INTRAVENOUS THROMBOLYSIS

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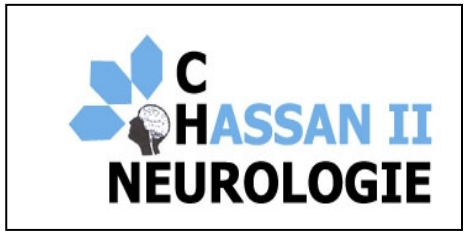


Disclosure of conflict of interest

NONE

Learning objective

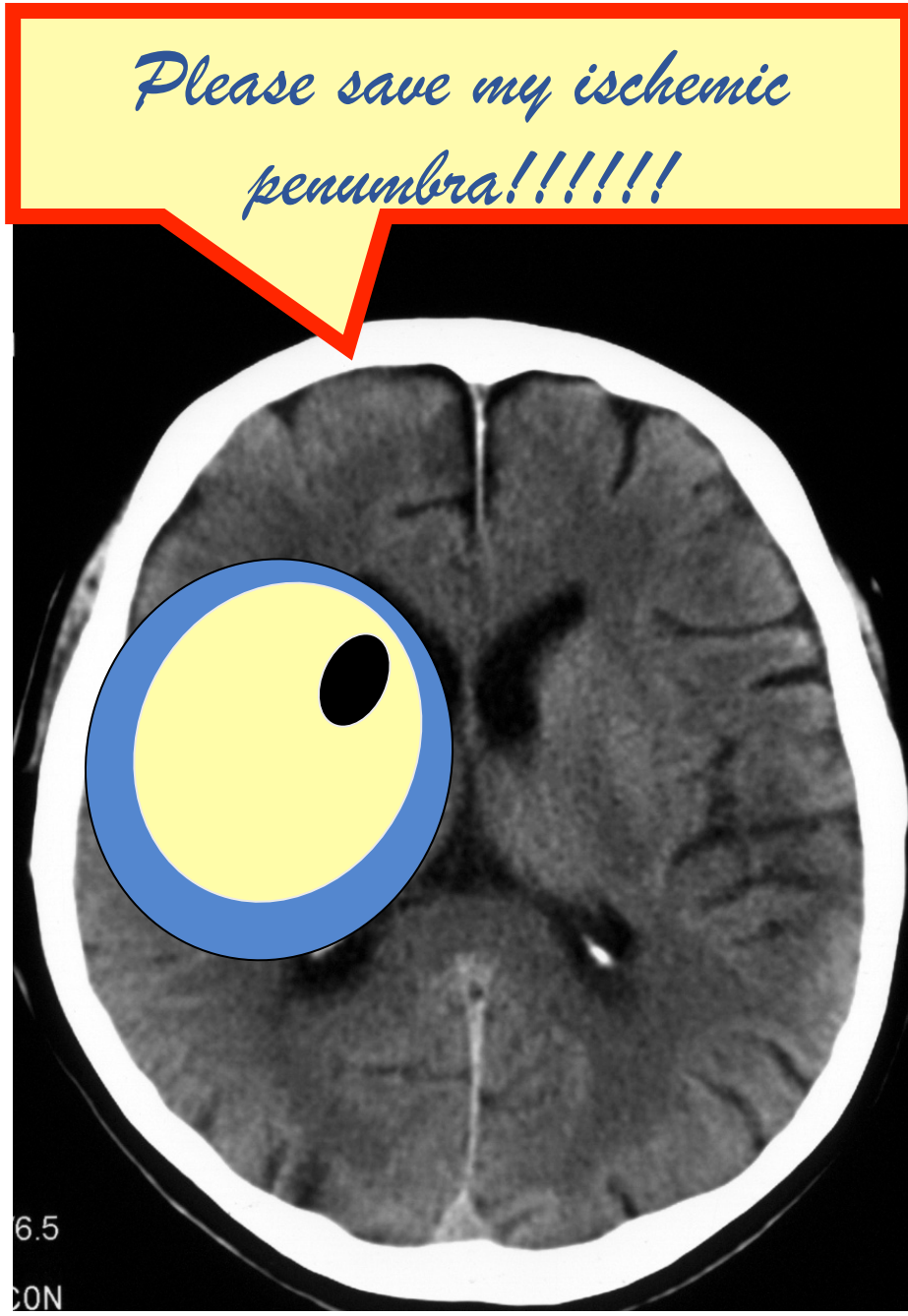
- Describe the different stages and evolution of concepts in intravenous thrombolysis of stroke
- List stroke thrombolysis inclusion and exclusion criteria
- Organize rapid clinical assessment for evaluating stroke
- Choose appropriate cerebral vascular imaging
- Describe rtPA side-effects and and risk factor for complications

INTRODUCTION

- **Ischemic stroke** is a major cause of mortality and morbidity
- Blockage of an artery in the brain by a **blood clot**.
- Thrombolytic drugs:
  - can **restore blood flow** before major brain damage has occurred
  - **improve recovery** after stroke in some people.
  - can also cause **serious bleeding** in the brain, which can be fatal.
- Recombinant tissue plasminogen activator (rt-PA), is licensed for use in selected patients
- Patients consulting **during the first hours** of stroke are candidate for thrombolysis and could take an advantage of this therapy.
- The final size of the infarct will depend on the extent of cerebral ischemic infarct and quality of care.

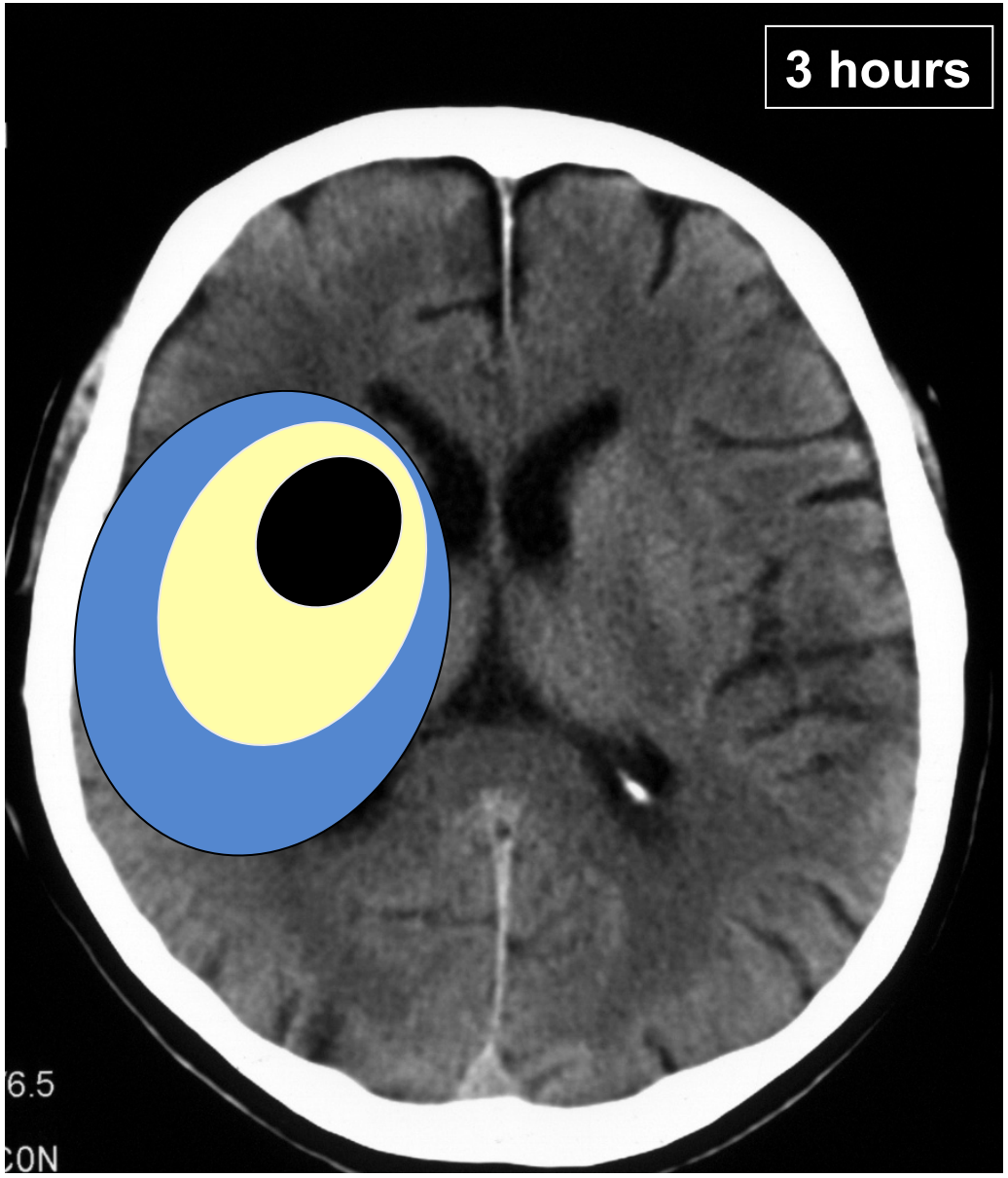
Rational for IVT

- **Decreased cerebral blood flow**, resulting from acute arterial occlusion, reduces oxygen and glucose delivery to brain tissue
- The ultimate result of ischemic cascade is **neuronal death**.
- Degree of cerebral blood flow reduction: not uniform.
- Tissue at the center of the zone is typically exposed to lower blood flow
- **Ischemic ‘‘penumbra’’:** viable but dysfunctional brain tissue, often surrounding a zone of irreversible damage
- **Ischemic ‘‘penumbra’’:** infarction in the absence of perfusion.
- **Restoration of blood flow to the penumbra:** goal of thrombolytic therapy.



Rational for IVT

As time passes, more and more of the hypoperfusion zone goes on to **infarction**, and the relative size of the penumbra decreases.



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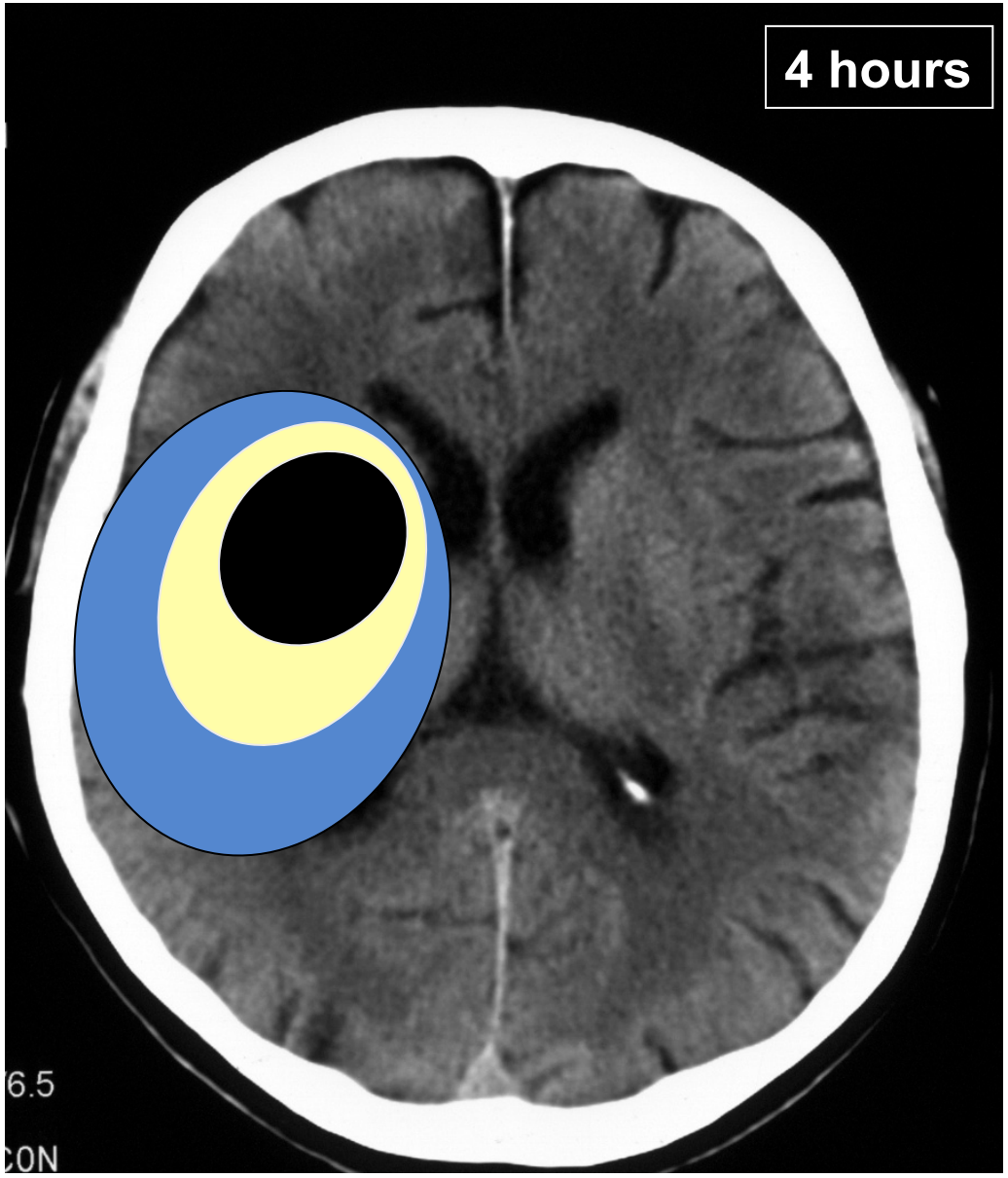
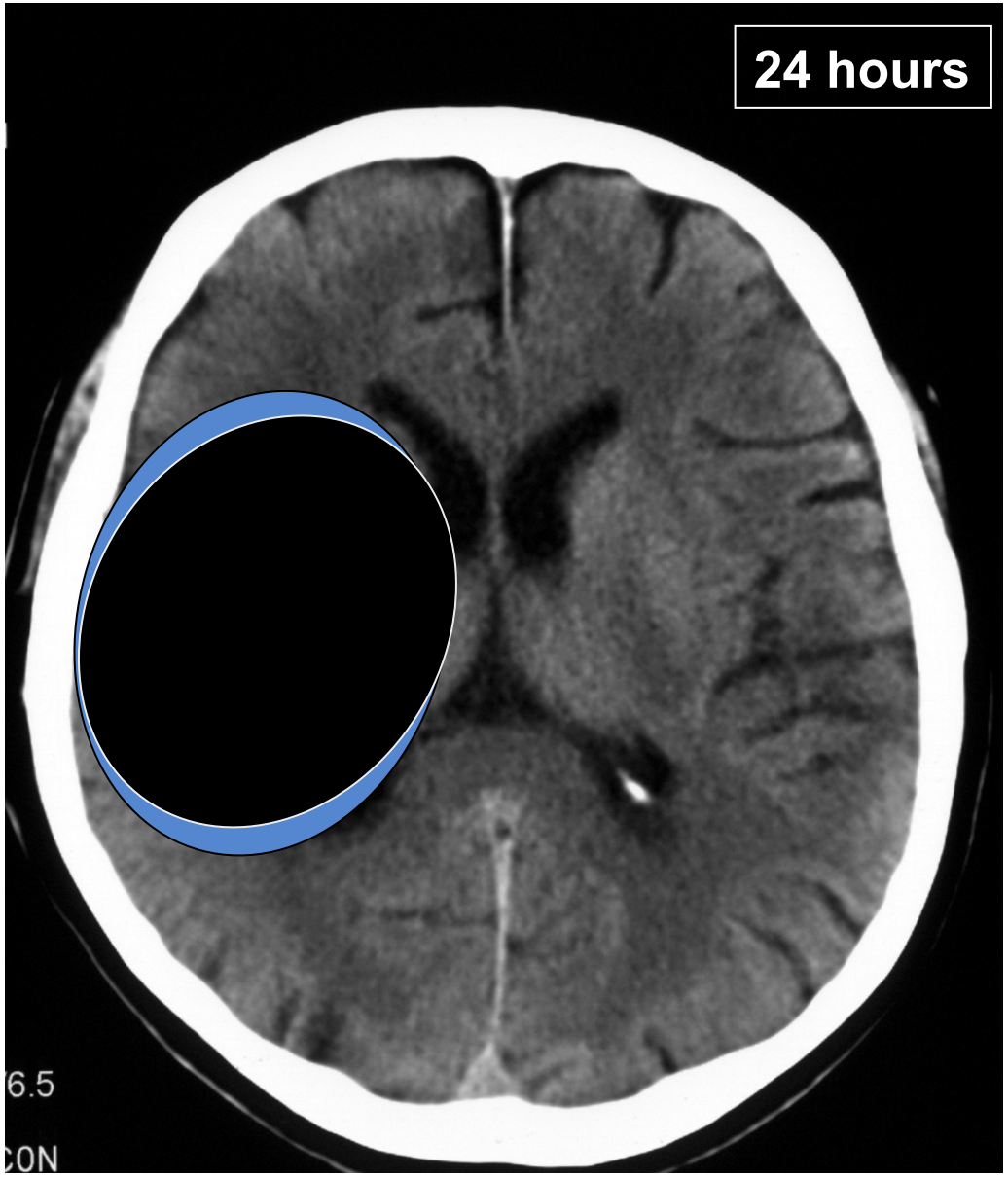


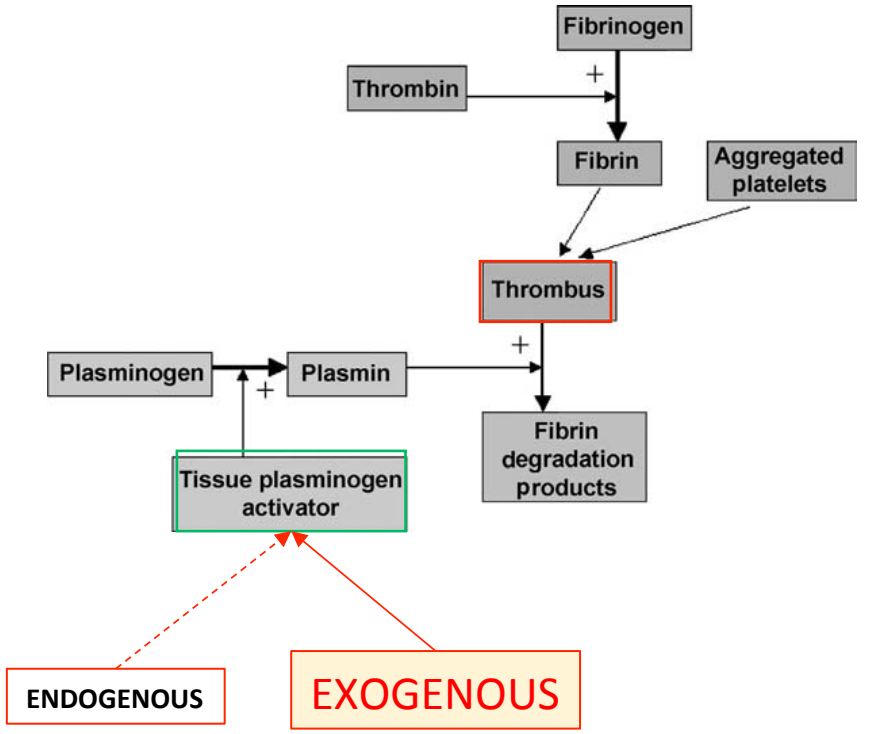
Rational for IVT

Late reperfusion, may be associated with hemorrhagic transformation of the infarction, with **worse outcomes** than those observed in the absence of reperfusion.



Rational for IVT

- THROMBUS: **plasminogen**, becomes trapped among the **fibrin** strands that constitute the bulk of the thrombus.
- **ENDOGENOUS t-PA,** cleaves plasminogen (surface of the thrombus) releasing active **PLASMIN (Plasmin begins to degrade fibrin)**
- The process continues until the thrombus is lysed.
- Such **spontaneous lysis** of the thrombus, and recanalisation of the artery, do not occur until after the ischaemic brain has become infarcted.
- **EXOGENOUS thrombolysis** aims to rapidly restore blood flow by lysing fresh thrombi before the ischaemic brain has become infarcted.
- Improvement or resolution of neurological deficits



Clinical trials

The New England
Journal of Medicine

Volume 333 DECEMBER 14, 1995 Number 24

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

NINDS (1995):

Study Question: Does **tPA** reduce morbidity and mortality in ischemic stroke?

Design: multicenter (8 US centers), double-blinded, randomized placebo-controlled

N=624 NINDS I: 291 - NINDS II: 333

Inclusion: acute ischemic strokes presenting <3 h from symptom onset

Results administration of tPA w/in 3 h from symptom onset demonstrated improved neurologic outcome at 90 days

Despite greater numbers of symptomatic ICH in the tPA group, mortality rate was not statistically significant between the groups.

ECASS I (1995), **ECASS** II (1998), **ATLANTIS A** (1999) and **ATLANTIS B** (1999): confirmed benefit within 3 hours of onset

Clinical trials

EXTENSION OF THE THERAPEUTIC WINDOW to 4.5 hours

ECASS III (2008):

Study Question: Is administration of tPA in acute stroke 3-4.5 h after symptom onset safe and effective?

Design: RCT, **n=821**

Same inclusion/exclusion as NINDS, but with additional exclusions below:

baseline NIHSS score >25, use of any oral anticoagulant, combined history of DM and prior stroke

Results:

IV tPA demonstrated improved neurologic outcome at 90 days when given within 3-4.5 h after symptom onset (**NNT= 14**).

Despite a greater incidence of intracranial hemorrhage in the tPA group (**NNH=11**), there was no significant difference in mortality between groups.

IST-3 (2012):

Largest RCT of tPA use in acute stroke to date **n= 3035**

Inclusion criteria broadened to include pts > 80 yo and a wider BP range (SBP 90-220; DBP 40-130)

Results:

Administration of IV tPA in acute stroke within 6 hours did not demonstrate improved functional neurologic outcome at 6 months.

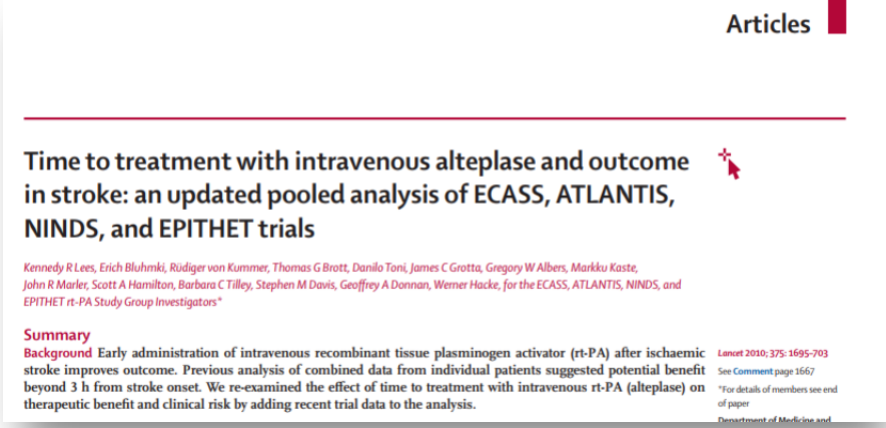
High incidence of symptomatic ICH in the tPA group.

IST-3 (2012): confirmed benefits of prior trials for up to 4.5 hours of onset; advised thrombolysis aged over 80 years old

Clinical trials

Meta-analysis (8 first clinical trials) 3670 thrombolysed patients

- benefit more important as the patients were thrombolysed early
- "Lost time is lost brain" (*time lost is brain lost*)
- The benefit gradually decreases with the extension of the delay.
  - **<90 min** x 2.5 the chances of 1 excellent result.
  - **1h 30 min-3 h**, increases 1.6 x the chances of 1 excellent result.
  - **3 h and 4h 30 min** Results were slightly lower between.
  - **4 h 30 min-6h** Not statistically significant between.
- Treatment delayed by 10 min: lost benefit for 1% of treated patients
  - **Mortality Reduced by 22%** if treatment <90 min.
  - **Mortality increases by 13%** between 1h 30 min-3 hours
  - **Mortality increases by 22%** between 3 h and 4 h 30 min NS.
  - mortality significantly increased by 49%> 4 h 30 min (risk exceeds benefice).



Articles

Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials

Kennedy R Lees, Erich Bluhmki, Rüdiger von Kummer, Thomas G Brott, Danilo Toni, James C Grotta, Gregory W Albers, Markku Kaste, John R Marler, Scott A Hamilton, Barbara C Tilley, Stephen M Davis, Geoffrey A Donnan, Werner Hacke, for the ECASS, ATLANTIS, NINDS, and EPITHET rt-PA Study Group Investigators*

Summary

Background Early administration of intravenous recombinant tissue plasminogen activator (rt-PA) after ischaemic stroke improves outcome. Previous analysis of combined data from individual patients suggested potential benefit beyond 3 h from stroke onset. We re-examined the effect of time to treatment with intravenous rt-PA (alteplase) on therapeutic benefit and clinical risk by adding recent trial data to the analysis.

Lancet 2010; 375: 1695-703
See Comment page 1667

*For details of members see end of paper
Department of Medicine and

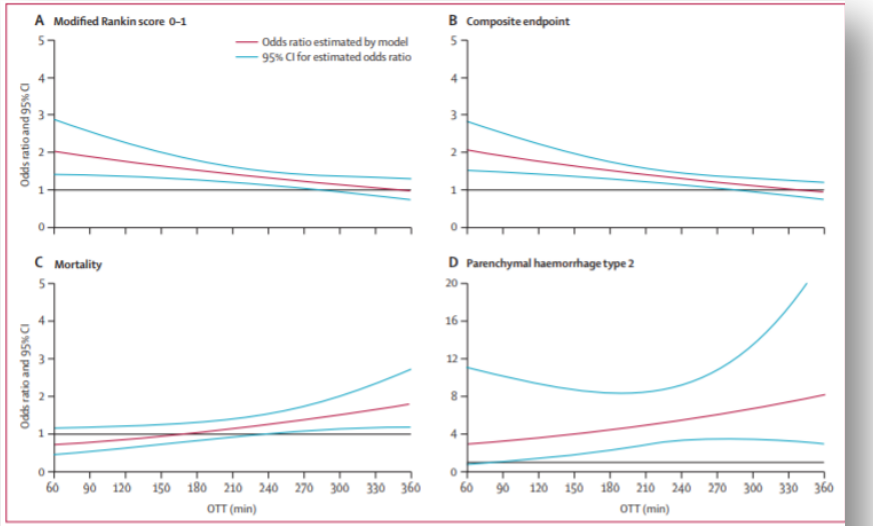
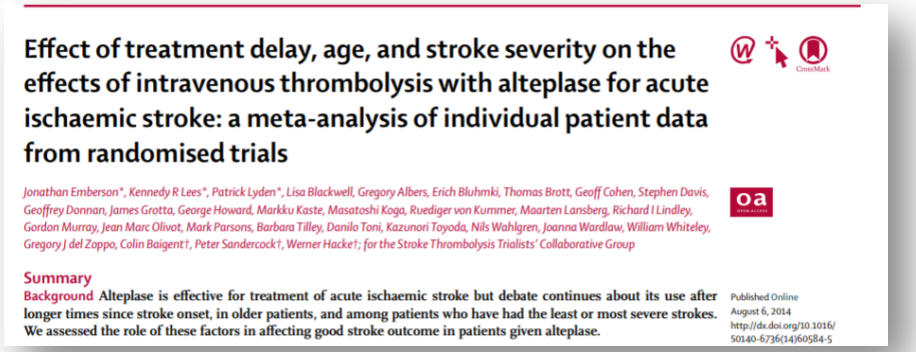


Figure 1: Relation of onset to treatment delay with treatment effect
Relation of stroke onset to start of treatment (OTT) with treatment effect after adjustment for prognostic variables assessed by (A) day 90 modified Rankin score 0-1 versus 2-6 (interaction p=0·0269, n=3530 [excluding EPITHET data p=0·0116, n=3431]); (B) global test that incorporates modified Rankin score 0-1 versus 2-6, Barthel

Clinical trials

Meta-analysis in 2014, ***Emberson J Lancet. 2014***



Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials

Jonathan Emberson*, Kennedy R Lees*, Patrick Lyden*, Lisa Blackwell, Gregory Albers, Erich Bluhmki, Thomas Brott, Geoff Cohen, Stephen Davis, Geoffrey Donnan, James Grotta, George Howard, Markku Kaste, Masatoshi Koga, Ruediger von Kummer, Maarten Lansberg, Richard I Lindley, Gordon Murray, Jean Marc Olivot, Mark Parsons, Barbara Tilley, Danilo Toni, Kazunori Toyoda, Nils Wahlgren, Joanna Wardlaw, William Whiteley, Gregory J del Zoppo, Colin Baigent†, Peter Sandercock†, Werner Hacke†; for the Stroke Thrombolysis Trialists' Collaborative Group

Summary

Background Alteplase is effective for treatment of acute ischaemic stroke but debate continues about its use after longer times since stroke onset, in older patients, and among patients who have had the least or most severe strokes. We assessed the role of these factors in affecting good stroke outcome in patients given alteplase.

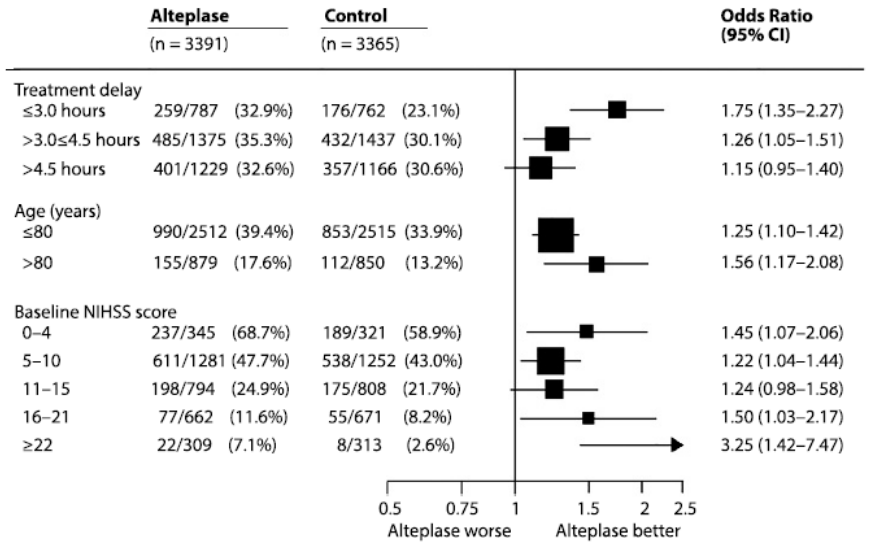
Published Online August 6, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60584-5

6756 patients (RCTs) Benefit of the rtPA according to the delay, of advanced age the initial severity of the stroke.

Regardless of age, initial severity *and despite an increased risk of fatal intracranial hemorrhage,*

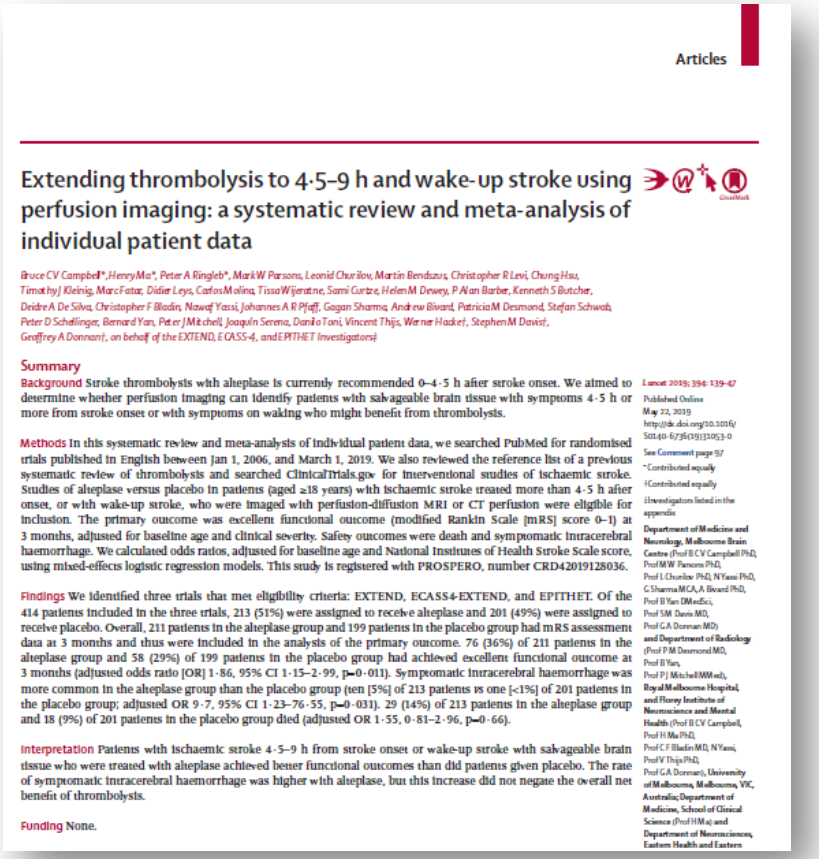
rtPA improves overall odds of a good outcome when administered within 4.5 hours

Earlier treatment is associated with better results



2019 Metaanalysis of 3 trials: EXTEND, ECASS4-EXTEND, and EPITHET.

- Patients with IS **4.5–9 h** after stroke onset or with **wake-up** stroke with **evidence of salvageable brain tissue** using **CTP** or **perfusion-diffusion MRI** who were given IV alteplase have improved functional outcomes/ placebo.
- Increased risk of symptomatic ICH, but not offset the net benefit of thrombolysis.
- The benefit to risk ratio seems to be larger in patients who meet ***automated perfusion mismatch criteria.***



Articles

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 CV 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, Joaquin Serena, Danilo Toni, Vincent Thijs, Werner Hacke†, Stephen M Davis†, Geoffrey A Donnan†, on behalf of the EXTEND, ECASS-4, and EPITHET Investigators‡

Summary

Background Stroke thrombolysis with alteplase is currently recommended 0–4·5 h after stroke onset. We aimed to determine whether perfusion imaging can identify patients with salvageable brain tissue with symptoms 4·5 h or more from stroke onset or with symptoms on waking who might benefit from thrombolysis.

Methods In this systematic review and meta-analysis of individual patient data, we searched PubMed for randomised trials published in English between Jan 1, 2006, and March 1, 2019. We also reviewed the reference list of a previous systematic review of thrombolysis and searched ClinicalTrials.gov for interventional studies of ischaemic stroke. Studies of alteplase versus placebo in patients (aged ≥18 years) with ischaemic stroke treated more than 4·5 h after onset, or with wake-up stroke, who were imaged with perfusion-diffusion MRI or CT perfusion were eligible for inclusion. The primary outcome was excellent functional outcome (modified Rankin Scale [mRS] score 0–1) at 3 months, adjusted for baseline age and clinical severity. Safety outcomes were death and symptomatic intracerebral haemorrhage. We calculated odds ratios, adjusted for baseline age and National Institutes of Health Stroke Scale score, using mixed-effects logistic regression models. This study is registered with PROSPERO, number CRD42019128036.

Findings We identified three trials that met eligibility criteria: EXTEND, ECASS4-EXTEND, and EPITHET. Of the 414 patients included in the three trials, 213 (51%) were assigned to receive alteplase and 201 (49%) were assigned to receive placebo. Overall, 211 patients in the alteplase group and 199 patients in the placebo group had mRS assessment data at 3 months and thus were included in the analysis of the primary outcome. 76 (36%) of 211 patients in the alteplase group and 58 (29%) of 199 patients in the placebo group had achieved excellent functional outcome at 3 months (adjusted odds ratio [OR] 1·86, 95% CI 1·15–2·99, p=0·011). Symptomatic intracerebral haemorrhage was more common in the alteplase group than the placebo group (ten [5%] of 213 patients vs one [<1%] of 201 patients in the placebo group; adjusted OR 9·7, 95% CI 1·23–76·55, p=0·031). 29 (14%) of 213 patients in the alteplase group and 18 (9%) of 201 patients in the placebo group died (adjusted OR 1·55, 0·81–2·96, p=0·66).

Interpretation Patients with ischaemic stroke 4·5–9 h from stroke onset or wake-up stroke with salvageable brain tissue who were treated with alteplase achieved better functional outcomes than did patients given placebo. The rate of symptomatic intracerebral haemorrhage was higher with alteplase, but this increase did not negate the overall net benefit of thrombolysis.

Funding None.

Lancet 2019; 394: 139–47

Published Online May 22, 2019 http://dx.doi.org/10.1016/S0140-6736(19)31053-0

See Comment page 97

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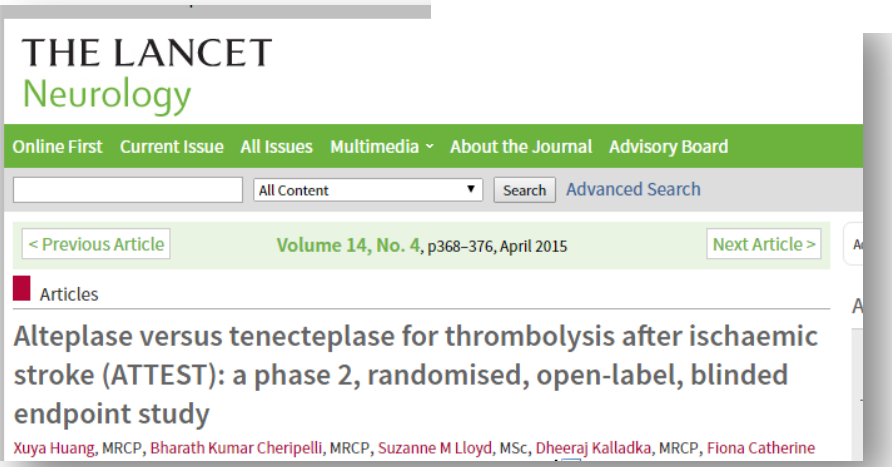
Fibrinolytic drugs: ALTEPLASE

- **Alteplase (**activateur tissulaire du plasminogène – tPA)
- 50 mg - 20 mg - 10mg
- **Dose 0,9mg /kg (max 90 mg)**
  - 10% as a bolus in 1 minute
  - 90% as a continuous infusion over 60 min

Fibrinolytic drugs: TENECTEPLASE



ATTEST study *Huang Lancet 2015*

- *Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (104:52/52)*
- tenecteplase 0·25 mg/kg VERSUS alteplase 0·9 mg/kg.
- No difference

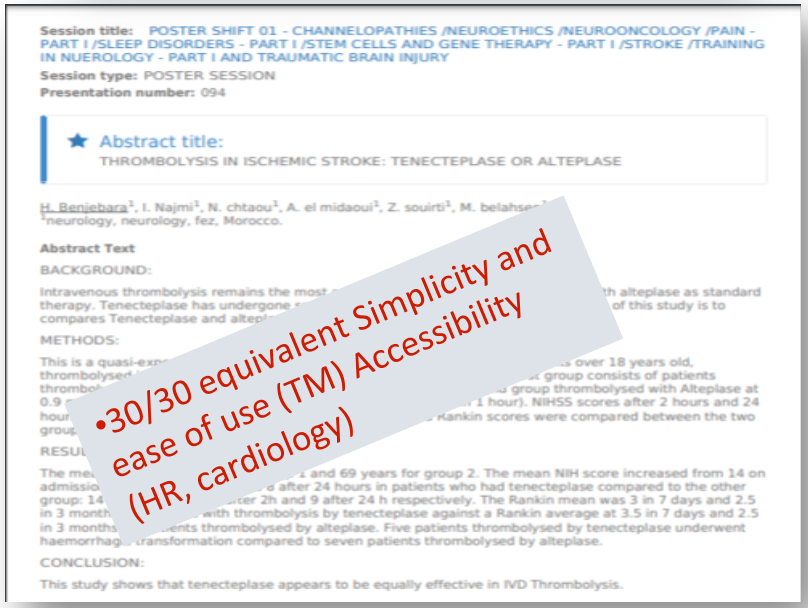
NORTEST study Logallo *Lancet 2015*

tenecteplase 0·4 mg/kg versus alteplase 0·9 mg/kg

1100 patients

tenecteplase (n=549) alteplase (n=551)

Rankin 0-1 64% versus 63% Similar safety efficiency profile



Patients selection

Inclusion criteria

1) Age 18 or older
2) Clinical diagnosis of acute ischemic stroke with measurable neurologic deficit
3) Time of onset is <180 min of when treatment can begin,
4) The Clinical Center administering the specific treatment site has adequate balance of patients between strata (enrollment into 90-180 min stratum was permitted only if the number of patients in 90-180 min. stratum is not more than 2 greater than in the 0-90 stratum).

Exclusion criteria

1) Only minor stroke or symptoms rapidly improving at time of infusion start
2) Evidence of hemorrhage on CT scan
   No other formal CT scan exclusion criteria.
3) Clinical presentation suggesting subarachnoid hemorrhage
4) Female & lactating or pregnant
5) Platelet count < 100,000, PT > 15, Heparin within 48 hrs & PTT > normal, or
   Patient on oral anticoagulants.
6) Major surgery or body trauma within 14 d prior; serious head trauma within 3 mo
7) Hx of GI or UT hemorrhage in prior 21 d.
8) Noncompressible arterial puncture within 7d; LP within 7 d
9) Systolic BP > 185 or diastolic > 110
10) Hx of stroke in prior 3 mo, prior ICH suggesting risk factor.
11) Serious medical illness that would interfere with trial
12) Glucose <50 or > 400
13) Clinical presentation consistent with MI or postMI pericarditis
14) Seizure at onset of stroke

were no formal CT scan-based exclusion criteria other than the finding of hemorrhage.

Minor stroke : Case 1

Mr L.F, 52 years old, journalist

history: Chronic smoking

18/05/2018 at 10.00 pm **right hemiplegia with facial asymmetry**.

Arrived to the emergency room at 11:50pm (OTD: 1h50min)

Improvement during the transport

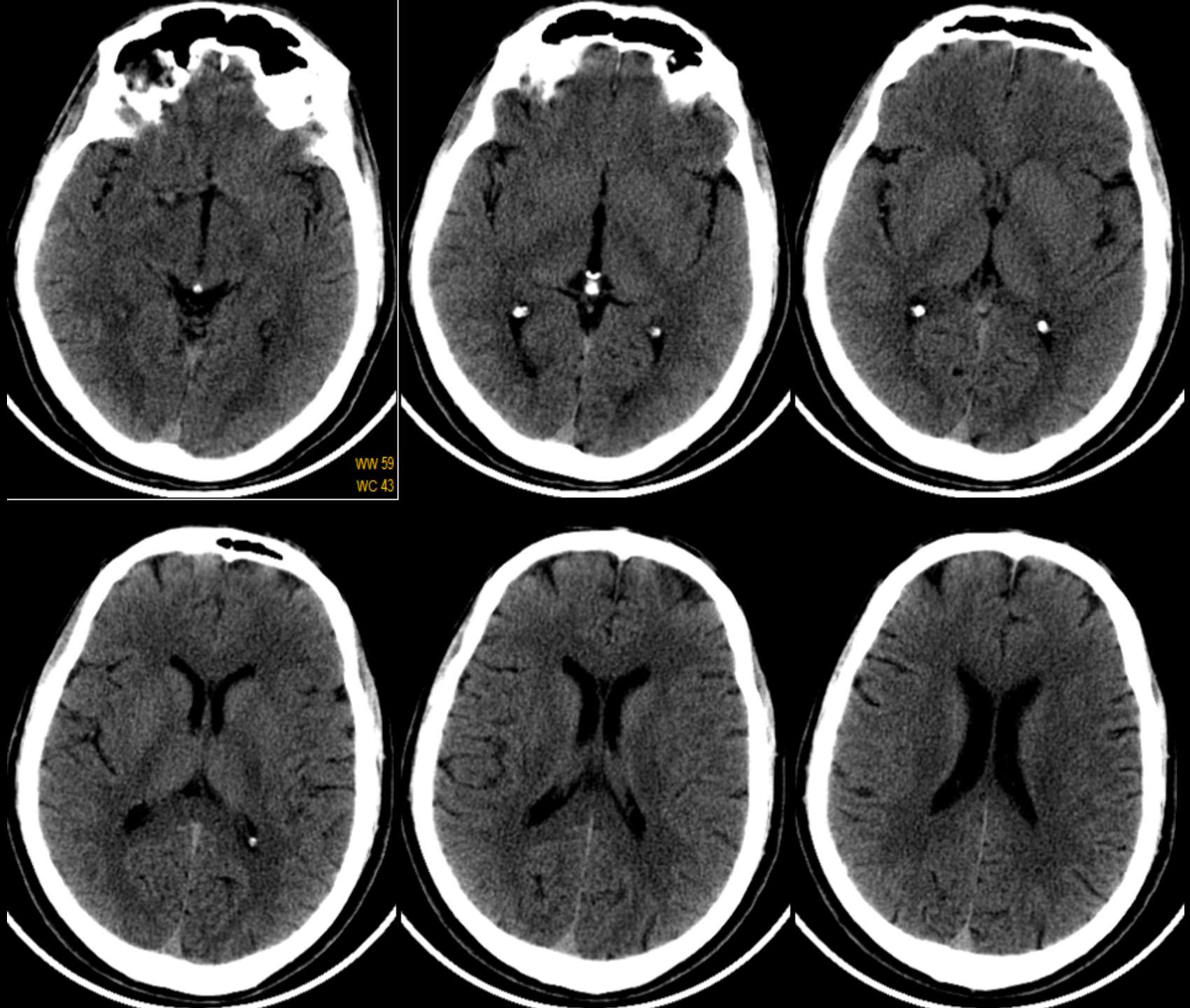
BP = 130/90 - capillar glycemia = 1.06 g/l - T = 36.8 °

Right hemiparesis + moderate facial paralysis

NIHSS = 3 (F1, RLL1, RUL1)

- **RIMS:** rapidly improving and/or mild symptoms

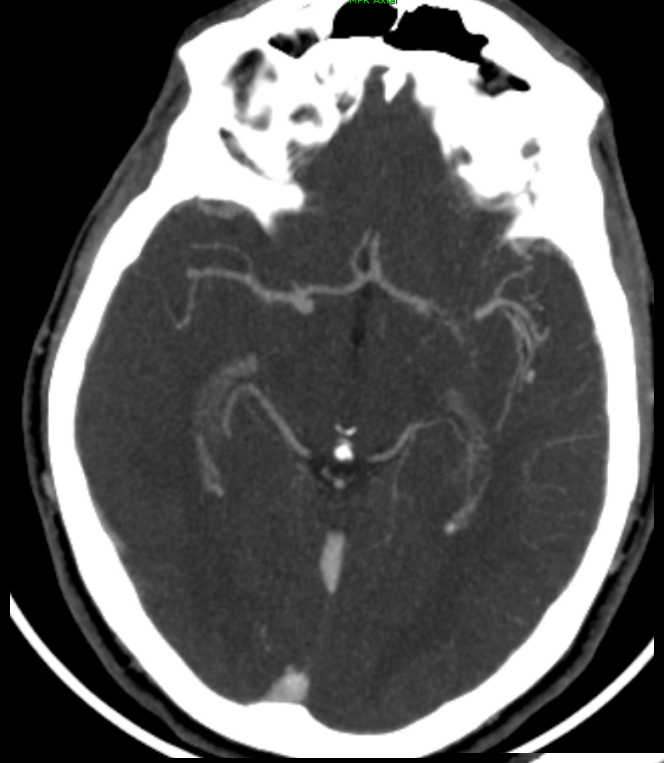
  The rapid improvement in symptoms was defined as an NIHSS score <4 which, by a previous examination, showed a more severe deficit.
- **END:** *early neurological deterioration*
- **ENDIE**: ***early neurologic deterioration with infarct expansion***

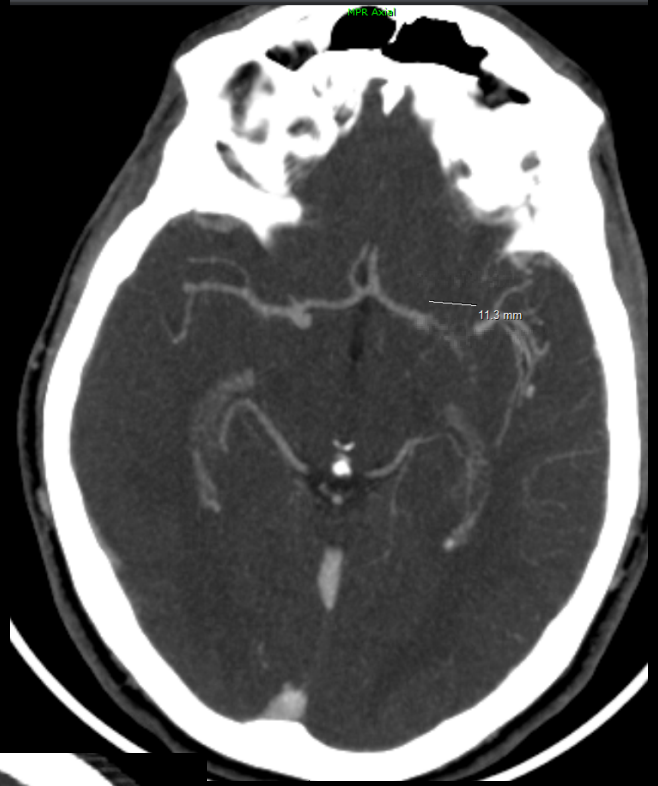

WW 59
WC 43

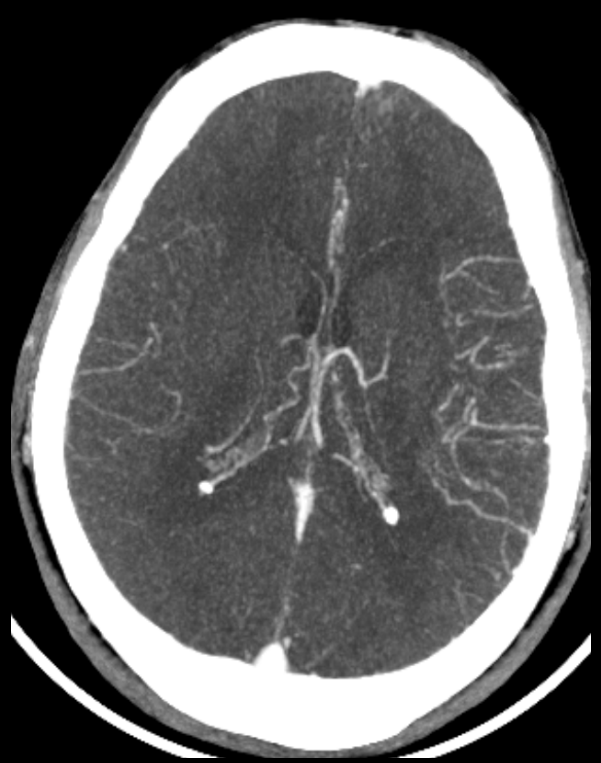
Minor stroke : Case 1

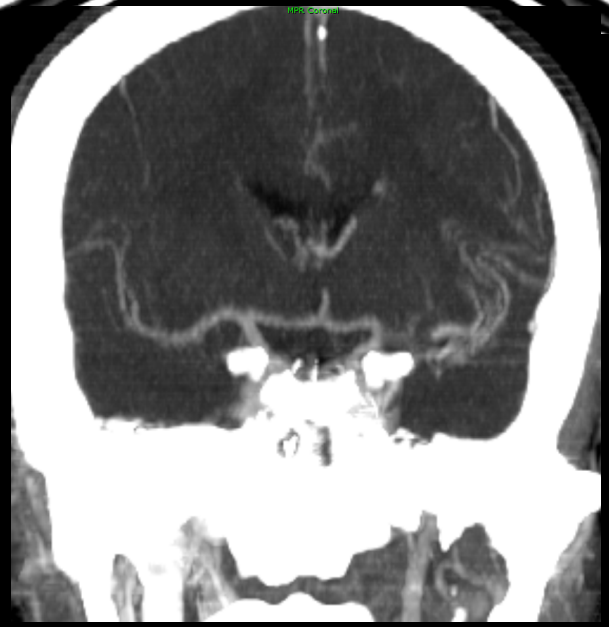
- **NIHSS = 3** (F1, RLL1, RUL1)
- ASPECTS at 10
- EKG: normal
- Biology: normal
- Delay:2h

?









- Occlusion of the M1 segment
- thrombus 11.3mm extended left ACM
- Collaterality +
- **RIMS:** rapidly improving and/or mild symptoms
- WITH
- ***LARGE VESSEL OCCLUSION***

Minor stroke : Case 1

- **Decision:**

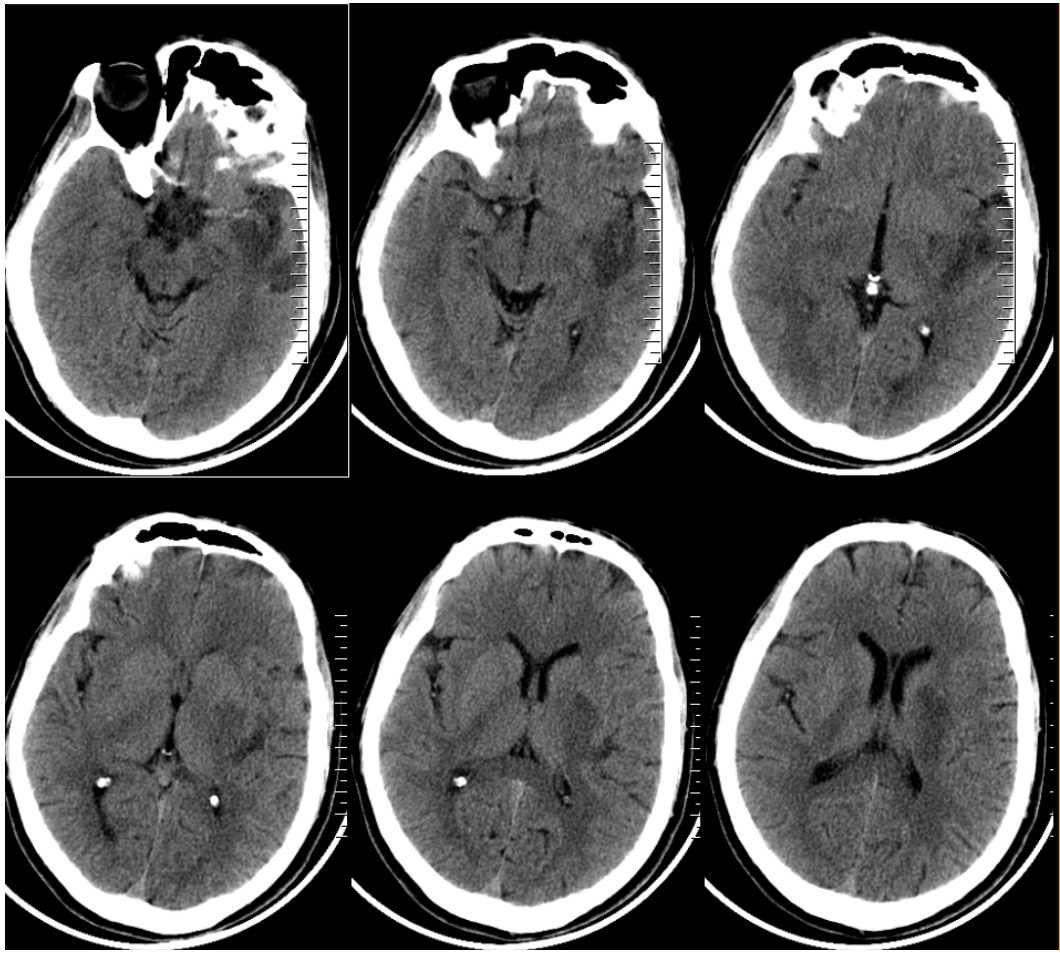
Thrombolysis by **TNK 0,25 mg/kg**

(4000UI) at 00h10 after **2h10 du délai**

- **Evolution:**

Improvement (***no « early neurological deterioration: END »***)

NIHSS at **1 after 24 h** (F1).



2006

CME

Early MRI and outcomes of untreated patients with mild or improving ischemic stroke

V. Rajajee, MD; C. Kidwell, MD; S. Starkman, MD; B. Ovbiagele, MD; J.R. Alger, PhD; P. Villablanca, MD; F. Vinuela, MD; G. Duckwiler, MD; R. Jahan, MD; A. Fredieu, MD; S. Suzuki, MD; and J.L. Saver, MD

Abstract—*Objective:* To determine the frequency of early neurologic deterioration with infarct expansion (ENDIE) and poor outcomes among ischemic stroke patients not treated with reperfusion therapies because of rapidly improving or mild symptoms (RIMS) and to study the predictive value of hyperacute MRI in these patients. *Methods:* We identified consecutive patients with symptoms of acute stroke undergoing multimodal MRI within 6 hours of onset without evidence of hemorrhage on imaging. Medical records were reviewed for evidence of early neurologic deterioration within 48 hours. All deteriorating patients had repeat MRI to ascertain causes of worsening. Poor outcome was defined as a discharge modified Rankin Scale (mRS) score of ≥3. *Results:* We identified 74 patients with stroke symptoms ≤6 hours from onset. Forty had RIMS, and 39 did not receive reperfusion therapies because of RIMS. Among these 39, 4 experienced ENDIE, and 8 were discharged with mRS score of ≥3. Eight of the 39 patients had large-vessel occlusions on MR angiography. Three of 8 patients with large-vessel occlusion as against only one of 31 patients without occlusion had ENDIE (odds ratio [OR] 18, 95% CI 1.6 to 209, $p = 0.02$). Four of 8 patients with large-vessel occlusion as against 4 of 31 patients without occlusion had a discharge mRS score of ≥3 (OR 7, 95% CI 1.2 to 38, $p = 0.04$). *Conclusions:* About 10% of patients eligible for acute reperfusion therapy excluded on the basis of mild or rapidly improving symptoms show early neurologic deterioration with infarct expansion within 48 hours, and about 20% show poor outcome at discharge. Persisting large-vessel occlusion substantially increases the risk of early worsening and poor functional outcome.

NEUROLOGY 2006;67:980–984

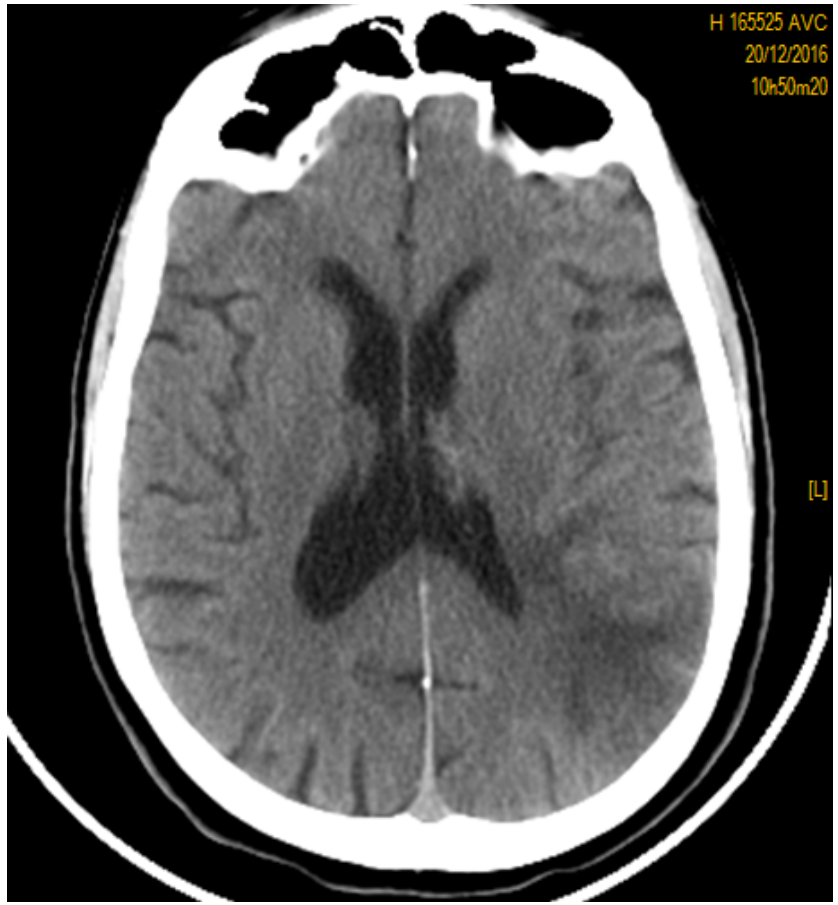
39 RIMS (no reperfusion)

4/39 ENDIE (10%)

8/39 mRS≥3

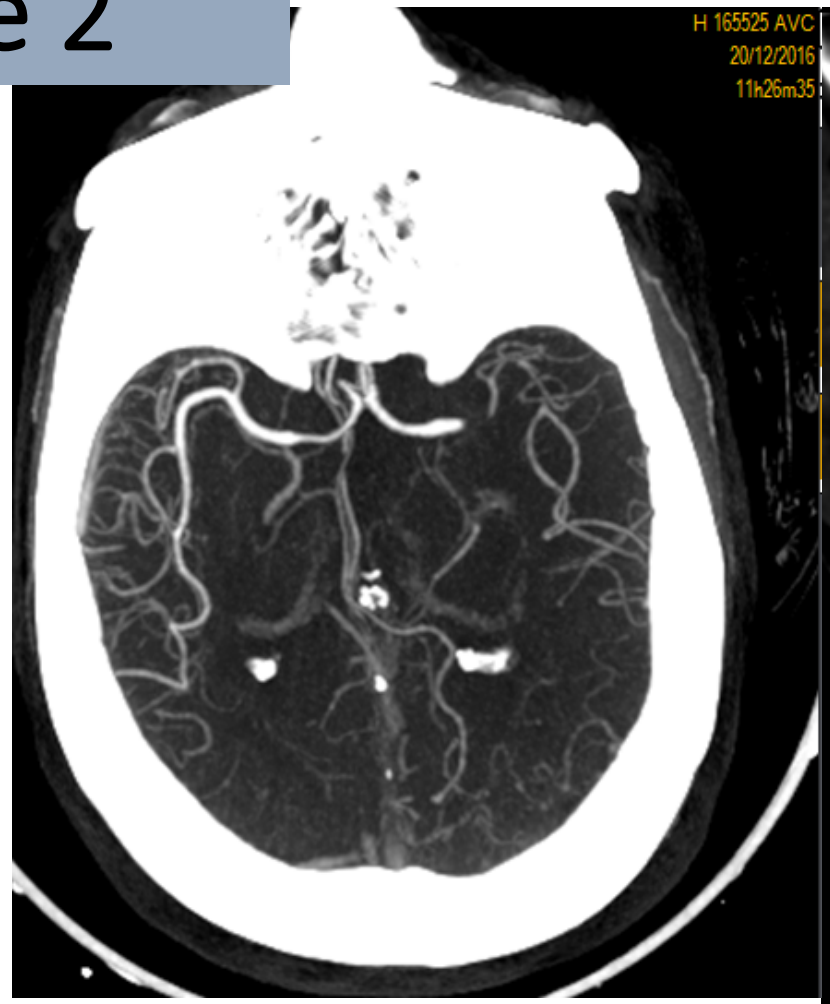
Recent stroke : Case 2

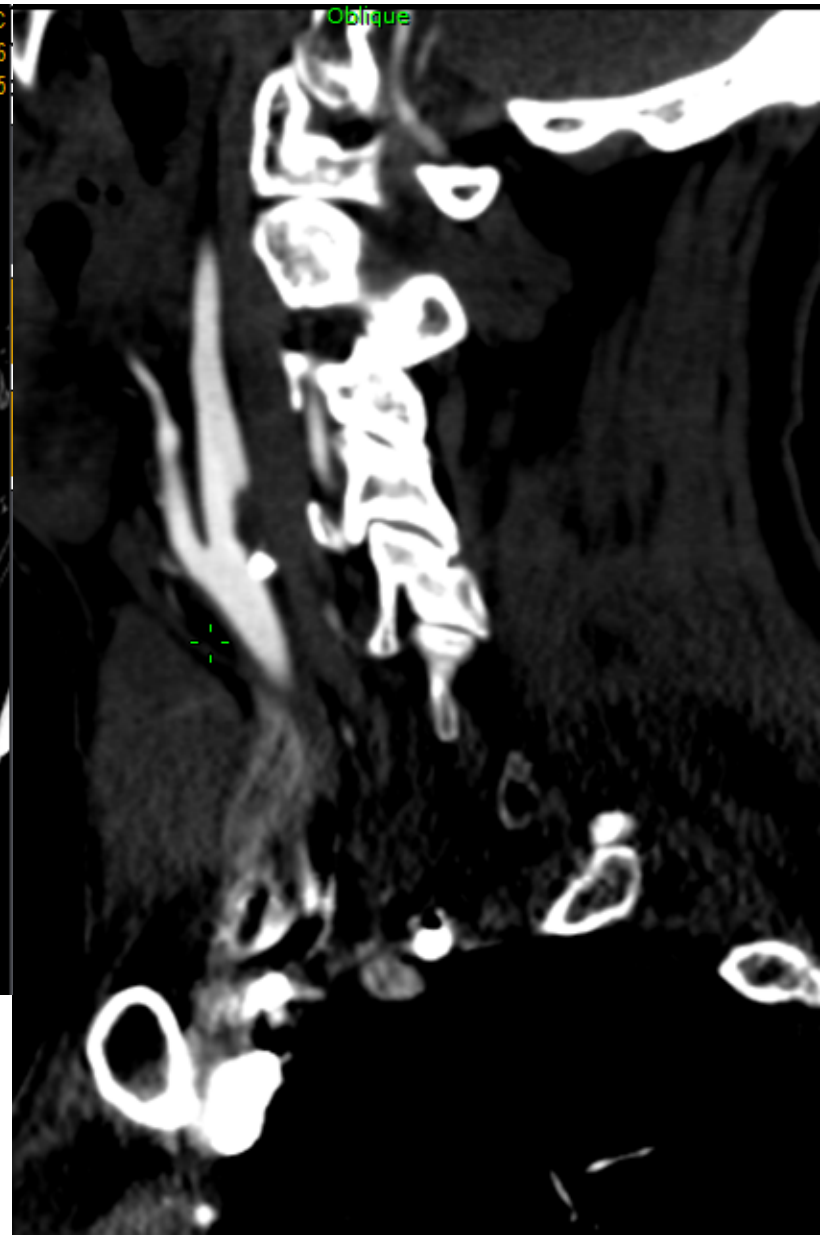
- 63 year old man
- Right Hemiplegia
- NIHSS at 15
- OTD 2h30min
- **Left MCA stroke** 7 days ago (Aphasia)

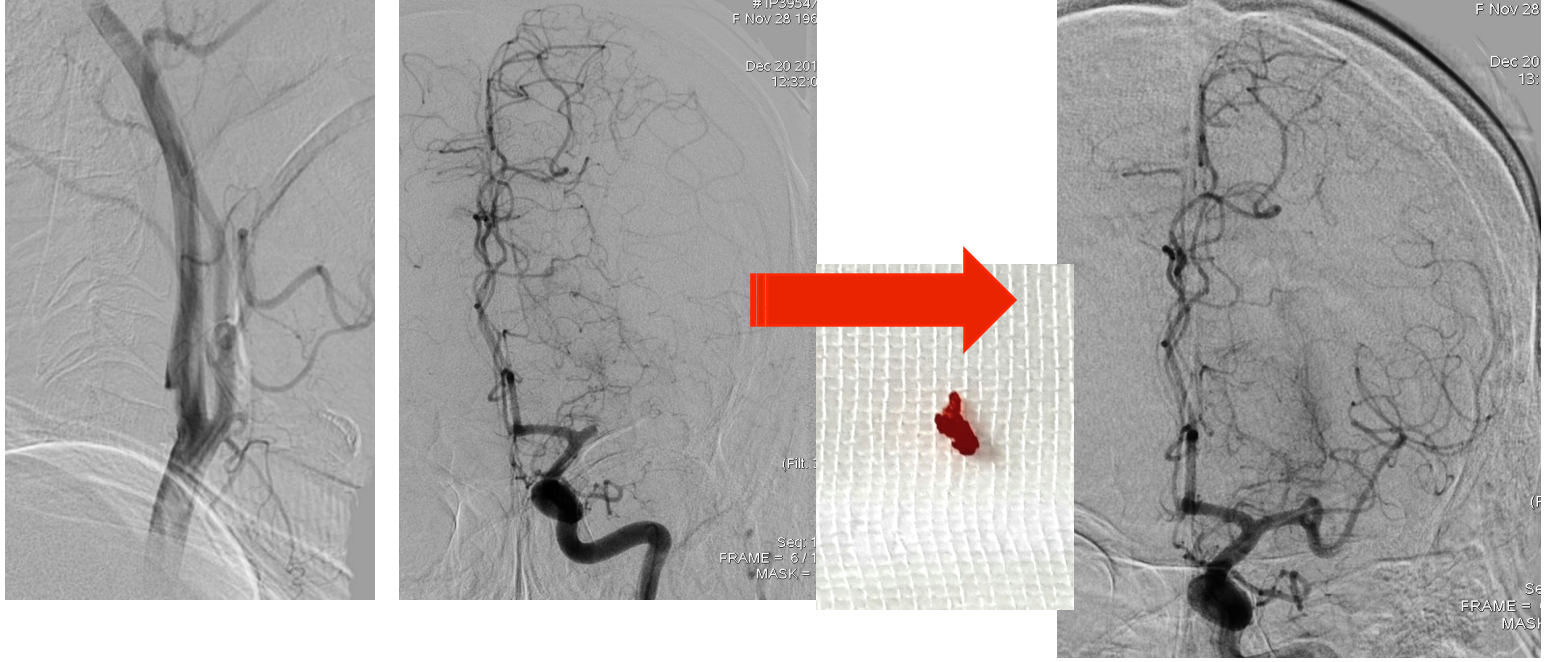


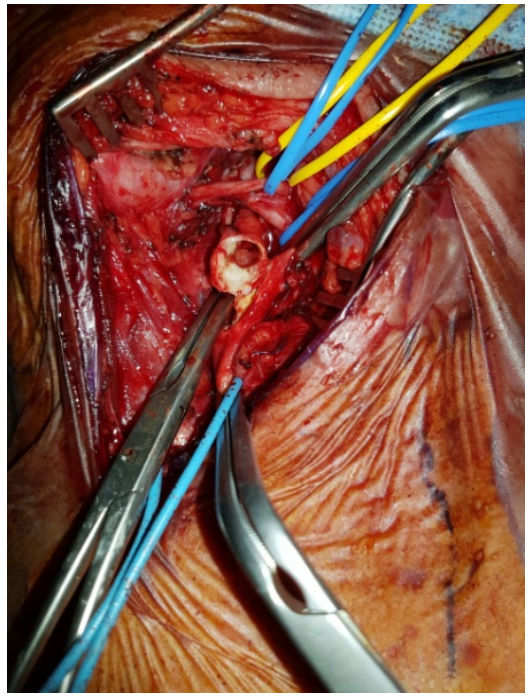
Recent stroke : Case 2

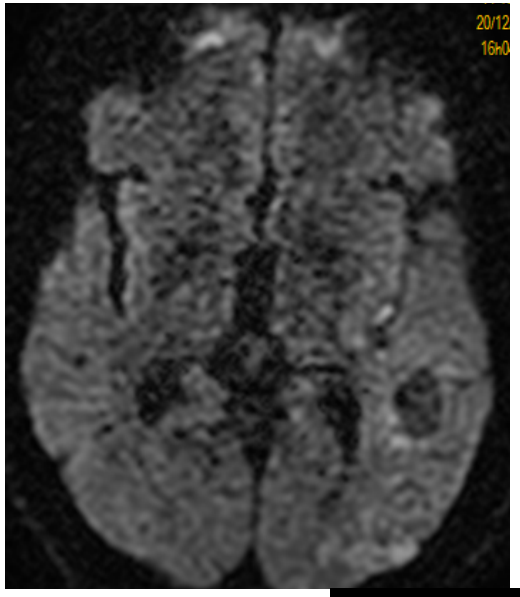
- 63 year old man
- Right Hemiplegia
- NIHSS at 15
- OTD 2h30min
- **Left MCA stroke** 7 days ago (Aphasia)
- **NO IVT**

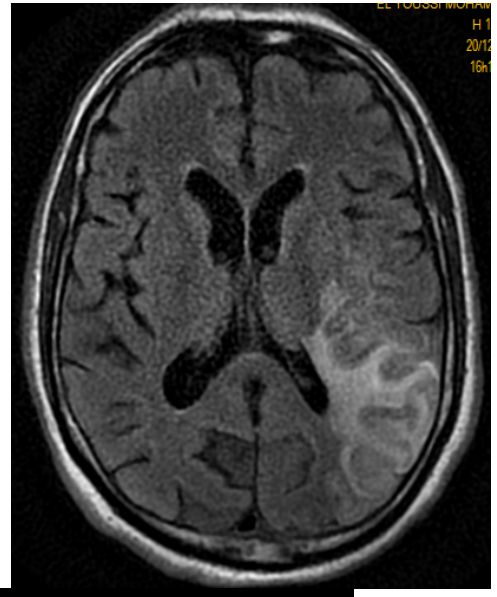


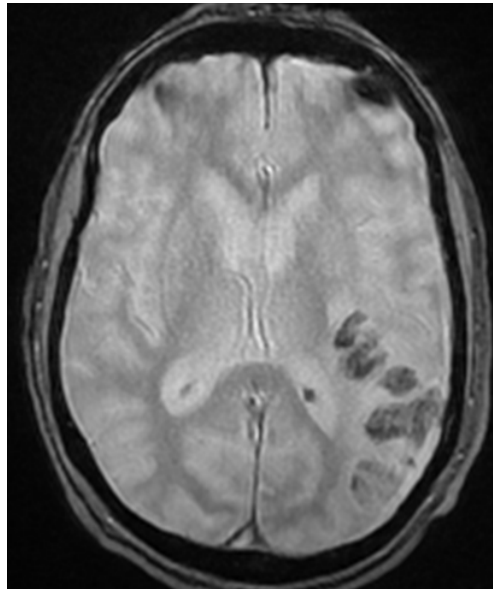












MRI 5 hours after MT

Endarteriectomy 48 hours laters
NIHSS at 4 (aphasia + hemianopia)
mRS 3 mois: 0

D7

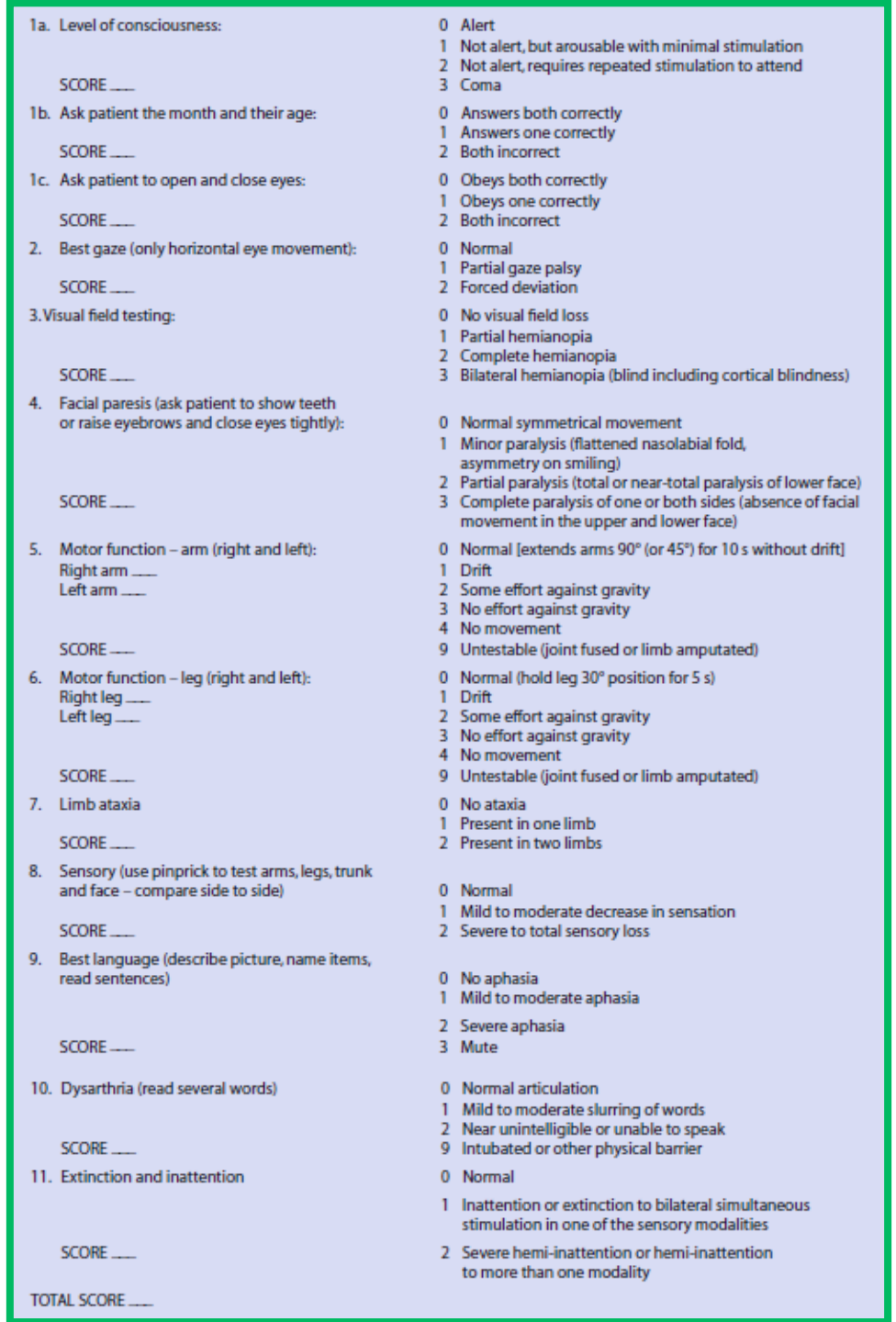
American Heart Association Guideline 2013[1]	American Heart Association Scientific Statement 2015[12]	US Food and Drug Administration (FDA) Package Insert 2015[13]
Indications		
Diagnosis of ischemic stroke with measurable neurologic deficit	Same	Same
Symptom onset[a] within 4.5 hours	Same	Within 3 hours
Age ≥18 years	Same	Warning for age >77 years with risk factors for intracranial hemorrhage
Contraindications		
Severe head trauma within 3 months	Same	Contraindicated
Ischemic stroke within 3 months	Risk increased, but degree is unclear	Removed[b]
Arterial puncture at noncompressible site within 7 days	Risk uncertain	Not listed
Previous intracranial hemorrhage	Same	Warning for recent intracranial hemorrhage (contraindicated if active intracranial hemorrhage)
Suspected subarachnoid hemorrhage	Same	Contraindicated
Intracranial neoplasm, arteriovenous malformation (AVM), or aneurysm	Probably recommended if extraaxial neoplasm is present; not recommended if intraaxial neoplasm is present; risk unclear for AVM; probably recommended if unruptured unsecured aneurysm <10 mm is present, but risk unclear if greater size	Contraindicated
Recent intracranial or intraspinal surgery (within 3 months)	Same	Contraindicated
Active internal bleeding	Same	Contraindicated
Systolic blood pressure (BP) >185 mm Hg or diastolic BP >110 mm Hg	Same, but treatment recommended if BP can be lowered safely	Contraindicated for severe uncontrolled hypertension (BP values removed[b]); warning for BP >175/110 mm Hg
Bleeding diathesis International normalized ratio (INR) >1.7 Heparin within 48 hours with abnormal activated partial thromboplastin time Platelets <100,000/mm^3 Current use of direct thrombin inhibitor or factor Xa inhibitor with abnormal coagulation tests[c]	Consider case by case in patients with history of bleeding diathesis; not recommended if INR >1.7, low-molecular-weight heparinoid within 24 hours, direct thrombin inhibitor or factor Xa inhibitor within 48 hours (unless coagulation tests[c] are normal)	Contraindicated for bleeding diathesis (laboratory values removed[b])

Continued on page 67

American Heart Association Guideline 2013[1]	American Heart Association Scientific Statement 2015[12]	US Food and Drug Administration (FDA) Package Insert 2015[13]
Contraindications (continued)		
Blood glucose <50 mg/dL	Consider recombinant tissue plasminogen activator (rtPA) if deficits still present after glucose normalization	Removed[b]
CT showing hypodensity >1/3 of the cerebral hemisphere	Same	Removed[b]
Relative contraindications		
Minor stroke (typically National Institutes of Health Stroke Scale [NIHSS] score <5)	rtPA should be administered to patients with mild but disabling symptoms within 3 hours of onset; possible risk and benefit should be weighed in patients with nondisabling symptoms	Removed[b]
Rapidly improving symptoms	rtPA should be administered if symptoms are still disabling	Not listed
Pregnancy	rtPA may be considered in moderate to severe stroke when anticipated benefit outweighs the anticipated risk of uterine bleeding	Warning (Category C)
Seizure at onset with postictal residual deficits	rtPA administration is reasonable if residual deficits are thought to be caused by a stroke	Removed[b]
Major extracranial trauma within 14 days	rtPA can be considered	Warning for recent trauma
Major surgery within 14 days	rtPA can be considered in carefully selected cases	Warning for recent surgery
Gastrointestinal or genitourinary surgery within 21 days	Consider rtPA if no structural bleeding lesions	Warning
Acute myocardial infarction within 3 months	Administer rtPA (stroke dose) if concurrent stroke and acute myocardial infarction (MI); it is also reasonable to give rtPA after recent MI unless it was a STEMI involving the left anterior myocardium	Not listed
Additional contraindications for 3- to 4.5-hour window		
Age >80 years	rtPA recommended	FDA has not approved rtPA for use after 3 hours
Warfarin use (regardless of INR)	rtPA probably recommended if INR <1.7	
NIHSS >25	Risk and benefit uncertain	
Previous stroke or diabetes mellitus	rtPA probably recommended	

INITIAL EVALUATION

- Initial evaluation in the ER should focus on establishing **whether the patient is eligible for reperfusion therapy**.
- Necessary information:
  - **Time** the patient was last known to be well
  - Medical **conditions** or recent surgery that could CI IVT
  - Neurologic examination to calculate the **NIHSS score**
  - A capillary **glucose level**
  - **Blood pressure**
  - **Brain imaging** (CT scan with or without a CT angiogram)



1a.	Level of consciousness:	0 Alert 1 Not alert, but arousable with minimal stimulation 2 Not alert, requires repeated stimulation to attend 3 Coma
	SCORE ____	
1b.	Ask patient the month and their age:	0 Answers both correctly 1 Answers one correctly 2 Both incorrect
	SCORE ____	
1c.	Ask patient to open and close eyes:	0 Obeys both correctly 1 Obeys one correctly 2 Both incorrect
	SCORE ____	
2.	Best gaze (only horizontal eye movement):	0 Normal 1 Partial gaze palsy 2 Forced deviation
	SCORE ____	
3.	Visual field testing:	0 No visual field loss 1 Partial hemianopia 2 Complete hemianopia 3 Bilateral hemianopia (blind including cortical blindness)
	SCORE ____	
4.	Facial paresis (ask patient to show teeth or raise eyebrows and close eyes tightly):	0 Normal symmetrical movement 1 Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 Partial paralysis (total or near-total paralysis of lower face) 3 Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)
	SCORE ____	
5.	Motor function – arm (right and left): Right arm ____ Left arm ____	0 Normal [extends arms 90° (or 45°) for 10 s without drift] 1 Drift 2 Some effort against gravity 3 No effort against gravity 4 No movement 9 Untestable (joint fused or limb amputated)
	SCORE ____	
6.	Motor function – leg (right and left): Right leg ____ Left leg ____	0 Normal (hold leg 30° position for 5 s) 1 Drift 2 Some effort against gravity 3 No effort against gravity 4 No movement 9 Untestable (joint fused or limb amputated)
	SCORE ____	
7.	Limb ataxia	0 No ataxia 1 Present in one limb 2 Present in two limbs
	SCORE ____	
8.	Sensory (use pinprick to test arms, legs, trunk and face – compare side to side)	0 Normal 1 Mild to moderate decrease in sensation 2 Severe to total sensory loss
	SCORE ____	
9.	Best language (describe picture, name items, read sentences)	0 No aphasia 1 Mild to moderate aphasia 2 Severe aphasia 3 Mute
	SCORE ____	
10.	Dysarthria (read several words)	0 Normal articulation 1 Mild to moderate slurring of words 2 Near unintelligible or unable to speak 9 Intubated or other physical barrier
	SCORE ____	
11.	Extinction and inattention	0 Normal 1 Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities 2 Severe hemi-inattention or hemi-inattention to more than one modality
	SCORE ____	
	TOTAL SCORE ____	

Modified Rankin Score (mRS: 3 months)

0 - No symptoms at all

1 - No significant disability despite symptoms: able to carry out all usual duties and activities

2 - Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance

3 - Moderate disability: requiring some help, but able to walk without assistance

4 - Moderate to severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance

5 - Severe disability: bedridden, incontinent, and requiring constant nursing care and attention

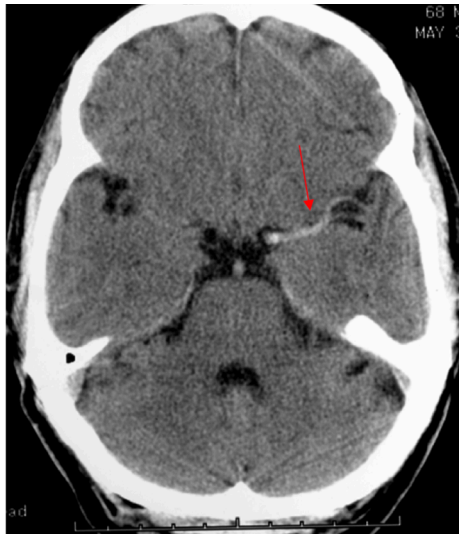
6 - Death

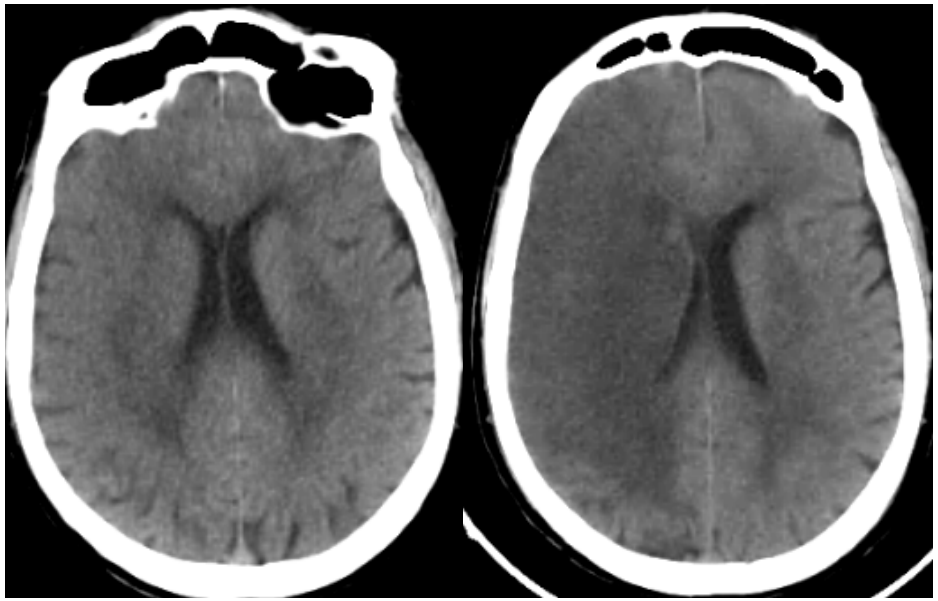
EVALUATION: IMAGING

Non Contrast CT

- Normal (negative NCCT)
- Showing **early ischemic changes**, which can be detected in the majority of patients with careful attention

  - ***Hypoattenuation***
  - ***Hypodensity***

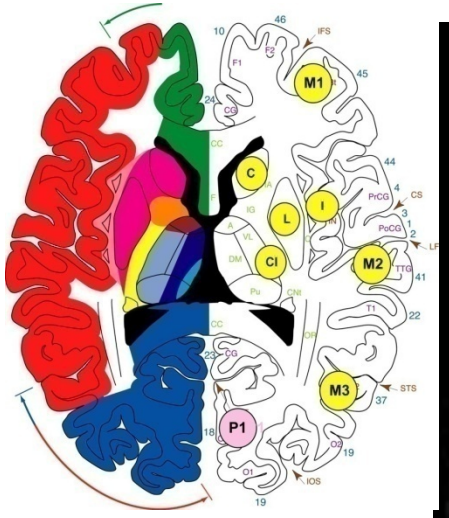


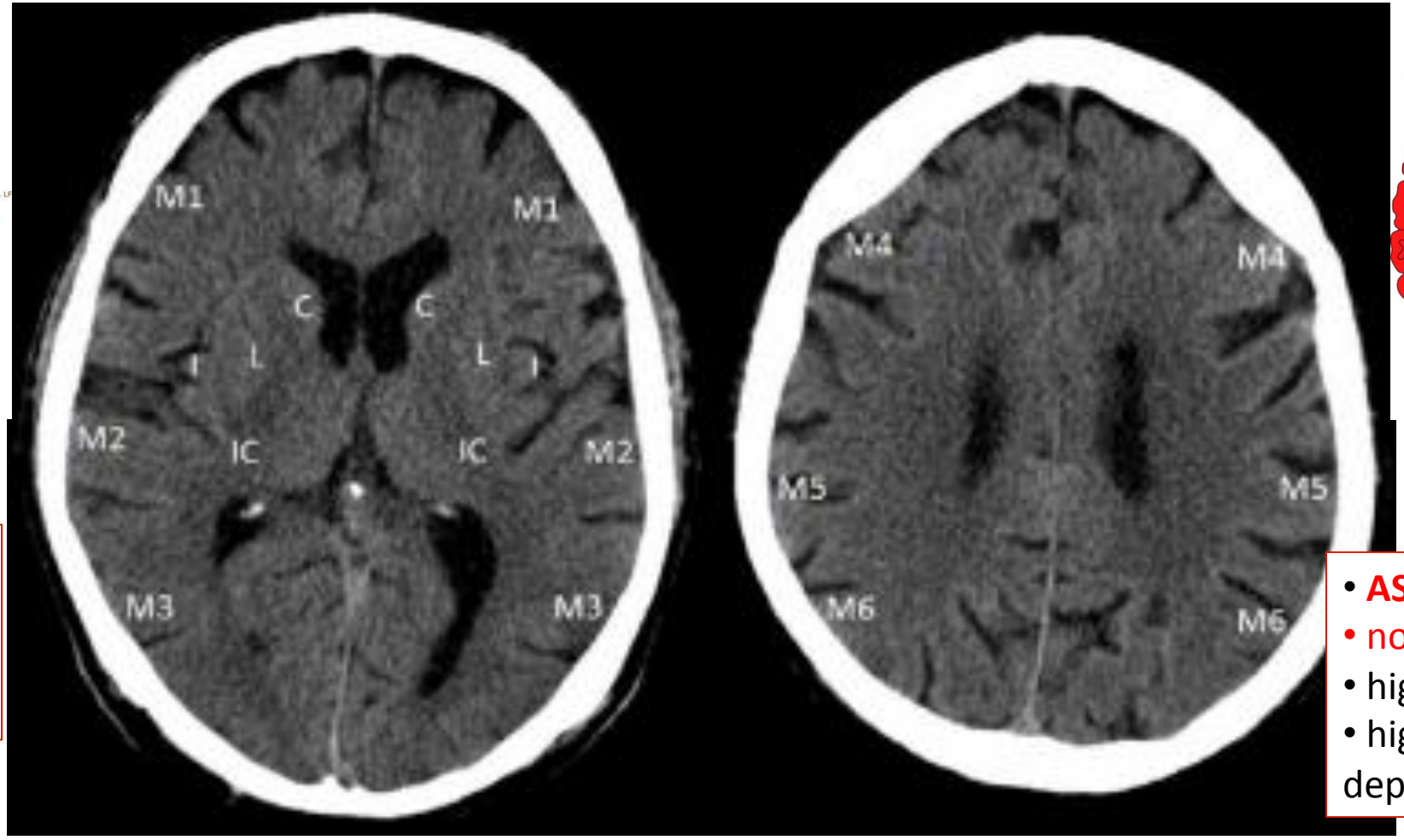


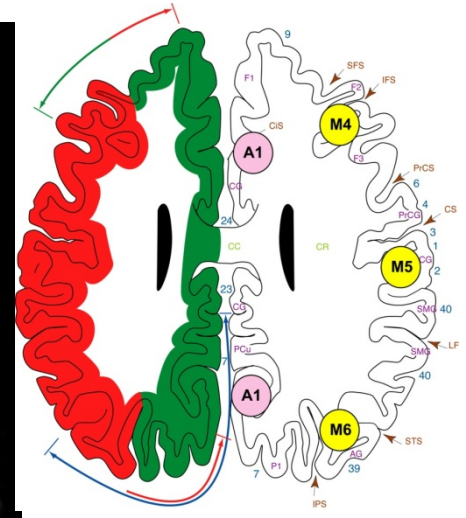
Use of the Alberta Stroke Program Early CT Score (ASPECTS) for Assessing CT Scans in Patients with Acute Stroke

AJNR Am J Neuroradiol 22:1534–1542, September 2001

CONCLUSION: ASPECTS is a systematic, robust, and practical method that can be applied to different axial baselines. Clinician agreement is superior to that of the 1/3 MCA rule.

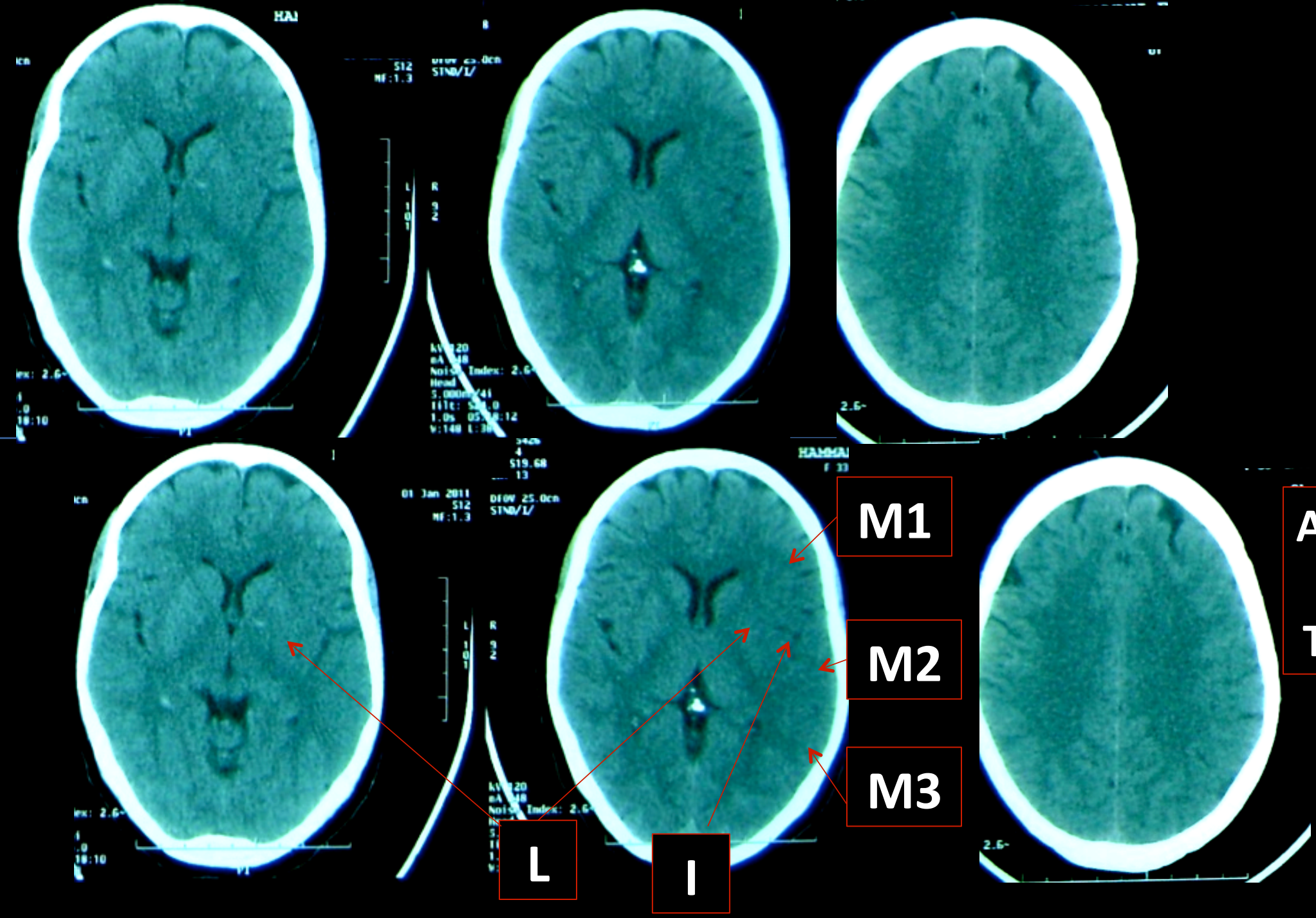




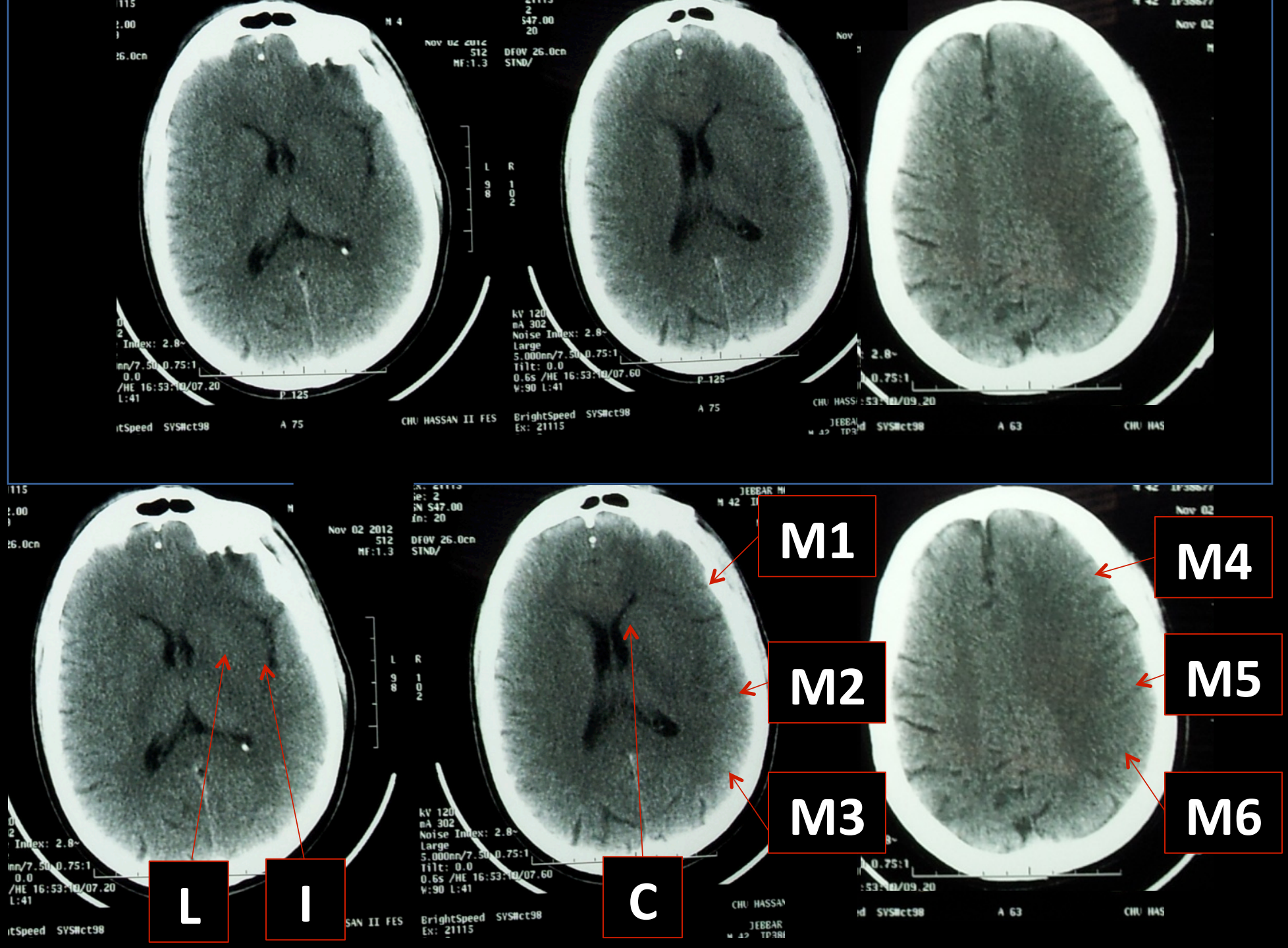


- **ASPECTS >7 thrombolysis:**
  - **good prognosis**

- **ASPECTS <7**
- no thrombolysis:
- high risk of bleeding
- high risk of dependency



ASPECTS = 5 (≤7)
NO
THROMBOLYSIS

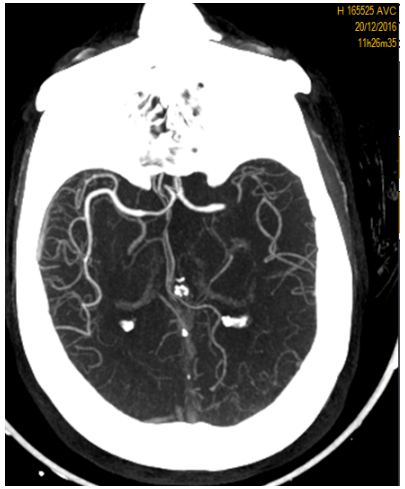


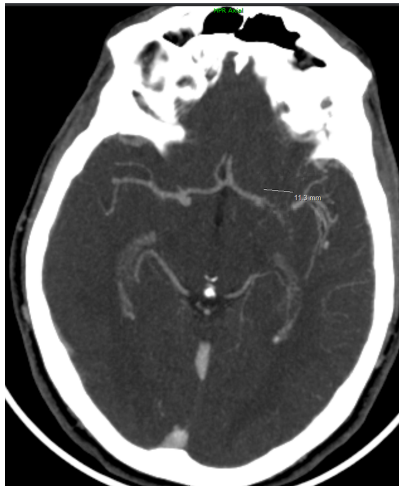
ASPECTS = 1 (≤7)
NO IVT

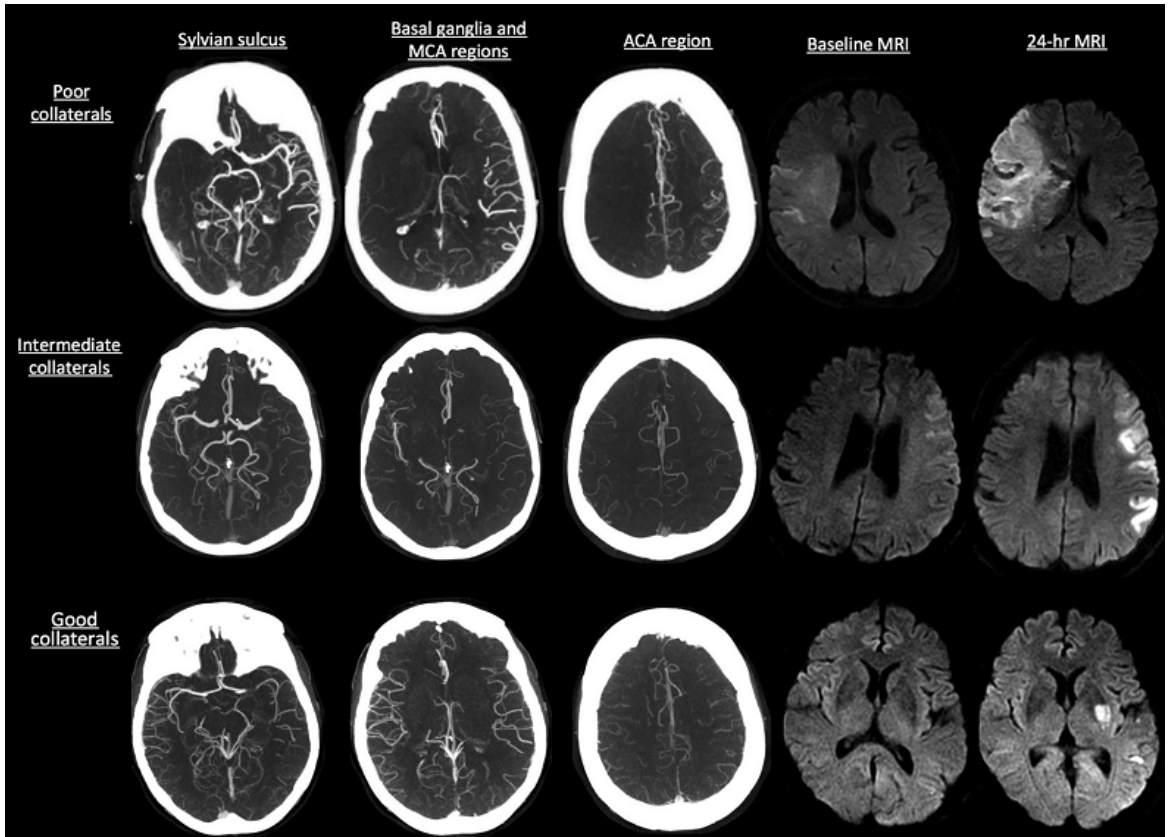
EVALUATION: IMAGING

CT Angiography

- Occlusion site
- thrombus size
- Collateralities +++

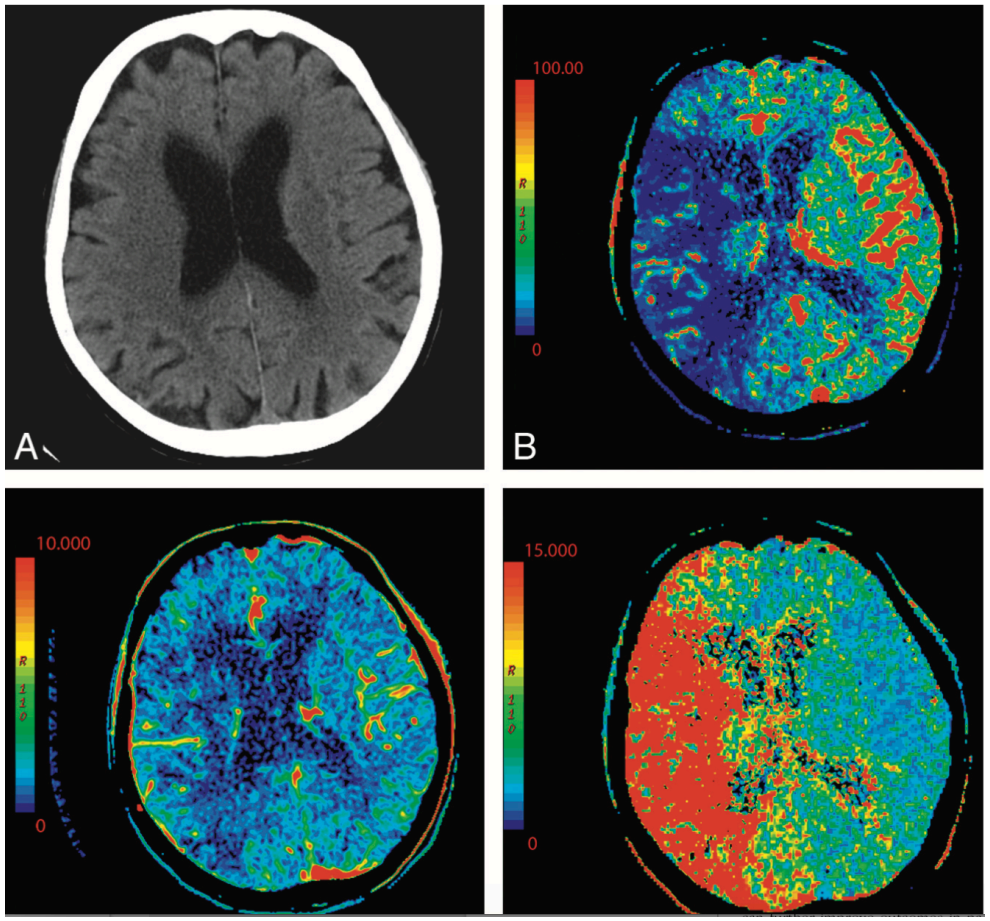




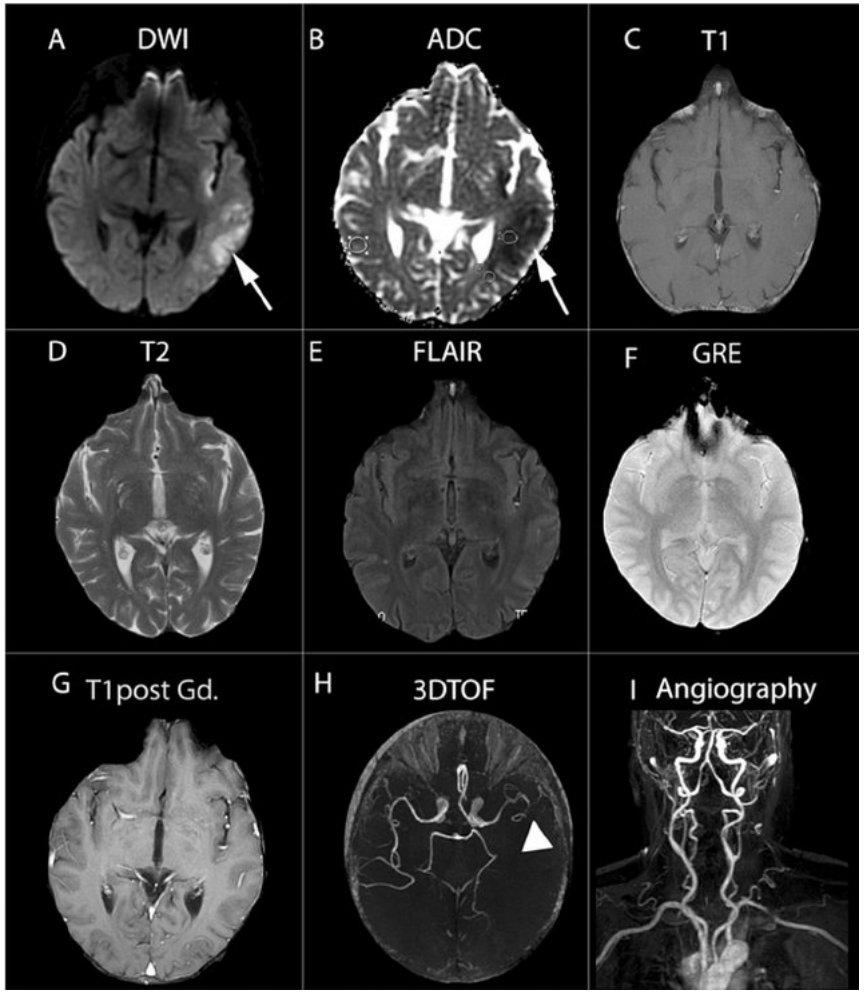


EVALUATION: IMAGING

CT Perfusion



MRI - MRA



Roldan-Valadez *Indian J Med Res 2014*

Stroke mimics

Common disorders other than stroke that may present with an acute neurological deficit

Seizure with postictal Todd's paresis
Migraine with aura
Hypoglycemia or hyperglycemia
Hyponatremia
Delirium (may be mistaken for aphasia)
Psychiatric (conversion, factitious disorder, malingering)

Journal of Stroke and Cerebrovascular Diseases
Volume 27, Issue 4, April 2018, Pages 1100-1106
ELSEVIER

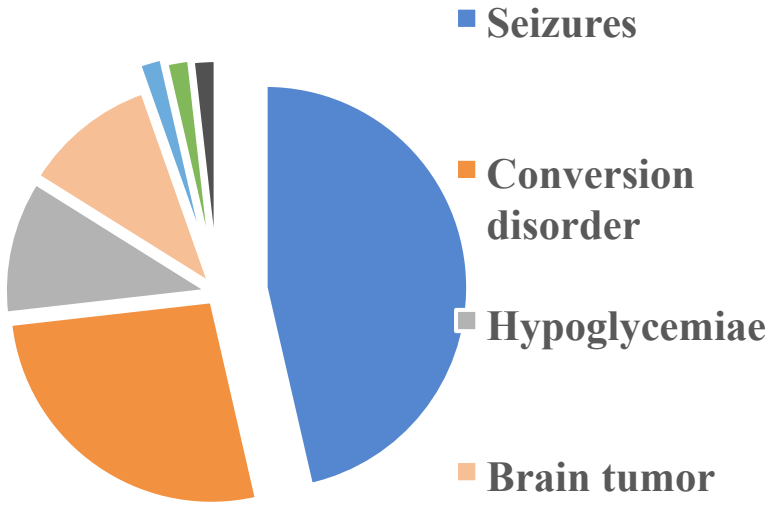
313 patients

Thrombolysis Alert in Hassan II University Teaching Hospital of Fez (Morocco): A Prospective Study of 2 Years

Moussa Toudou Daouda MD*, Siham Bouchal MD*, Naima Chtaou PhD*†, Aouatef Midaoui PhD*†, Zouahyr Souirti PhD*‡§, Faouzi Belahsen PhD*†

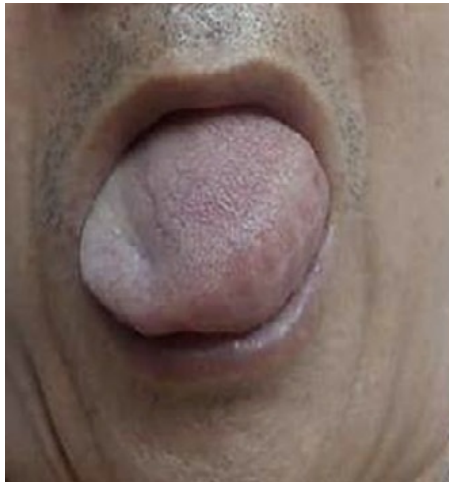
Stroke mimics: 17.9% (56/313)

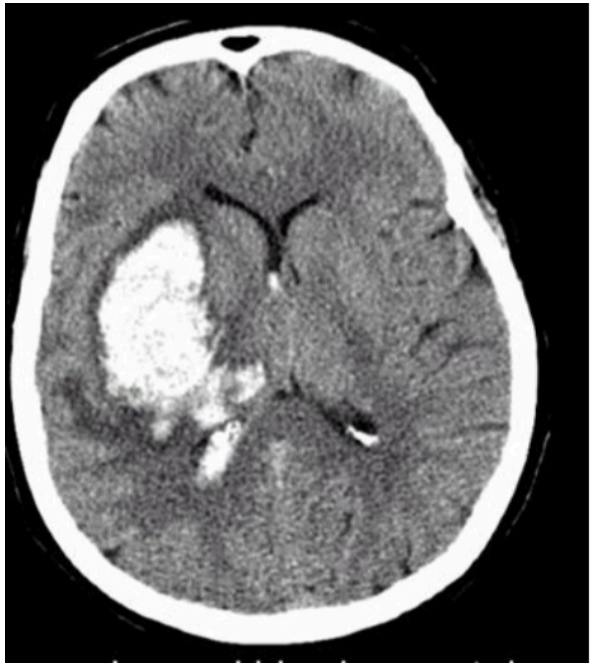
- **Post-stroke epilepsy (46.4%)**
- **Conversion disorders (26.8%)**
- Hypoglycemia (10.7%)
- Brain tumors (10.7%)
- Chronic subdural hematoma (1.8%)
- CO intoxication (1.8%)
- Cavernoma (1.8%)



Thrombolysis side effects and complications

- Allergic rash
- Bronchospasm
- Severe Hypotension
- Anaphylactic reaction
- Bleeding/ICH





Diestro, J. D. B.,. *Journal of Stroke and Cerebrovascular Diseases.2019 ir press*

How to increase the number of IVT?

- Reducing prehospital delay
- Reducing intrahospital delay
- Increase delay beyond 4.5 hours for selected patient (mismatch:

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2007;23:294–298
DOI: 10.1159/000098330

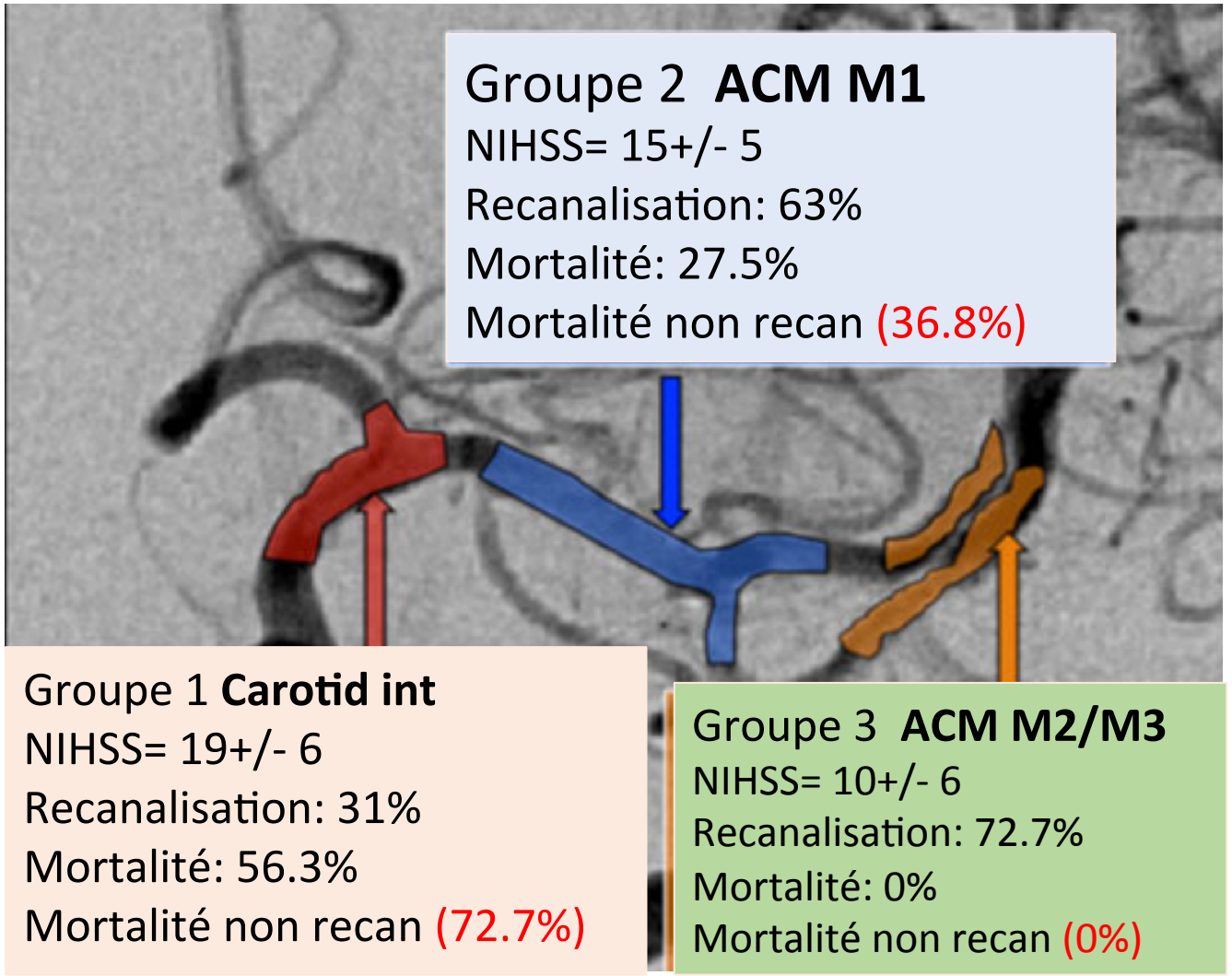
Received: March 20, 2006
Accepted: October 20, 2006
Published online: December 29, 2006

Estimating the Number of Stroke Patients Eligible for Thrombolytic Treatment if Delay Could Be Avoided

Bep Boode[a] Vivian Welzen[a] Cees Franke[c] Robert van Oostenbrugge[b]

[a]Department of General Practice, Maastricht University, [b]Department of Neurology, University Hospital Maastricht, Maastricht, and [c]Department of Neurology, Atrium Medical Centre, Heerlen, The Netherlands

LIMITS OF THROMBOLYSIS



Rohit Bhatia et al. Low rates of acute recanalization with intravenous rt-PA in ischemic stroke, Stroke 2010

IVT±MT: Case 3

74 year old patient

19/02/2019 at 6:00 pm left

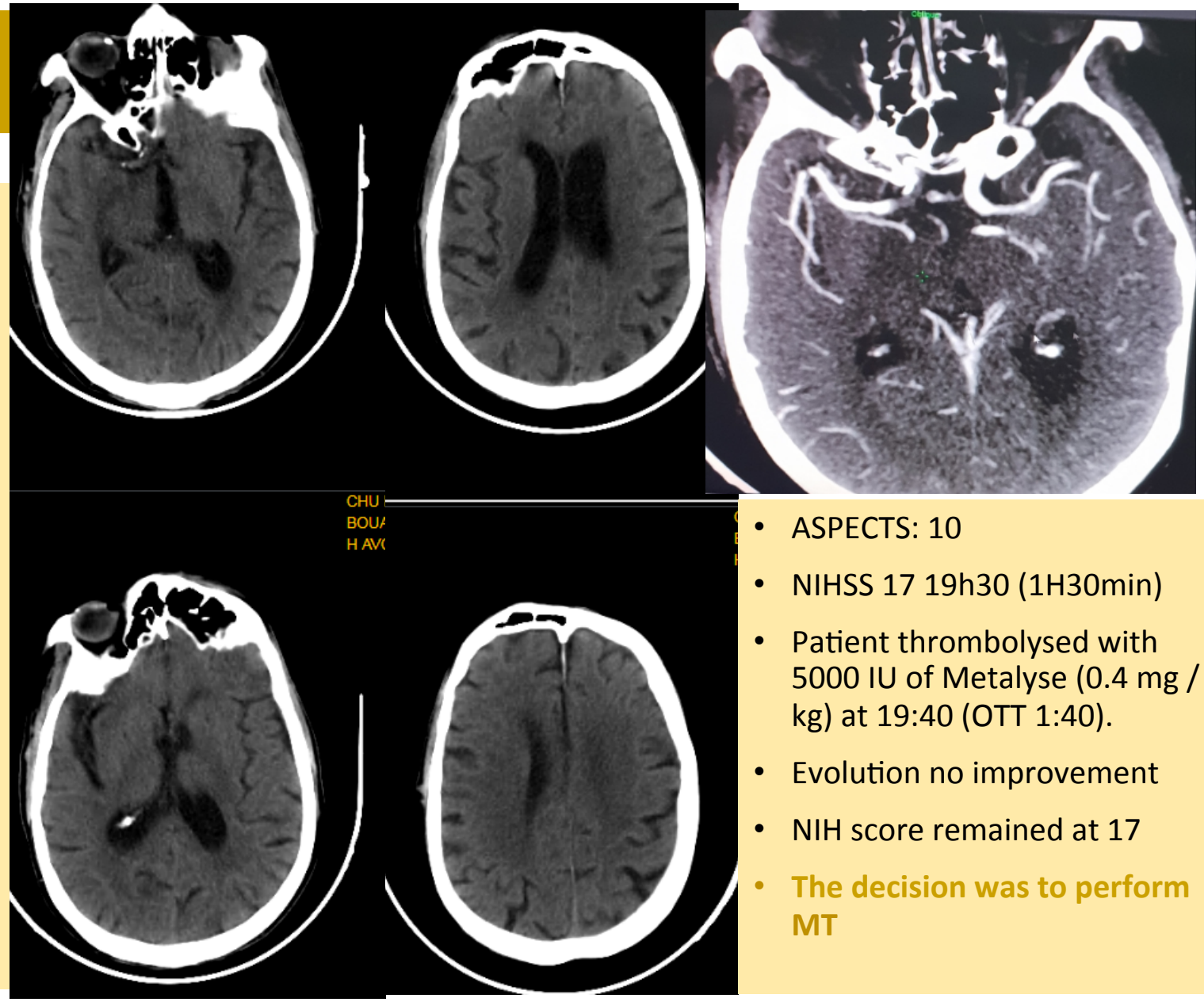
hemiplegia with facial asymmetry.

Emergency room at 7:10 pm (OTD: 70 min)

NIHSS = 17

EKG normal

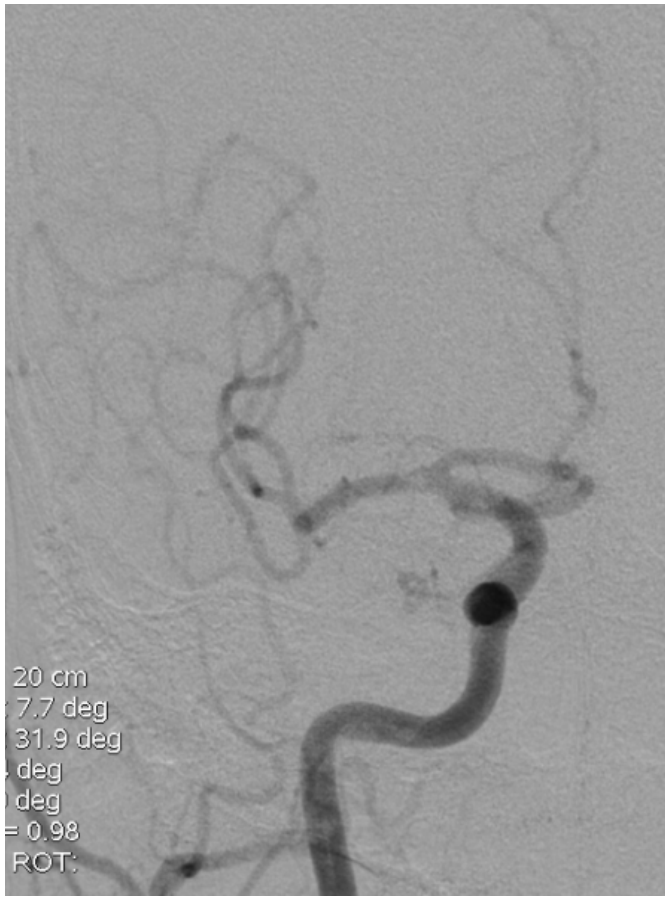
Biology normal

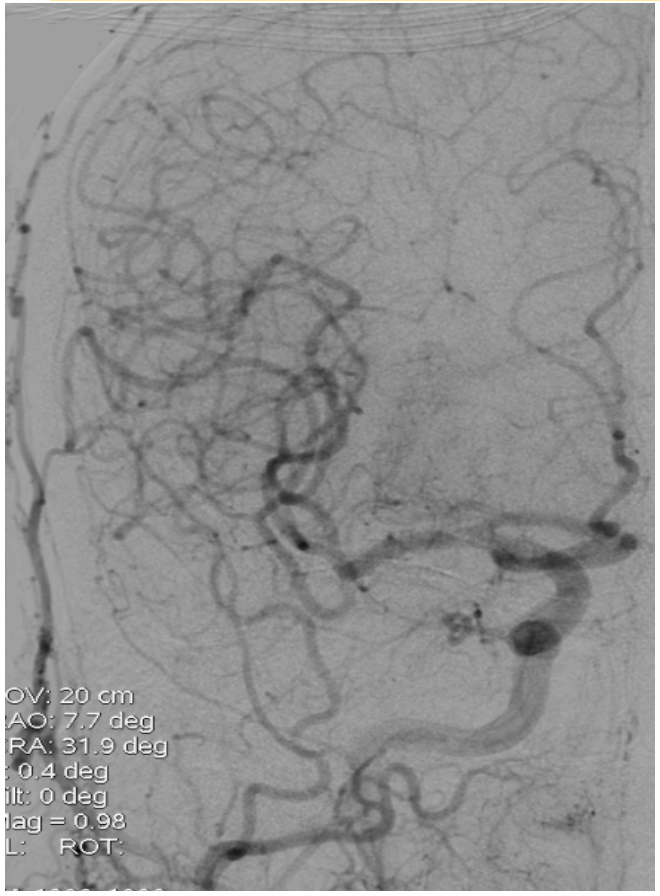


- ASPECTS: 10
- NIHSS 17 19h30 (1H30min)
- Patient thrombolysed with 5000 IU of Metalyse (0.4 mg / kg) at 19:40 (OTT 1:40).
- Evolution no improvement
- NIH score remained at 17
- **The decision was to perform MT**

IVT+MT: Case 3

- Patient installed for angiography at 21:30 (50 minutes after IVT).
- He recovered 4 points on the table (PF: 1, MS: 2, MI: 1, Dysarthria: 1)
- He was sedated by the agitation.





- No thrombectomy
- **Full recanalization by IVT alone**
- NIHSS score from 17 to 1 (LUL**1**).
- CT control: partial superficial sylvian stroke
- NIHSS from 1 to 0 after

IVT before Mechanical Thrombectomy

IVT ➡ MT

The NEW ENGLAND JOURNAL of MEDICINE

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*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 1, 2015 VOL. 372 NO. 1

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

O.A. Berkhemer, P.S.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J.H. Wermer, M.A.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L.M. de Kort, W.J.J. van Rooij, J.S.P. van den Berg, B.A.A.M. van Hasselt, L.A.M. Aerden, R.J. Dallinga, M.C. Visser, J.C.J. Bot, P.C. Vroomen, O. Eshghi, T.H.C.M.L. Schreuder, R.J.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E.S. Sprengers, S.F.M. Jenniskens, L.F.M. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B.W.E.M. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B.L.M. Majoie, and D.W.J. Dippel, for the MR CLEAN Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2015 VOL. 372 NO. 24

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

Jeffrey L. Saver, M.D., Mayank Goyal, M.D., Alain Bonafe, M.D., Hans-Christoph Diener, M.D., Ph.D., Elad I. Levy, M.D., Vitor M. Pereira, M.D., Gregory W. Albers, M.D., Christophe Cognard, M.D., David J. Cohen, M.D., Werner Hacke, M.D., Ph.D., Olav Jansen, M.D., Ph.D., Tudor G. Jovin, M.D., Heinrich P. Mattle, M.D., Raul G. Nogueira, M.D., Adnan H. Siddiqui, M.D., Ph.D., Dileep R. Yavagal, M.D., Blaise W. Baxter, M.D., Thomas G. Devlin, M.D., Ph.D., Demetrius K. Lopes, M.D., Vivek K. Reddy, M.D., Richard du Mesnil de Rochemont, M.D., Oliver C. Singer, M.D., and Reza Jahan, M.D., for the SWIFT PRIME Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

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*

ORIGINAL ARTICLE

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

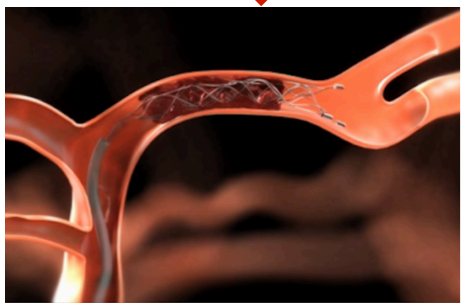
T.G. Jovin, A. Chamorro, E. Cobo, M.A. de Miquel, C.A. Molina, A. Rovira, L. San Román, J. Serena, S. Abilleira, M. Ribó, M. Millán, X. Urra, P. Cardona, E. López-Cancio, A. Tomasello, C. Castaño, J. Blasco, L. Aja, L. Dorado, H. Quesada, M. Rubiera, M. Hernández-Pérez, M. Goyal, A.M. Demchuk, R. von Kummer, M. Gallofré, and A. Dávalos, for the REVASCAT Trial Investigators*

MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND IA

TIV + MT>>> TIV seule

?

OR



IVT + MT>>> IVT

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EXTEND-IA TNK

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey,

RESULTS

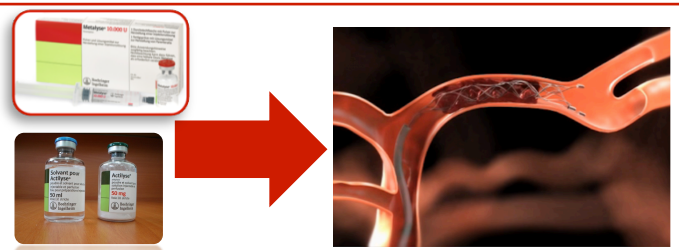
Of 202 patients enrolled, 101 were assigned to receive tenecteplase and 101 to receive alteplase. The primary outcome occurred in 22% of the patients treated with tenecteplase versus 10% of those treated with alteplase (incidence difference, 12 percentage points; 95% confidence interval [CI], 2 to 21; incidence ratio, 2.2; 95% CI, 1.1 to 4.4; P=0.002 for noninferiority; P=0.03 for superiority). Tenecteplase resulted in a better 90-day func- tional outcome than alteplase (median modified Rankin scale score, 2 vs. 3; common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04). Symptomatic intracerebral hemorrhage oc- curred in 1% of the patients in each group.

CONCLUSIONS

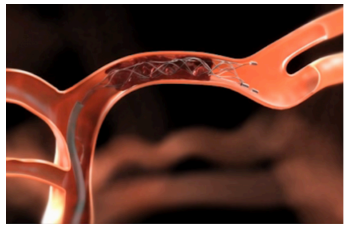
Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset.

IVT(TNK) + MT> IVT(rtPA) + MT>>> TIV alone

TIV + MT/MT alone ?



- The fibrinolytic process of IVT could increase the speed and chances of success of TM reperfusion
- Reduce the number of passages required with a retriever stent and decrease the frequency of microvascular thromboses
- Patients of distal occlusions
- TIV alone may have recanalization, avoiding the use of TM.



- IVT may increase the risk of bleeding complications
- IVT can result in thrombus fragmentation, reducing the effectiveness of TM in achieving complete reperfusion of distal vessels.
- IVT may delay the start of the TM procedure, (primary center / full center)
- IVT is an expensive therapy

Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke (SWIFT DIRECT)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03192332

Recruitment Status : Recruiting
First Posted : June 20, 2017
Last Update Posted : March 7, 2019

See Contacts and Locations

SWIFT DIRECT

Sponsor:
University Hospital Inselspital, Berne

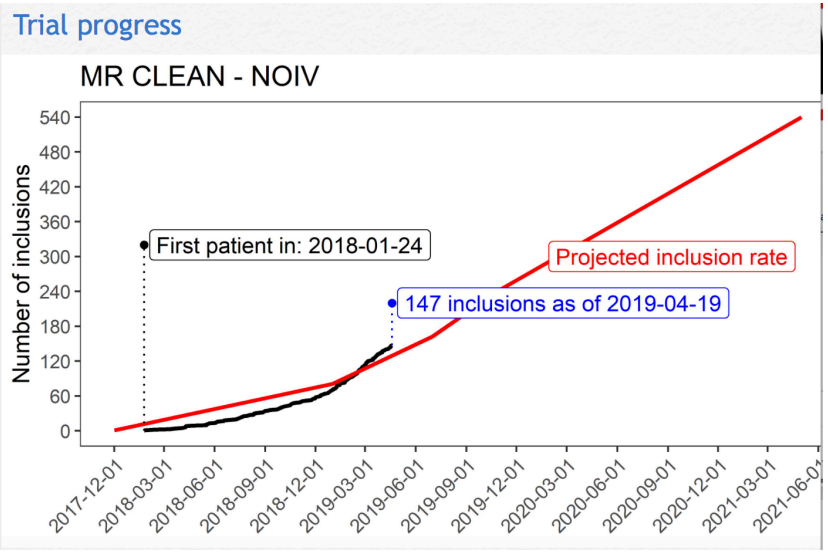
Collaborator:
Medtronic

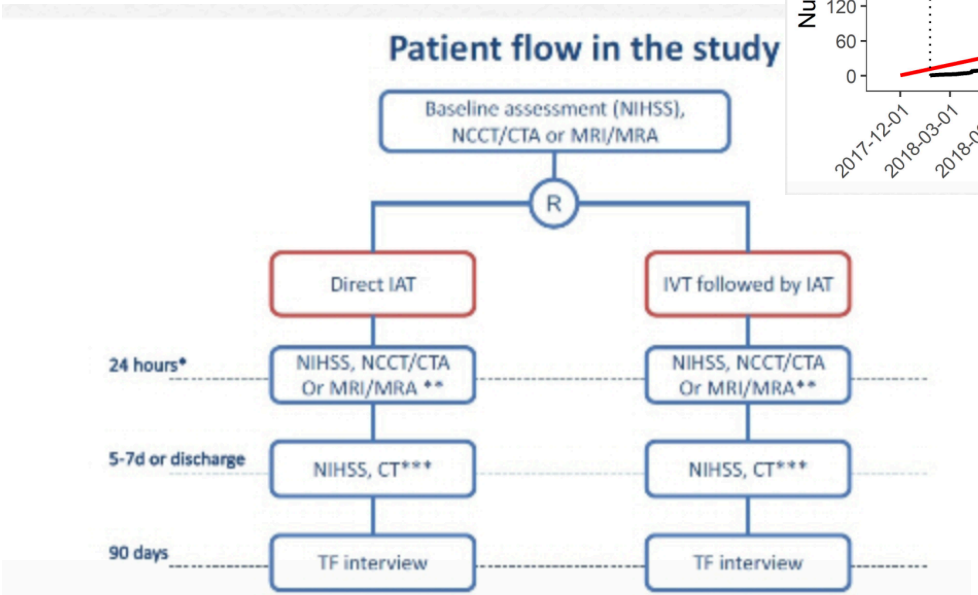
Information provided by (Responsible Party):
University Hospital Inselspital, Berne

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	404 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Prospective, randomized, open label, blinded endpoint (PROBE)
Masking:	Single (Outcomes Assessor)
Masking Description:	Assessment of the primary outcome will be performed by an independent and blinded person.
Primary Purpose:	Treatment
Official Title:	Solitaire™ With the Intention For **Thrombectomy** Plus Intravenous t-PA Versus DIRECT Solitaire™ Stent-retriever **Thrombectomy** in Acute Anterior Circulation **Stroke**
Actual Study Start Date :	November 29, 2017
Estimated Primary Completion Date :	December 31, 2020
Estimated Study Completion Date :	December 31, 2021

MR CLEAN NO IV





Key messages: IVT

- IVT has been shown to improve acute stroke outcomes if given within 4.5 hours of symptom onset.
- IVT beyond 4.5 hours for selected patients
- Time from symptom onset remains critical
- Better patient selection and triage criteria: to reduce risk and increase efficacy
- Centers must develop an organized response to acute ischemic stroke with clinical protocols and quality of care assessment tools.

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THANK YOU FOR YOUR ATTENTION