaging-based) approach using various indirectly implied (DWI/clinical mismatch, DWI/fluid attenuated inversion recovery mismatch, collateral status)
- Direct (perfusion imaging of core and tissue at risk)
- Shown substrates of the ischemic penumbra concept is REAL
- Speed to treatment is invaluable

- “IMAGE GUIDED IVT/*EVT* FOR STROKE IS SHATTERING THE TIME WINDOW!:……

- Randolph Marshall

CORE PRINCIPLES OF AIS MANAGEMENT

- Waste no time assembling focused clinical stroke history and examination
- Waste no time imaging the brain and blood vessels
- Waste no time synthesizing clinical & radiological pictures
- Waste no time diagnosing
- Waste no time offering definitive fast treatment

CONCLUSIONS

- Identify disabling strokes
- Image the brain & vessels (quickly)
- Identify target patients
- Treat fast

- *“Everything comes at the Right Time, but if the Right Time is too late to be patient, go earlier before it becomes too late” – Michael Bassey Johnson*


NEVER EVER
GIVE UP